AARHUS UNIVERSITY

Multimorbidity and cardiovascular disease

Population-based studies of risk, prognosis, and prediction

Doctoral dissertation

Morten Schmidt

2022

DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Multimorbidity and cardiovascular disease

— Population-based studies of risk, prognosis, and prediction —

Doctoral dissertation

Morten Schmidt

Health

Aarhus University

2022

AARHUS UNIVERSITY

Defence

The Faculty of Health at Aarhus University has on 14 October 2021 accepted this doctoral dissertation and the accompanying papers for public defence for the higher doctoral degree in Medical Science, DMSc (in Danish, dr.med.).

Aarhus University, 14 October 2021

Hans Erik Bøtker
Acting Dean

The defence will take place on 25 February 2022 at 2 pm in the Small Anatomy Auditorium at Aarhus University (Building 1231, Room 424, Wilhelm Meyers Allé 3, 8000 Aarhus C, Denmark).

Assessment committee

Daniel R. Witte, MD, PhD, Professor (chairman)
Department of Public Health
Aarhus University, Denmark

Eva Prescott, MD, DMSc, Professor
Department of Clinical Medicine
Copenhagen University, Denmark

Frits Rosendaal, MD, PhD, Professor
Department of Clinical Epidemiology
Leiden University, Netherlands

Funding

This work was made possible through financial support from:

- The Novo Nordisk Foundation (grant NNF19OC0054908)
- The Clinical Epidemiological Research Foundation
- The Aarhus University Research Foundation
- The Danish Medical Research Council
- The Arvid Nilsson Foundation
- The Danish Heart Association
- Aarhus University

Dedication

Frede J. Schmidt

*11.3.1951 † 3.6.2020

"The failure to classify and analyze co-morbid diseases has led to many difficulties in medical statistics"

Alvan R. Feinstein (*J Chron Dis, 1970)*

Preface

The present dissertation is based on population-based studies performed in the period from 2008 to 2020. The work was conducted during my employments at the Departments of Clinical Epidemiology and Cardiology at Aarhus University Hospital.

Pivotal parts of my research during this period were carried out during research stays at foreign institutions. I warmly thank Timothy L. Lash for hosting me at Boston University in Boston, Massachusetts (2009); John A. Baron for his hospitality at Dartmouth University in Hanover, New Hampshire (2009); Stanley Lemeshow for welcoming my wife and I into the buckeye family at Ohio State University in Columbus, Ohio (2012); Karin Petersen for including us in the dynamic team at California Pacific Medical Center Research Institute in San Francisco, California (2013); and Liam Smeeth and Laurie A. Tomlinson for an unforgettable stay in the inspiring atmosphere surrounding the John Snow Water Pump at the London School of Hygiene and Tropical Medicine in London, UK (2015–2016).

I thank all co-authors and affiliated departments for their contributions to the research described in this dissertation. The research is based on three pillars: epidemiology, biostatistics, and cardiology. Special thanks go to the individuals who inspired me within each of these pillars, in particular: Henrik Toft Sørensen and John A. Baron (in clinical epidemiology); Timothy L. Lash and Kenneth J. Rothman (in modern epidemiology); Lars Pedersen, Stanley Lemeshow, and Erzsébet Horváth-Puhó (in applied biostatistics); and Hans Erik Boetker (in cardiology).

I extend a particular gratitude to my mentor Henrik Toft Sørensen, who has been the red line through my entire research carrier. Sharing his knowledge, experience, and network, Henrik Toft Sørensen has shaped me as the researcher that I am today.

Loving thoughts go to my family, in particular my wife, Sigrún, and our wonderful children. I am grateful for your enduring patience and unconditional support.

Finally, I dedicate this dissertation to my father who suffered life-changing consequences of multimorbidity. His strong moral character and integrity will continue to inspire me, in life as in research.

Morten Schmidt

Aarhus, 2021

Dissertation studies

Papers on comorbidity

I. 25 year trends in first time hospitalization for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study

Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT

BMJ 2012;344:e356[1]

II. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study

Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Sørensen HT

Eur J Heart Fail 2016;18(5):490–9[2]

III. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity

Schmidt M, Jacobsen JB, Johnsen SP, Bøtker HE, Sørensen HT

Neurology 2014;82(4):340–50[3]

IV. The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: A nationwide cohort study

Schmidt M, Horvath-Puho E, Ording AG, Bøtker HE, Lash TL, Sørensen HT

Int J Cardiol 2020;308:1-8[4]

V. The DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI): Development, Validation and Comparison with Existing Comorbidity Indices

Albertsen LW, Heide-Jørgensen U, Schmidt SAJ, Grey C, Jackson R, Sørensen HT, Schmidt M

Clin Epidemiol 2020;12:1299–311[5]

Papers on cardiac comedication

VI. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin–angiotensin system blockade: a UK general practice-based cohort study

Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sørensen HT, Smeeth L, Tomlinson LA

BMJ Open 2017;7(1):e012818[6]

VII. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study

Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sørensen HT, Smeeth L, Tomlinson LA

BMJ 2017;356:j791[7]

VIII. Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular events following coronary stent implantation

Schmidt M, Johansen MB, Robertson DJ, Maeng M, Kaltoft A, Jensen LO, Tilsted HH, Bøtker HE, Sørensen HT, Baron JA

Aliment Pharmacol Ther 2011;35(1):165–74[8]

Papers on non-cardiac comedication

IX. Diclofenac use and cardiovascular risks: series of nationwide cohort studies.

Schmidt M, Sørensen HT, Pedersen L

BMJ 2018:k3426–10[9]

X. Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study

Schmidt M, Pottegård A

Eur Heart J Cardiovasc Pharmacother. 2020;37:1015[10]

XI. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study

Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT

BMJ 2011;343:d3450[11]

XII. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism

Schmidt M, Christiansen CF, Horvath-Puho E, Glynn RJ, Rothman KJ, Sørensen HT

J Thromb Haemost 2011;9(7):1326–33[12]

XIII. Preadmission use of nonaspirin nonsteroidal anti-inflammatory drugs and 30-day stroke mortality

Schmidt M, Hováth-Puhó E, Christiansen CF, Petersen KL, Bøtker HE, Sørensen HT

Neurology 2014;83(22):2013–22[13]

Studies XI–XIII were included in the PhD thesis 'Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use', Aarhus University 2014.[14] *The remaining studies have not previously been submitted with a view to conferring an academic degree, and therefore form the foundation for the assessment of the dissertation.*[15]

Dissertation structure

The dissertation is based on thirteen studies, which are referred to in the text by their Roman numerals (studies I–XIII). The studies are divided into the three pillars of the dissertation (Figure 1): comorbidity (studies I–V),[1-5] cardiac comedications (studies VI–VIII),[6-8] and non-cardiac comedications (studies IX–XIII).[9-13]

The *Introduction* introduces the concepts of multimorbidity and polypharmacy. In the context of an index cardiovascular disease, these concepts are further detailed in terms of comorbidity and comedication.

After the study *Methods* and main *Results* are summarized, the *Discussion* section summarizes the main findings, addresses the validity of the results, and points out the contributions that these studies have made to the advancement of science (Figure 1). These contributions are discussed in terms of the impacts made on research, clinical practice, and regulatory actions. The *Discussion* section is followed by *Conclusions.*[15]

The last chapters of this dissertation include the *Summaries*, in English and Danish, *Supplementary material*, *References*, and *Appendices*. The Appendices include the published versions of the dissertation studies.

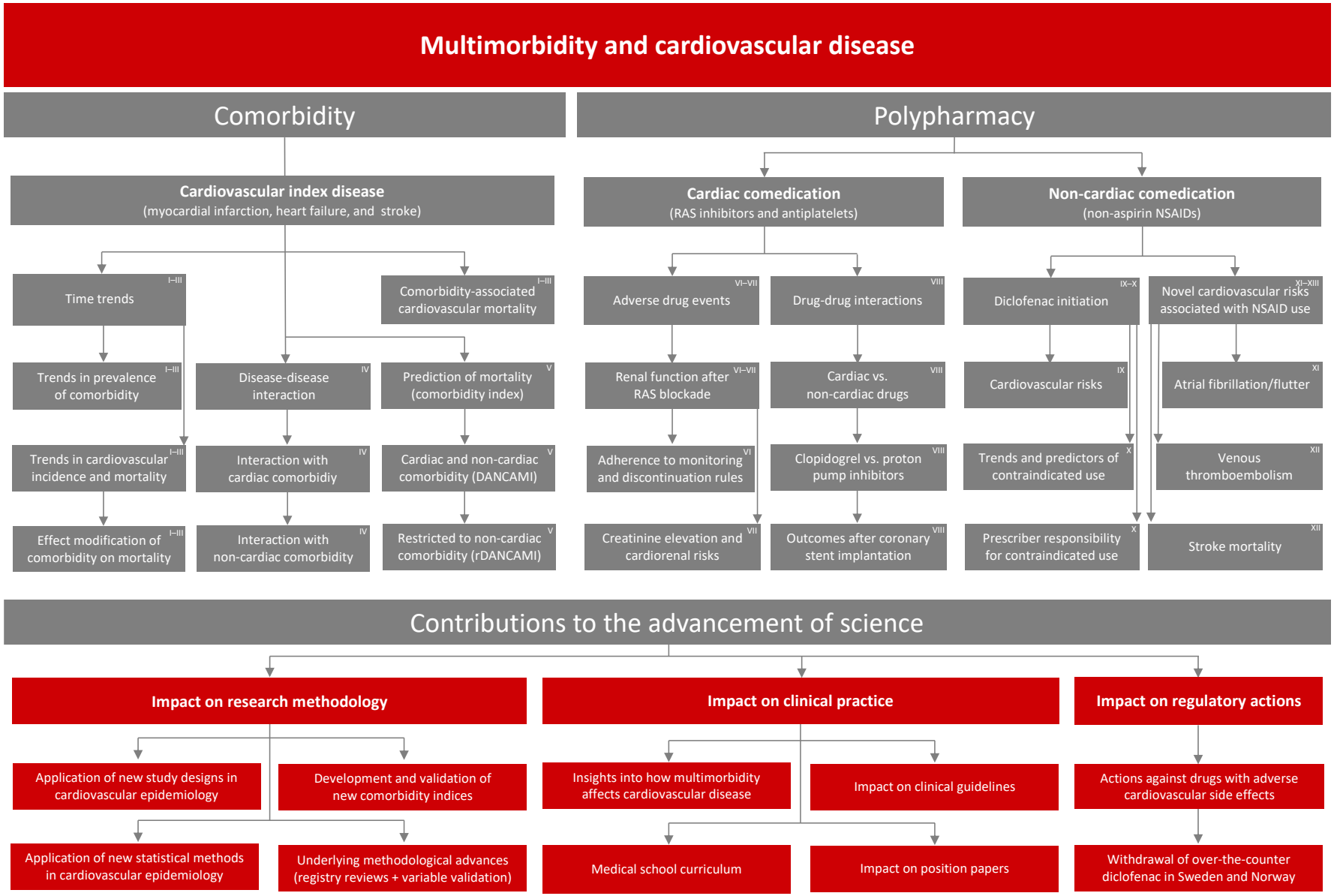


Figure 1 | Overview of the content of the dissertation and its contributions to the advancement of science. Roman numerals correspond to the publications listed under Dissertation studies on page vii. Abbreviations: DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction; NSAID, non-steroidal anti-inflammatory drug; RAS, renin-angiotensin system; rDANCAMI, DANCAMI restricted to non-cardiovascular comorbidities.

Table of contents

1. Introduction

1.1. Cardiovascular disease

Cardiovascular disease is the number one cause of death globally.[16] Representing 31% of all global deaths, an estimated 18 million people died from cardiovascular diseases in 2016.[16] Of these deaths, 85% was due to acute myocardial infarction (MI) or stroke. More than 75% of deaths from cardiovascular disease takes place in low- and middle-income countries.[16] Out of the 17 million premature deaths (before age 70 years) due to noncommunicable diseases in 2015, 37% was caused by cardiovascular disease.[16]

Most cardiovascular diseases can be prevented by addressing lifestyle and non-behavioral risk factors. Lifestyle risk factors include tobacco use, unhealthy diet, obesity, physical inactivity, and harmful use of alcohol. The most important modifiable non-behavioral risk factors include hypertension, diabetes, and hyperlipidemia. Some underlying determinants of cardiovascular disease ('the causes of the causes'), which drive social, economic, and cultural changes, include globalization, urbanization, and population ageing.[16]

From a Danish perspective, cardiovascular disease has remained the second most common cause of death, following cancer, over the last 25 years.[17] However, although the age-standardized mortality rate per 100,000 individuals due to cardiovascular disease was close to that due to cancer in 1995 (331 *vs.* 303), cardiovascular disease-related mortality has improved more rapidly than cancer-related mortality. In 2018, the age-standardized mortality due to cardiovascular disease was close to half of that due to cancer (118 *vs.* 227 per 100,000 individuals).[17] Nevertheless, the prevalence of cardiovascular disease in Denmark is >10%, and among Danish individuals over the age of 55 years, more than half will experience cardiovascular disease.[18] Although cardiovascular disease mortality has halved during the last three decades,[17] every fourth death in Denmark (~12,400 per year) is attributed to cardiovascular disease, particularly ischemic heart disease.[1-3,19,20]

1.2. Multimorbidity

Increasingly, healthcare systems must manage individuals with multiple coexisting diseases; currently, these conditions have become the norm, rather the exception.[21] Multimorbidity is defined as the existence of two or more chronic diseases in a single individual.[22] However, measuring multimorbidity is not straightforward.[23] Heterogeneous definitions in the medical literature[24,25] have contributed to large differences in prevalence estimates, ranging from 3.5% to 98.5% in older general populations.[26] These competing definitions impede the ability to collate evidence in a coherent way; thus, it is difficult to evaluate the implications of the available research, including the potential for improving patient care.[27] Therefore, the Academy of Medical Science recommends the definition of multimorbidity established by the World Health Organization: 'the coexistence of two or more chronic conditions, each one of which is either a non-communicable disease, a mental health disorder, or an infectious disease of long duration'.[28]

Overall, there are four possible hypotheses concerning the etiological aspects of multimorbidity: (1) There is no etiological association between diseases; (2) there is a direct causal link between diseases; (3)

concurrent diseases have associated or shared risk factors; and (4) diseases develop independently (i.e., co-existence is due to a third, distinct disease or condition).[29] Despite the varying definitions of multimorbidity, some risk factors and adverse effects are well established. The established risk factors for multimorbidity include advanced age, female sex, and less advantaged backgrounds.[28] Currently, multimorbidity is increasing globally, particularly in high-income countries, due to the aging population, urbanization, and the growing burden of non-communicable diseases, such as obesity and type 2 diabetes.[27,30]

Multimorbidity negatively influences a range of outcomes, including healthcare use (utilization, organization, quality, and costs), quality of life,[31] and mortality:[32] Healthcare utilization and costs are increased due to more frequent emergency department contacts, avoidable inpatient admissions, treatment complications, longer hospital stays, and higher readmission rates.[32-34] In the United States, about 80% of Medicare spending is attributed to patients with four or more chronic conditions, and the costs increase exponentially as the number of chronic conditions increases.[33] Healthcare organizations are influenced by the challenges related to accessibility, coordination, and consultation times. The quality of healthcare is reduced, due to fragmented and ineffective care,[35] polypharmacy, and nonadherence to guidelines;[34] Reduced quality of life is related to psychological distress, and in particular, multimorbidity clusters of concurrent physical and mental health conditions;[28] Multimorbidity increases the risk of premature death,[28] and mortality increases with both the number and particular combinations of morbidities.[36,37] Thus, the presence of multimorbidity raises the already high risk of death among patients with low socioeconomic status and/or high stress.[36-38]

Although multimorbidity is a growing global health concern, the available evidence on its causes, impact, prevention, and treatment remains inadequate.[28] Thus, the Academy of Medical Science has called for urgent, advanced research to tackle multimorbidity, by specifically investigating: (i) 'the scale and nature of multimorbidity and how it is changing over time', (ii) 'which clusters of conditions cause the greatest problems for patients', and (iii) 'how doctors can increase the benefits and reduce the risks of treatment for patients with multimorbidity'.[28]

1.3. Comorbidity

In clinical practice, patients are not referred for evaluations of multimorbidity; instead, they are referred for evaluations of a particular (index) disease. Similarly, medical school, postgraduate medical training (except pediatrics and geriatrics), and the organization of healthcare systems typically focus on specific index diseases. In the context of an index disease, addressing multimorbidity means addressing comorbidity. The concept of comorbidity was first defined by Alvan R. Feinstein, in 1970, as "*any additional co-existing ailment in a patient with a particular index disease"*.[39] However, the term comorbidity has not been uniformly conceptualized. For example, the terms 'co-existing' and 'co-occurring' have been used interchangeably,[22,39] although an important distinction exists: 'co-existing' refers to the simultaneous presence of multiple health conditions, without an index disease (*i.e.*, multimorbidity); in contrast, 'co-occurring' implies a cluster of one or more additional diseases in an individual with an index disease, where the additional diseases occur at a higher rate than expected by chance alone (*i.e.*, comorbidity).[40] In addition, comorbidity has been variously

expressed as a count (a sum of the number of diseases) or an index (a combination of the number and severity of diseases).[41]

As early as 1970, Feinstein stressed that "the failure to classify and analyze co-morbid diseases has led to many difficulties in medical statistics".[39] Supporting this view, comorbidities have been assessed from various sources, including medical records, physical examinations, personal interviews, questionnaires, and registries. In addition, the nature of the conditions that co-occur have variously included diseases, disorders, conditions, illnesses, and health problems.[29] Some, but not all, of these terms and concepts can be linked to classification systems, which makes reproducibility difficult. The chronologic aspects of comorbidity are also important, because the time interval in which the co-occurrence of two or more conditions is assessed and the sequence in which comorbidities appear can have prognostic impacts.[29] Moreover, it is important to separate comorbidity from complications. Complications arise after the index disease is diagnosed, and therefore, they qualify as either an endpoint or an intermediate step between the exposure and a more distant point in the clinical pathway.[42] Finally, patient complexity is an emerging construct, which, in addition to health-related characteristics, takes into account the socioeconomic, cultural, environmental, and patient behavioral characteristics.[43,44]

Feinstein also commented on the prognostic importance of comorbidity, with the statement: "the omissions of co-morbid diseases create misleading (…) fatality rates for an individual disease."[39] In other words, comorbidity can change the clinical course and survival of an index disease.[39] In addition to its prognostic effects, comorbidity can affect symptoms and signs, time to detection, stage at diagnosis, time to treatment, choice of acute interventional and medical treatments, treatment response, choice of tertiary medical prevention, rehabilitation, and compliance to treatment for an index disease. Nonetheless, comorbidity remains widely neglected in clinical guidelines for many patient groups.

Guidelines within cardiology are largely based on the results of randomized controlled trials (RCTs), which typically exclude patients of advanced age or with multimorbidity.[45] Therefore, RCTs generally do not quantify harms well.[46,47] Nevertheless, RCTs often lead to broad implementation of long-term treatments, even when the benefits and harms have not been examined in individuals with shorter life expectancies (*e.g.*, older individuals).[48,49] To obtain presumably 'homogeneous' comparison groups and to increase internal validity (by reducing systematic errors, particularly confounding), the controlled settings of RCTs come at the cost of external validity; thus, extrapolating the results to the more heterogeneous clinical reality becomes uncertain.[39]

Previous reviews have emphasized four reasons for measuring comorbidity in research: (1) to identify effect modification; (2) to adjust for confounding; (3) to predict outcomes; and (4) to create comprehensive comorbidity indices that improve statistical efficiency.[41] Our rationale for measuring comorbidity in patients with a cardiovascular (index) disease include the aforementioned four reasons and three additional reasons: (5) to increase our understanding of the prevalence of comorbidity, and (6,7) to understand its prognostic impact, by elucidating its (6) associations and (7) interactions with cardiovascular mortality (detailed below).

1.3.1. Trends in prevalence of comorbidity at first-time cardiovascular disease

Nearly half of the adult population has at least one chronic disease. That proportion increases to 90% when considering only individuals older than 65 years.[33] In Denmark, the median ages at a first-time MI are 68 years for men and 75 years for women.[1] Risk factors that are shared between ischemic heart disease and other chronic diseases, such as smoking, physical inactivity, obesity, diabetes, chronic obstructive pulmonary disease, and cancer, contribute to the high prevalence of comorbid diseases.[27] However, it remains largely unknown whether trends in comorbidity prevalence have changed over time among patients with cardiovascular disease.

1.3.2. Association between comorbidity and cardiovascular mortality

There is a high prevalence of comorbidity among individuals with a first-time cardiovascular disease. Currently, with the availability of new therapies,[50] it is increasingly important to understand the impact of comorbidity on the prognosis of cardiovascular disease and its association with mortality.[51] Furthermore, it is unclear whether comorbidities are associated with long-term and/or short-term outcomes. Associations with short-term outcomes could indicate a potential biological interaction (see below) between comorbidity and cardiovascular disease. Therefore, it is important to establish whether and to what extent comorbidity is associated with short- and/or long-term cardiovascular mortality.

1.3.3. Effect modification by comorbidity on cardiovascular mortality trends

Effect measure modification is the variation in the selected effect measure for the variable of interest across levels of another variable. The outcome of many major cardiovascular diseases, such as ischemic heart disease, has improved considerably during the last few decades.[1,52] Improvements in mortality are explained by a reduction in major risk factors and by the availability of evidence-based medical therapies.[52-54] However, comorbidity can modify the effectiveness of newer therapies, and hence, the clinical course of a cardiovascular disease.[55] Therefore, it is important to examine whether comorbidity modifies trends in cardiovascular mortality; or put another way, whether trends in survival apply to all patients, independent of their comorbidity burden.

1.3.4. Interaction effect of comorbidity on cardiovascular mortality

Although the magnitude of the association between comorbidity and short- and long-term outcomes is yet to be established, comorbidity burden is expected to be associated with higher long-term mortality, due to its adverse prognostic effect. However, if comorbidity increases the cardiovascular mortality rate beyond what could be expected from their independent effects, it would suggest a synergistic interaction.[56] This differs from the effect measure modification (described above), which is defined in terms of the effect (mortality risk over time) of one variable (*e.g.*, MI) varying across the strata of a second variable (comorbidity burden). In contrast, an interaction is defined in terms of the combined (including synergistic) effects of comorbidity and an MI on mortality.[57] A biological interaction differs from a statistical interaction. A statistical interaction is defined as the interaction coefficients in a statistical model; in general, a statistical interaction does not correspond to an

interaction in the sense of sufficient cause.[58] A biological interaction (or synergism) is quantified on the additive scale (risk difference), as opposed to the multiplicative scale. Using the additive scale can provide insights into the impact on public health.[59,60] No previous study has examined the biological interaction effect of cardiac and non-cardiac comorbidities on cardiovascular disease mortality.[61]

1.3.5. Prediction of cardiovascular mortality using comorbidity indices

A comorbidity index characterizes the combined burden of prespecified diseases or conditions as a single measure on a scale. In addition to the etiological (deterministic) models needed to address the questions listed in the previous sections, comorbidity prediction models (indices) are widely used to predict disease outcome, based on the comorbidity burden, regardless of causal inference (hence, probabilistic). In addition to outcome prediction, comorbidity indices are used to quantify comorbidity burden as a covariable in other analyses, *e.g.*, risk-adjustment and stratification.[62]

There is no universally agreed upon measure or list of diseases to define comorbidity; therefore, numerous indices have been developed. More than 35 comorbidity indices have been used to measure comorbidity in community and population studies.[62] In addition, a variety of comorbidity indices have been developed for patients admitted to hospital or with specific diseases. Accordingly, indices have been developed specifically for patients with cardiac diseases[63-66] and for mixed populations, with subsequent testing in patients with cardiac diseases.[67-70] Commonly known comorbidity indices include the Kaplan-Feinstein Index, the Cumulative Illness Rating Scale, the Index of Co-existing Disease, the Elixhauser Comorbidity Index (ECI), and the most widely used index, the Charlson Comorbidity Index (CCI).[41]

The CCI was initially developed with a small cohort of 559 patients admitted to a medical center in the New York Hospital during a 1-month period, in 1984.[67] The CCI assigns one to six points to 19 comorbid diseases, depending on the strength of their relationship to one-year mortality. The CCI has been validated as a prognostic marker of comorbidity for several cardiovascular index diseases (*e.g.*, acute[61,71,72] and chronic ischemic heart disease,[61,73] heart failure,[61] aortic stenosis,[74,75] and ischemic stroke[61,76]), but it has several limitations. Since 1984, the impact of comorbidities on survival has changed with improvements in prophylaxis and with treatments that prolong survival.[1,57] Additionally, the CCI does not include psychiatric diseases, which can confer substantial morbidity, even in patients with a physical index disease.[45,75] Moreover, the CCI evaluates disease severity only for a few diseases (diabetes, liver disease, and cancer) and to a very limited extent.[42] In addition, it does not consider the prognostic impact of disease duration; it is likely, that the prognostic impact increases with duration, for some diseases (*e.g.*, diabetes), and decreases with duration for others (*e.g.*, a successfully treated ulcer disease or cancer).[42] In summary, the CCI does not seem ideal for assessing the predictive ability of comorbidity burden in contemporary patients with cardiac diseases.

1.4. Polypharmacy

The increasing use of multiple medications has paralleled the rise in multimorbidity prevalence. The definitions of polypharmacy are many,[77] but they often include concomitant prescriptions of ≥5 drugs.[78] Polypharmacy is

increasingly common, due to the greater availability of effective drugs, guideline-recommended treatments for many chronic conditions, and changes in patient expectations.[78] For example, the proportion of adults with polypharmacy in Scotland doubled to 21% between 1995 and 2010.[78] Standard treatment regimens for chronic cardiovascular diseases, such as ischemic heart disease, arterial hypertension, dyslipidemia and congestive heart failure, fulfil the criteria for polypharmacy alone; hence, polypharmacy has become the rule, rather than the exception, in patients with cardiovascular diseases. In addition to cardiac comedications, noncardiac comedications can increase the number of comedications and often result in excessive polypharmacy, defined as the concomitant prescription of ≥10 drugs.

Polypharmacy comes at the risk of adverse drug events (ADEs), drug-drug interactions, drug-disease interactions, and inappropriate dosing.[77] Approximately 6–12% of all emergency hospital admissions are attributable to ADEs,[79] and at least half of these are judged preventable.[80] An estimated 3% of deaths in the general population are attributed to ADEs.[81] Thus, ADEs represent a major healthcare burden, by causing significant morbidity and increasing mortality risk and healthcare costs.[79] The main risk factors or predictors of ADE-related admissions are advanced age, comorbidity, and polypharmacy.[78,79] Older patients are particularly susceptible to ADEs, due to age-related cognitive impairment, functional impairment, and changes in pharmacokinetics and pharmacodynamics.[79]

Three out of the eight most common groups of drugs that cause ADE-related hospital admissions in older individuals are non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), antithrombotic drugs (anticoagulant and antiplatelet drugs), and other cardiovascular drugs, including diuretics, cardiac glycosides, angiotensin-converting enzyme inhibitors (ACEIs), beta blockers, antiarrhythmic drugs, and calcium channel blockers.[79] Moreover, among all preventable ADE-related hospital admissions, the following four drug classes account for more than 50%: antiplatelet drugs (16%), diuretics (16%), NSAIDs (11%), and anticoagulant drugs (8%). The most common underlying causes of ADEs are related to incorrect prescribing (median 31%), non-adherence (33%), and/or a lack of monitoring (22%).[80] Trials often fail to account for co-interventions with therapies outside the study protocols; consequently, the reliability of trial data is often limited for guiding clinical decision-making related to polypharmacy. Therefore, phase 4 studies and post-marketing surveillance are essential for detecting ADEs and drug-drug interactions.

1.5. Cardiac comedication

In this section, we will review ADEs and drug-drug interactions related to certain cardiac comedications. First, we will examine adherence to guidelines for monitoring renal function after renin-angiotensin system (RAS) blockade by use of ACEIs or angiotensin-II receptor blockers. Then, we will examine the potential cardiorenal risks associated with renal dysfunction after such RAS blockade. Third, we will quantify potential drug-drug interactions between clopidogrel and proton pump inhibitors (PPIs).

1.5.1. Adverse drug events

1.5.1.1. Adherence to monitoring and discontinuation rules after RAS blockade

A blockade of the RAS with ACEI/ARBs is a mainstay in treating hypertension,[82] heart failure,[83] diabetic microalbuminuria or proteinuria renal diseases,[84] and in tertiary prevention of MI.[85] However, some patients experience a sudden decline in kidney function when they initiate these drugs, presumably due to antagonism of the efferent arteriolar constriction mediated by angiotensin II or impaired kidney potassium excretion.[86,87]

The potential impact of a RAS blockade on kidney function should be evaluated by periodically comparing pre- and post-initiation levels of serum creatinine and potassium.[88] Guidelines recommend treatment discontinuation, when the creatinine level exceeds 30% above the patient's baseline value, or when hyperkalemia develops.[89] However, it remains unclear whether these recommendations are routinely followed in clinical practice.[90]

A few studies have compared baseline and follow-up creatinine/potassium monitoring results,[90] but there is a lack of large studies that use contemporary data with reference to current guidelines. Consequently, it remains unknown whether the individual risk of renal impairment influences the likelihood that an individual will be monitored.[90] Therefore, it is important to examine adherence to creatinine and potassium monitoring and treatment discontinuation guidelines after the initiation of ACEI/ARB and to determine whether patients are monitored according to their individual risk profile.

1.5.1.2. Cardiorenal risks associated with creatinine elevation after RAS blockade

Clinical trials have indicated that ACEI/ARB-induced renal impairment is uncommon.[89,91] However, in routine clinical practice, patients are, on average, older, and they have more comorbidities than the participants eligible for trials.[92] Consequently, the absolute risk of experiencing a ≥30% increase in creatinine is not uncommon in the community setting.[6] Although a 30% creatinine increase after ACEI/ARB initiation raises concern about the long-term risk-benefit balance, smaller increases (<30%) do not prompt a consideration of treatment discontinuation, according to current guidelines. The rationale for the 30% threshold in the context of adverse clinical outcomes is unclear,[89] because little evidence is available on the actual risks associated with creatinine increases <30%. Due to the high prevalence of ACEI/ARB use in general practice, the identification of previously unrecognized ADEs would have major clinical and public health implications.

1.5.2. Drug-drug interactions

The thienopyridine, clopidogrel, is a mainstay in tertiary prevention of vascular events in patients with ischemic heart disease or ischemic stroke.[93] Clopidogrel is a pro-drug that is metabolized by hepatic cytochrome P450 (CYP) enzymes (primarily the 2C19 and 3A4 isoforms) to an active thiol metabolite. This thiol irreversibly inhibits the binding of adenosine-5-diphosphate to the platelet P2Y12-receptor. Thus, concomitant drugs that are metabolized by CYP2C19 and CYP3A4 might interact with clopidogrel metabolism.[94] This interaction might be clinically important, because patients with high residual adenosine-5-diphosphate-inducible platelet reactivity are at increased risk of major adverse cardiovascular events (MACE) after a percutaneous coronary intervention (PCI).[95] It was shown in *ex vivo* experiments that the clopidogrel

antiplatelet effect was diminished with concomitant use of CYP2C19-metabolizing PPIs,[96-99] CYP3A4-metabolizing lipophilic statins,[100-103] and CYP3A4-metabolizing calcium channel blockers.[104-106] However, it is debated whether those finding would translate into adverse clinical outcomes *in vivo*.[94,107]

These potential interactions are important to public health authorities, due to the large number of PCIs performed annually, the increasing use of coronary stents, with the associated need for long-term antiplatelet treatment,[93] and the possibility of preventing adverse interactions by avoiding co-administration of interacting drugs.[94] No previous studies have examined whether the interaction between clopidogrel and PPI in patients undergoing a PCI might affect the clinical outcome based on a time-varying drug assessment that could accommodate intermittent lapses in therapy.[108]

1.6. Non-cardiac comedication

1.6.1. NSAIDs

Cardiovascular-musculoskeletal multimorbidity is the most prevalent combination of morbidities, and NSAIDs are the drugs most frequently used to treat musculoskeletal disease.[109] Therefore, the cardiovascular risks associated with NSAIDs are of particular importance when treating patients with or at risk of cardiovascular disease. Thus, NSAIDs serve as an example of non-cardiac comedication.

NSAIDs are indicated for fever, inflammation, and pain syndromes.[110] Symptoms of inflammation include painful, stiff, and/or swollen joints. Pain treatment may be indicated, when the effect of non-pharmacological and other analgesic treatments are insufficient (*e.g.*, for cancer-related, lower back, or postoperative pain), or when concurrent inhibition of prostaglandin synthesis is beneficial (*e.g.*, dysmenorrhea or ureteral stones).[110]

NSAIDs are available as prescription and over-the-counter (OTC) drugs.[111] In Denmark, the mean prevalence of prescribed NSAID use has been 15% for the last 20 years. This mean percentage reflects an increase from 14% in 1999, which rose to 17% in 2005, and then steadily declined to 12% in 2019.[111] However, the prevalence is higher among women, and it increases with age.[111] Ibuprofen, naproxen, and diclofenac are the NSAIDs most frequently used among younger individuals. Etodolac is used almost exclusively among individuals over 40 years.[111] The overall prevalence of NSAID use is expected to increase, due to the aging population and the associated increasing prevalence of painful, degenerative, and inflammatory conditions.

Traditional NSAIDs were developed throughout the 1960s, as a safer alternative to aspirin (acetylsalicylic acid), which is associated with gastrointestinal erosions and ulcers.[110] However, traditional NSAIDs also exhibited gastrointestinal toxicities, which could cause dyspepsia, ulcers, bleeding, and perforation.[112] Silent ulceration is a particular concern. Based on the rationale that selective cyclooxygenase (COX)-2 isoenzyme inhibition would provide anti-inflammatory, analgesic, and antipyretic activity, without increasing the risk of adverse gastrointestinal events, newer COX-2 inhibitors (coxibs) were developed.

Coxibs were introduced into clinical practice in 1999, but shortly after that, they became associated with cardiovascular toxicity. Rofecoxib was withdrawn in 2004, and valdecoxib was withdrawn in 2005.[113] The pharmacodynamic effects of NSAIDs have been described in detail previously.[114] In brief, selective COX-2

inhibition is thought to shift the prothrombotic/antithrombotic balance on endothelial surfaces towards thrombosis by inhibiting the COX-2–derived generation of vascular prostacyclin without affecting the COX-1–mediated generation of thromboxane A_2 (Figure 2).[114] Other factors that contribute to the cardiovascular hazard of selective COX-2 inhibition include acceleration of atherogenesis, blood pressure elevation, risk or exacerbation of heart failure, and proarrhythmic effects (Figure 2).

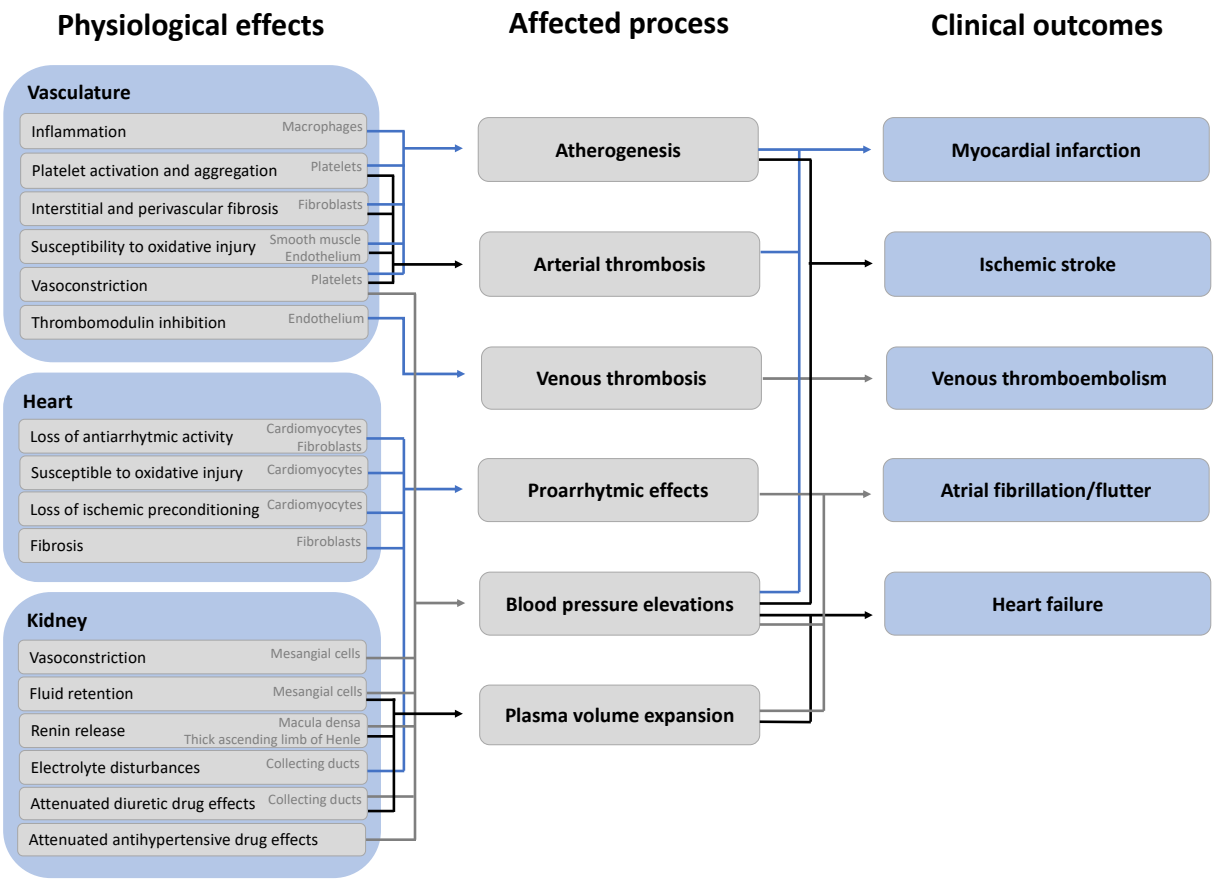


Figure 2 | Biological rationale for the cardiovascular risks associated with selective cyclooxygenase (COX)-2 inhibition

1.6.2. Diclofenac

1.6.2.1. Cardiovascular risks

The COX selectivity of NSAIDs can be represented as a continuum (Figure 3A).[115] It has become apparent that a subset of the traditional NSAIDs also has a COX-2 preference (Figure 3B).[116] These so-called older COX-2 inhibitors include diclofenac, meloxicam, and etodolac.[116] The COX-2 selectivity of diclofenac is similar to that of some coxibs (*e.g.*, celecoxib, Figure 3A).[116] However, the cardiovascular risks associated with diclofenac have never been compared head-to-head with other traditional NSAIDs in RCTs.[117] Current concerns about these risks[118] have made it unethical to conduct such a RCT. The European Medicines Agency (EMA) recently called for a further safety assessment of diclofenac.[119] Underscoring its clinical and public health importance, diclofenac is the most frequently used NSAID in low-, middle-, and high-income countries,

and it is available OTC in most countries.[120] A novel emulated trial design has provided a unique opportunity to study the cardiovascular risks associated with diclofenac use.[121] In this design, the reference group can be expanded from non-users to include active comparators. It is particularly important clinically to compare the risks of diclofenac with those of non-selective NSAIDs (ibuprofen and naproxen) and non-NAID alternatives (acetaminophen/paracetamol) to establish the best risk-benefit balance, when analgesia is needed.

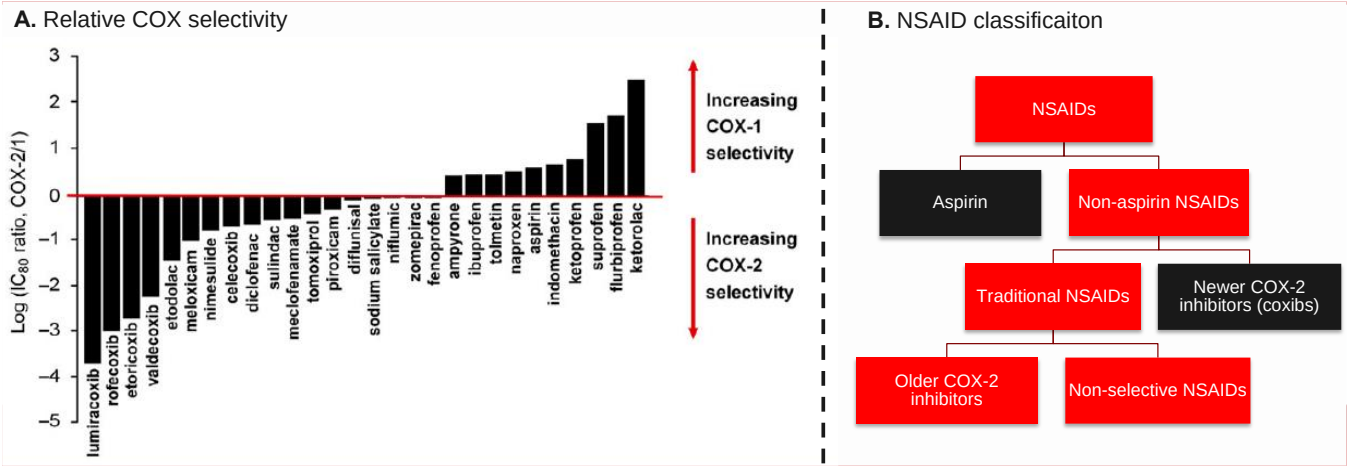


Figure 3 | NSAID selectivity for COX-1 or COX-2 and NSAID classification. (A) The continuum of relative COX selectivity for different NSAIDs. IC_{80}, concentration required to inhibit COX-1 and COX-2 activity by 80%. (B) The proposed classification of NSAIDs; those selected for focus in this dissertation are highlighted in red. Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug. Modified from Schmidt M *et al.* Eur Heart J 2016,[118] Schmidt M. Dan Med J 2015,[14] and Warner TD *et al.* FASEB J 2004.[115]

1.6.2.2. Trends and predictors of contraindicated NSAID use

Consistent with their previous initiatives (Figure 4), EMA has recently called for a further safety assessment of diclofenac.[119] First, in 2006, EMA assessed the cardiovascular safety of traditional NSAIDs. At that time, they suggested that the magnitude of the cardiovascular risk associated with diclofenac could be the same as that associated with coxibs.[122] In 2013, EMA's Pharmacovigilance Risk Assessment Committee concluded that the increased cardiovascular risk associated with diclofenac was comparable to that of coxibs, and that the precautions in place for coxibs should be applied to diclofenac.[123] Therefore, EMA subsequently implemented risk minimization measures, which included (1) a contraindication in patients with congestive heart failure, ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease; (2) a caution for patients with certain cardiovascular risk factors (*e.g.*, hypertension, hyperlipidemia, diabetes mellitus, and smoking); and (3) a recommendation for using diclofenac at the lowest dose and the shortest duration possible.[124] In 2016, a position paper by the European Society of Cardiology stated that diclofenac should be avoided altogether.[118] It recommended that, when NSAID use could not be avoided, low-dose ibuprofen (≤1200 mg/day) or naproxen (≤500 mg/day) were the least harmful alternatives for patients with or at high risk of cardiovascular disease.[118] The overall use of diclofenac has decreased by 75% since 2008 in Denmark, where national warnings were first issued from the Danish Medicines Agency and the Danish Society for Cardiology.[111] However, it remains unclear whether the clinical and health authority recommendations for cautious NSAID use have led to similar trends in patients with established cardiovascular disease.

1.6.2.3. Prescriber responsibility for contraindicated use

The physician issuing a prescription is accountable for the prescription and must ensure that good clinical practice is followed. As described above, incorrect prescribing is one of the most common underlying causes of ADE.[80] However, little is known about which clinical specialty dispenses the majority of NSAID prescriptions. General practitioners are considered to play an important role, but the lack of data on prescriber responsibility has limited insight into the proportions of NSAIDs prescribed by general practitioners and other healthcare providers, including the hospital sector and private practice specialists.

Currently, in Denmark, diclofenac is available only by prescription. Therefore, the key to facilitating more appropriate NSAID use is to assess prescriber responsibility. Only one previous study has investigated prescriber responsibility. They found that, among all diclofenac prescriptions in Germany, 61% were issued by general practitioners, 22% by orthopedists, 6.8% by surgeons, and 9.1% by others.[125] However, no study has examined the degree to which different healthcare providers are responsible for prescribing NSAIDs to patients with cardiovascular contraindications.

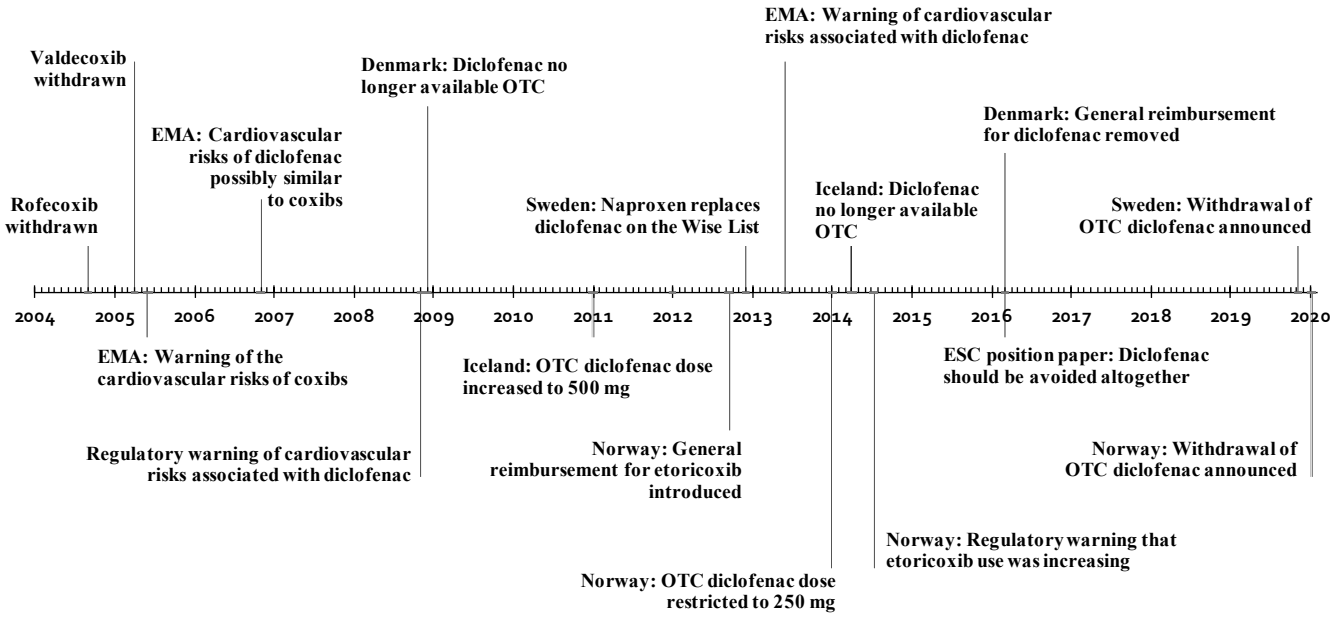


Figure 4 | Timeline of important regulatory actions taken regarding diclofenac and coxibs in the Nordic countries. Regulatory actions prompted by studies described in this dissertation are marked in red. Abbreviations: EMA, European Medicines Agency; ESC, European Society of Cardiology; OTC, over the counter. Modified from Kristensen KB *et al*. Pharmacotherapy 2019[126]

1.6.3. Novel cardiovascular risks

Previous studies have provided a timeline of the cardiovascular risks established for coxibs and traditional NSAIDs.[118] Many side-effects, including non-fatal MI, non-fatal ischemic stroke, hypertension, heart failure, and cardiac death are considered to be caused by coxibs, diclofenac, and high-dose ibuprofen (compared to non-use).[117,127] However, the nature of the associations with other cardiovascular diseases remains unclear. As shown in Figure 2, biological links have been proposed between NSAIDs and venous thrombosis and arrhythmia. Moreover, the prognostic effect of NSAIDs on stroke mortality remains unknown. The following

three sections of this dissertation elaborate on these unexplored outcomes. A literature overview is provided in the Supplementary material (Table S1).[15]

1.6.3.1. Atrial fibrillation/flutter

Atrial fibrillation/flutter is the most common cardiac rhythm disorder observed in clinical practice.[128] The overall incidence rate (per 1000 person-years) is 4, which reflects a range from <0.5, in individuals under 40 years of age, to >25, in individuals above 80 years of age.[128] The corresponding prevalence is 0.1% in individuals under 40 years of age and >10% in individuals above 80 years of age.[128] Of clinical and public health importance, atrial fibrillation/flutter is associated with a reduced quality of life[129] and elevated risks of heart failure,[130] systemic embolisms (particularly ischemic stroke),[131] and death.[132]

NSAID use may increase the risk of atrial fibrillation/flutter through several cardiovascular- and renal-related effects (Figure 2), as follows:[133] (1) Direct proarrhythmic effects may increase the susceptibility to atrial fibrillation/flutter.[114] Indeed, COX-2-derived prostacyclin acts as an endogenous antiarrhythmic agent through its inhibition of epicardial sympathetic nerve activity.[134-136] Experimental animal studies have shown that selective deletion of cardiomyocyte COX-2 expression in mice induced interstitial and perivascular fibrosis associated with an enhanced susceptibility to arrythmias.[137] Moreover, coxibs, independent of their COX-2 inhibition, might inhibit delayed-rectifier potassium channels, and thereby, induce arrhythmia.[138] (2) Adverse renal effects, such as fluid retention and expansion of the plasma volume, may increase left atrial pressure/stretch.[139] Even short-term NSAID use (<14 days) has been shown to increase left ventricular end-diastolic and end-systolic dimensions on echocardiography.[140] In addition, due to reduced potassium excretion from the distal nephron, NSAID use might also cause proarrhythmic fluctuations in potassium levels.[139] (3) Heart failure and elevated blood pressure might occur, due to plasma volume expansion, increased peripheral resistance, and the attenuation of diuretic and antihypertensive drug effects[141,142]

The role of COX inhibition in atrial fibrillation/flutter occurrence has only been investigated sparsely (Table S1).[143,144] A meta-analysis of 114 clinical trials suggested that the use of rofecoxib was associated with a 3-fold increased risk of any type of cardiac arrhythmia (relative risk=2.90, 95% CI: 1.07–7.88),[144] but that analysis included relatively few events (n=286), and the precision was limited; consequently, atrial fibrillation and atrial flutter could not be examined separately.[144]

1.6.3.2. Venous thromboembolism

Venous thromboembolism (VTE) is a common disease that affects 1–3 per 1000 individuals in Western populations annually; thus, VTE represents the third leading vascular disease, after MI and stroke.[145] However, the annual incidence rate increases exponentially with age for both men and women. Thus, the annual VTE incidence varies from <0.5 per 1000 persons among those under 40 years of age to about 10 per 1000 persons among those aged 80 years or more.[146,147] The classic risk factors for VTE include immobilization, recent surgery, trauma, cancer, pregnancy, and the use of oral contraceptives or postmenopausal hormonal replacement therapy.[148] Based on the presence or absence of these classic risk factors, VTE can arbitrarily be categorized as provoked or unprovoked, respectively.[148] VTE is associated with increased morbidity and

mortality.[20,148] It occurs predominantly in the deep vessels of the lower limbs (*i.e.*, deep vein thrombosis), and it increases the risk of pulmonary embolism and post-thrombotic syndrome.[149] Among patients with pulmonary embolism, 2–4% develop chronic thromboembolic pulmonary hypertension with disabling dyspnea, both at rest and upon exertion.[150] The recurrence rate after stopping anticoagulant drug therapy is 5% per year, overall, and it is higher for unprovoked (8%) than for provoked (3%) VTE.[151] Therefore, recurrent VTE is a major clinical problem. Recent data show that patients with VTE are at increased risk of death within the first 30 days after the diagnosis (absolute risks are 3% for deep vein thrombosis and 31% for pulmonary embolism) but also during the following 30 years, with VTE as an important cause of death.[20]

Traditionally, atherosclerotic and venous thrombosis have been considered two separate disease entities, because arterial thrombi mainly comprise platelets, and venous thrombi mainly comprise red blood cells and fibrin.[152] However, platelets also play a role in venous thrombosis. Indeed, the biochemical interaction between platelets and the coagulation pathway (platelet-fibrin units) is essential for thrombus growth.[153,154] Moreover, each of these disorders are associated with an increased risk of the other.[155,156] Accordingly, treatments previously reserved for arterial thrombosis might also be effective for venous thrombosis.[157,158]

COX-2 is expressed in greater amounts in venous smooth muscle cells than in arterial cells.[159] Furthermore, prostaglandins stimulate the expression of thrombomodulin, a strong inhibitor of blood coagulation in human smooth muscle cells.[160] Therefore, the selective suppression of COX-2-derived prostacyclin may induce a prothrombotic state[160] and also promote venous thrombosis (Figure 2).[114,161]

The association between NSAID use and VTE has received little attention (Table S1). The VIGOR trial initially failed to report all cardiovascular events,[162] but later re-analyses revealed that the rate of VTE had been five-fold higher in the rofecoxib group than in the naproxen group. That finding indicated that COX-2 was strongly associated with the risk of VTE.[114,163,164] However, the precision of the risk estimates was low for naproxen *vs.* rofecoxib (risk ratio=0.17, 95% CI: 0.00–1.37), because the trial was not powered to detect differences in individual thromboembolic events.[114,163,164] Subsequent observational studies showed conflicting results on whether[165,166] or not[167,168] traditional NSAIDs were associated with VTE.

1.6.3.3. Stroke mortality

Stroke is a leading cause of death and disability worldwide.[169] The incidence rate of hospitalized stroke in Denmark is around 3 per 1000 person-years,[170] which reflects a range (in 1000 person-years) of 1–2 in individuals under 45 years of age to 13–15 in individuals above 75 years of age.[169,170] Thus, more than two-thirds of all strokes occur in individuals 65 years or older,[171] and this group has the highest prevalence of musculoskeletal comorbidity and NSAID use.[3,111]

Numerous studies have examined the association between NSAID use and stroke risk.[113,172,173] Although the evidence is inconsistent,[117,172] the use of different coxibs or diclofenac confers an increase in cerebrovascular risks.[113,172,173] Thus, the rate of cerebrovascular events increased more than two-fold over controls, in both the APPROVe trial (hazard ratio [HR]=2.32, 95% CI: 0.89–6.74) and in a meta-analysis of ibuprofen (HR=3.4, 95% CI: 1.00–11.60), diclofenac (HR=2.86, 95% CI: 1.09–8.36), etoricoxib (HR=2.67, 95% CI: 0.82–8.72), and lumiracoxib (HR=2.81, 95% CI: 1.05–7.48).

It remains unknown whether NSAID use also affects stroke prognosis. Given the reported thromboembolic properties of COX-2 inhibitors,[116,172,173] their use may lead to larger, more fatal thromboembolic occlusions compared to non-use. The effect of NSAID use on stroke mortality might, in part, also be mediated by stroke recurrence,[113,172,173] MI,[113] or atrial fibrillation/flutter, which increase the subsequent risk of heart failure and ischemic stroke.[11] COX-2 inhibition might also impair the pathophysiological response to a stroke by inhibiting the neuroprotective effect of prostaglandin E_2.[174] In fact, any anti-ischemic preconditioning response to a prior sublethal ischemic insult could be counteracted by COX-2 inhibition.[175-177]

Despite experimental evidence that supports a role for COX enzymes in cerebral ischemia,[174,178-180] only one study has examined the association between preadmission NSAID use and stroke outcome in a clinical setting (Table S1).[181] That study showed that NSAID use was associated with an increased risk of stroke with mild functional outcome.[181] No study has examined the effect of preadmission NSAID use on stroke mortality.

2. Aims

The overall aim of the dissertation studies was to improve the understanding of how multimorbidity influences the risk, prognosis, and prediction of cardiovascular disease (Figure 1). This aim is detailed in the following three pillars of the dissertation:

- *Comorbidity*: To examine the prognostic impact of comorbidity on major cardiovascular diseases, including MI, heart failure, and stroke. Specifically, we examined: (1) the trends in prevalence of comorbidity among individuals with a first-time cardiovascular disease; (2) the association between comorbidity and cardiovascular mortality; (3) the effect modification of comorbidity on cardiovascular mortality trends; (4) the interaction between comorbidity and cardiovascular mortality; and (5) the ability of comorbidity indices to predict cardiovascular mortality.
- *Cardiac comedication:* To examine ADEs and drug-drug interactions. Specifically, we examined: (1) adherence to guidelines for creatinine and potassium monitoring and treatment discontinuation after a RAS blockade, and the cardiorenal risks associated with increases in creatinine; and (2) drug-drug interactions between clopidogrel and PPIs in patients that depend on appropriate post-PCI antiplatelet therapy after coronary stent implantation.
- *Non-cardiac comedication*: To examine various cardiovascular risks associated with NSAID use. Specifically, we examined: (1) the cardiovascular risks associated with diclofenac initiation; (2) trends, predictors, and prescriber responsibility for NSAID use in patients with cardiac diseases; and (3) associations between NSAID use and atrial fibrillation/flutter, VTE, and stroke mortality.

Table 1 | Summary of dissertation studies, grouped according to comorbidity (red), cardiac comedication (grey), and non-cardiac comedication (blue)

Comorbidity	Comorbidity-MI mortality (I)	Comorbidity-HF mortality (II)	Comorbidity-stroke mortality (III)	Comorbidity-MI interaction (IV)	Comorbidity Index (V)
Aim*	To examine 25-year trends in MI hospitalization and mortality rates, and the prognostic impact of sex and comorbidity	To examine 30-year trends in HF hospitalization and mortality rates, and the prognostic impact of comorbidity	To examine 18-year trends in stroke mortality and the prognostic impact of comorbidity	To examine whether comorbidity and MI interact to reduce survival beyond their independent effects	To develop and validate the DANCAMI for adjustment of comorbidity burden in studies of MI prognosis
Design	Population-based cohort study	Population-based cohort study	Population-based cohort study	Population-based matched cohort study	Prediction study (2 cohort studies)
Data source	CRS, DNPR, RCD	CRS, DNPR	CRS, DNPR	CRS, DNPR, NPR	DK: CRS, DNPR, AUPD, LABKA; NZ: NMDS, MORT, NPC
Study region	Nationwide	Nationwide	Nationwide	Nationwide	DK (Northern/Central); NZ (nationwide)
Study period	1984–2008	1983–2012	1994–2011	1995–2016	2000–2013 (DK) and 2007–2016 (NZ)
Study population	Patients ≥15 years old with first-time MI (based on In; A+B), n=234,331	Patients ≥15 years old with first-time HF (based on In; A+B), n=317,161	Patients ≥15 years old with first-time stroke (based on In; A+B), n=219,354	Patients >18 years old with first-time MI (based on In; A+B) (n=179,515) *vs.* matched comparison cohort members (n=880,347)	Patients ≥15 years old with first-time MI (based on In; A+B) in DK (development, n=36,685) or NZ (validation, n=75,069)
Follow-up	1 year	5 years	5 years	5 years	1 year
Exposure	Calendar time; CCI scores 0, 1, 2, ≥3 (based on In+Out; A+B; Hx5)	Calendar Time; CCI scores 0, 1, 2, ≥3 (based on In+Out; A+B; Hx5)	Calendar Time; CCI scores 0, 1, 2, ≥3 (based on In+Out; A+B; Hx15)	CCI scores 0, 1, 2–3 ≥4 and cardiac/noncardiac comorbidities (based on In+Out; A+B; Hx10)	Continuous/categorical DANCAMI, rDANC-AMI, CCI, ECI (based on In+Out; A+B; Hx5)
Outcome	CCI prevalence; 30-day and 31–365-day mortality	CCI prevalence; 1- and 5-year mortality	CCI prevalence; 30-day, 1- and 5-year mortality	30-day, 31–365-day, and >1–5-year mortality	1-year all-cause mortality
Covariables	Age, sex, CCI categories/diseases	Age, sex, CCI categories/diseases	Age, sex, CCI categories/diseases	Age, sex, CCI categories/diseases	Potential predictors: Age, sex, and 41 comorbidities (based on In+Out; A+B; Hx5)
Statistics	Kaplan-Meier, Cox, bootstrapping, three knot cubic splines	Kaplan-Meier, Cox	Kaplan-Meier, Cox	Stratified Cox, absolute interaction effect (contrast=difference in rate differences), Cochran-Armitage test for trends (dose-response)	Cox, fractional polynomials, Kaplan-Meier, performance (R^2, C-statistics, IDI, NRI)
Confounder control	Age standardization, stratification, regression-model adjustments	Age standardization, stratification, restriction, regression model adjustments	Age standardization, stratification, restriction, regression model adjustments	Age standardization, matching (on age, sex, and individual CCI scores), stratification, restriction, regression model adjustments	Not applicable (prediction model)
Additional analyses	(1) Stratification by age, sex, CCI, and calendar period; (2) Comparison of the proportions of MI recorded as cause of death, but not as a hospital diagnosis, over time	(1) Stratification by age, sex, calendar period, acute/nonacute, A/B, pulmonary edema, and high-risk groups; (2) Including outpatient HF diagnoses (since 1995); (3) Temporal use of TTE, ICD, LVAD, and heart transplantation	(1) Stratification by age, sex, calendar period, and stroke types (ischemic *vs.* hemorrhagic); (2) Restriction to period after 2003 (radiology data available) and CT/MRI confirmed cases	(1) Stratification by age, sex, calendar period, baseline CCI score/category/comorbidities, MI type, and compliance with standard post-MI medical therapy (among 1-year survivors); (2) Sensitivity to comorbidity look-back period (1 *vs.* 5 years)	(1) Stratification by age, sex, ethnicity; (2) Restriction to MI survivors; (3) Sensitivity to HR cut-off (1.10 *vs.* 1.20); use of exact β; HR *vs.* β for score components; adding novel variables to CCI (4) split-sample internal validation (2000–9 *vs.* 2010–13)
Conclusions*	50% decline in MI incidence and mortality during 1984–2008. Comorbidity burden did not modify trends, but strongly affected prognosis; sex did not affect prognosis	HF rates declined since 2000. 1- and 5-year mortality declined >40% over 30 years. Comorbidity burden did not modify trends, but strongly affected prognosis	Short- and long-term stroke mortality improved considerably during 1994-2011. Comorbidity burden did not modify trends, but strongly affected prognosis	Cardiac and non-cardiac comorbidity interacted in a dose-dependent manner with MI to increase short- and long-term mortality	DANCAMI assessed comorbidity burden of MI patients, outperformed existing indices, and generalized to patients outside Denmark

Cardiac comedication	Adverse side effects (RAS blockade)		Drug-drug interaction
	Renal function monitoring (VI)	**Creatinine elevation-CV risks (VII)**	**Clopidogrel-PPI interaction (VIII)**
Aim*	To examine Cr/K monitoring and discontinuation after ACEI/ARB initiation	To examine long-term cardiorenal risks associated with increased Cr after ACEI/ARB initiation	To examine the effect of the clopidogrel - PPI interaction on MACE after PCI
Design	General practice-based cohort study	General practice-based cohort study	Population-based cohort study
Data source	CPRD, HES, IMD	CPRD, HES, IMD	CRS, DNPR, WDHR, RCD
Study region	UK primary care (7% coverage)	UK primary care (7% coverage)	Western Denmark (55% coverage)
Study period	2004–2014	1997–2014	2000–2005
Study population	Adults initiating ACEI/ARB (n=223,814)	Adults initiating ACEI/ARB without previous ESRD (n=122,363)	Patients with coronary stent implantation (n=13,001)
Follow-up	2 months	Through 31 March 2014	12 months
Exposure	Renal function monitoring	(1) Cr increase ≥30% *vs.* <30%; (2) 10% incremental Cr increase	Time-varying clopidogrel and/or PPI use
Outcome	(1) Cr/K monitoring; (2) Increases in Cr ≥30%/K>6 mmol/L; (3) discontinuation	ESRD, MI, HF, and death	MACE (primary); MI, IS, stent thrombosis, TLR, or cardiac death (secondary); UGIB
Covariables	Age, sex, calendar period, SES, lifestyle (smoking, BMI, alcohol), CKD, DM, HF, MI, HTN, PAD, arrhythmia, eGFR, CKD stage	Age, sex, calendar period, SES, lifestyle (smoking, BMI, alcohol), CKD, DM, HF, MI, HTN, PAD, arrhythmia, sBP, dBP, HTN drugs, NSAIDs	Age, sex; DM, HTN, obesity (In+Out; A+B; Hx1977); time-varying use of ASA, CCB, and lipophilic statins
Statistics	Proportions, logistic regression	Kaplan-Meier, Poisson regression, fractional polynomials, test for linear trend	Cox, relative interaction effect (ratio of stratum-specific HRs), Wald chi^2 test
Confounder control	Regression-model adjustments	Stratification, restriction, regression-model adjustments	Stratification, regression model adjustments, bias analysis (unmeasured confounder examined in a follow-up paper)
Additional analyses	(1) Sensitivity to extending first FU monitoring to 3 weeks; restriction to 2009–14; exclusion if hospital contact within 1 month; re-defining continuation as drug use >90 days; (2) subgroups (HF, MI, HTN, CKD, PAD, DM)	(1) Restriction to 2004–14, patients without DM/CKD stage 4, continuing users, or only DM; (2) Patients excluded if DM/CKD stage 4 or K>6 mmol/L; (3) Estimating reduction in median sBP/dBP; (4) Omit complete monitoring restriction	(1) PPI subtypes (esomeprazole, lansoprazole, omeprazole, pantoprazole); (2) Stratification by pre-PCI PPI use, age, sex, PCI indication, DM
Conclusions*	Among ACEI/ARB initiators, only 10% receive guideline-recommended Cr monitoring, and 20% follow discontinuation criteria	Cr increases after ACEI/ARB initiation were associated with adverse cardiorenal outcomes in a dose-reponse manner	As a class, PPIs did not modify the protective effect of clopidogrel, but were associated with MACE, particularly among previous PPI users

Non-cardiac comedication	Diclofenac		Novel cardiovascular risks		
	Diclofenac-CV risks (IX)	**Contraindicated NSAID use (X)**	**NSAID-AF risk (XI)**	**NSAID-VTE risk (XII)**	**NSAID-Stroke mortality (XIII)**
Aim*	To examine CV risks of diclofenac *vs.* other traditional NSAIDs, paracetamol, and no NSAID use	To examine trends, predictors, and prescriber responsibility for NSAID use in patients with cardiac disease	To examine whether NSAID use is associated with risk of AF	To examine whether NSAID use is associated with risk of VTE	To examine whether NSAID use is associated with stroke mortality
Design	Emulated trial (series of cohort studies)	Drug utilization study (cohort study)	Population-based case-control study	Population-based case-control study	Population-based cohort study
Data source	CRS, DNPR, NPR, RCD, NHISR	CRS, DNPR, NPR	CRS, DNPR, AUPD	CRS, DNPR, AUPD	CRS, DNPR, DNDRP
Study region	Nationwide	Nationwide	Northern DK	Northern DK	Nationwide
Study period	Each month during 1996–2016 (=252)	1996–2017	1999–2008 (≥1 yr prescription history)	1999–2006 (≥1 yr prescription history)	2004–2012 (≥6 month prescription history)
Study population	Adults + no NSAID use within 1 year + no exclusion criteria (CVD, CKD, liver/ulcer disease, C, SCZ, dementia (In+Out; A+B; Hx5/Px1)	First-time CVD: SAP, MI, IS (based on In); AF, HF, VTE, VHD, IE (based on In+Out)	AF cases (n=32,602); Age/sex-matched controls (n=325,918)	VTE cases (n=8368); Age/sex-matched controls (n=82,218)	First-time stroke (n=100,043)
Follow-up	30 days	5 years	N/A	N/A	30 days
Exposure	Diclofenac *vs*. (1) ibuprofen/naproxen; (2) paracetamol; (3) no use	Time (calendar year)	NSAIDs (current, new, long-term, former, no use)	NSAIDs (current, new, long-term, former, no use)	Pre-admission NSAIDs (current, new, long-term, former, no use)
Outcome	MACE (primary); AF, IS, HF, MI, cardiac death (secondary); UGIB	1- and 5-year prevalence, predictors, and prescribers of NSAIDs	AF	VTE: overall, DVT, pulmonary embolism	30-day all-cause mortality
Covariables	Age, sex, comorbidity (DM, COPD, HTN, obesity, HT, OP, RA, OA, SCTD) (In+Out; A+B; Hx5), and comedication use (<90 days)	Age, sex, calendar period, comorbidity (DM, COPD, HTN, obesity, HT, OP, RA, OA, SCTD) (In+Out; A+B; Hx1977) and comedication use (<90 days)	Comorbidity (Alc, C, CVD, CKD, COPD/asthma, DM, HT, hypothyroidism, liver disease, CP, RA, SCTD) (In+Out; A+B; Hx1977), CORT (<60 days)	Age, sex, CVD, COPD/asthma, DM, liver disease, obesity, SCTD, OA, RA, OP, CKD, recent admission, antipsychotics, HRT (In+Out; A+B; Hx1977), CORT, VKA (<60 days)	MI, AF, PAD, DM, obesity, dementia, SAP, VHD, VTE, CKD, HTN, COPD, Alc, C, RA, SCTD, OA, OP (In+Out; A+B; Hx1977); CV drugs, CORT, SSRI, bisp (<90 days)
Statistics	SD, logistic regression (PS), PS distribution graphics, Cox, robust variance, Kaplan-Meier	Standardized prevalence proportions, logistic regression	Risk-set sampling, conditional logistic regression	Risk-set sampling, unconditional logistic regression	Cox, logistic regression (PS calculation)
Confounder control	Stratification, restriction, regression model adjustments, PS matching, unmeasured confounder analysis	Standardization, regression model adjustments, stratification	Restriction, stratification, regression model adjustments, bias analysis (unmeasured confounder)	Restriction, stratification, regression model adjustments, bias analysis (unmeasured confounder)	Restriction, PS matching, regression model adjustments, stratification
Additional analysis	(1) Stratification by age, sex, period, pill dose, MI type, baseline risk; (2) Omitting healthcare-seeking criteria; excluding OTC period; censoring when other NSAIDs were filled; 1 trial entry/person; low-dose cut-off limits	(1) Stratification by sex, age, NSAID types (2) Median prescribed pill strength; (3) 1-year accumulated dose distribution; (4) treatment duration (number of prescriptions filled among initiators)	(1) Stratification by age, sex, CVD, CKD, OA, RA, SCTD, and pill dose; (2) Sensitivity to using ibuprofen as reference; (3) Restriction to primary diagnosis, cardioversion, and no previous digoxin/VKA/inflammatory conditions	(1) Stratification by age, sex, C, CVD, DM, OA, RA, SCTD, obesity, trauma/fracture, recent hospitalization, and pill dose; (2) Sensitivity to changing exposure window (60 *vs*. 15, 30, 90, 120 days) and using ibuprofen as reference	(1) Stratification by age, sex, RA, OA, MI, AF, HTN, and DM; (2) Sensitivity to change in exposure window (60 *vs*. 30 days); (3) Restriction to CT or MRI scan-confirmed diagnoses
Conclusions*	Diclofenac poses a CV health risk compared to no use, paracetamol use, and use of other traditional NSAIDs	NSAID use is declining. Shorter durations, declining COX-2I use, and increasing naproxen/low-dose ibuprofen use suggest adherence to guidelines. GPs prescribe 90% of NSAID prescriptions.	Use of NSAID was associated with AF risk, strongest for new and COX-2I users	Use of nsNSAIDs or COX-2Is was associated with a two-fold or more increased risk of VTE.	Preadmission use of COX-2Is, but not nsNSAIDs, was associated with increased 30-day IS mortality

Abbreviations: **A** | A+B, Primary and secondary diagnoses; ASA, aspirin; Alc, alcoholism-related disease; ACEI, ACE inhibitors; ARB, angiotensin-II receptor blockers; AF, atrial fibrillation/flutter; AUPD, Aarhus University Prescription Database; **B** | β, beta coefficients; bisp, bisphosphonates; BMI, body mass index**;** BP, blood pressure**; C** | C, cancer; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; CCI, Charlson Comorbidity Index (including 19 CV and non-CV comorbidities); CCI scores were 0 (none), 1 (low), 2 (moderate), and ≥3 (severe); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CORT, glucocorticoids; Cox, Cox proportional-hazards regression; COX, cyclooxygenase; COX-2I, COX-2 selective inhibitor; CP, chronic pancreatitis; CPRD, UK Clinical Practice Research Datalink; C-statistic, Harrell's C-statistic (measures discriminative ability; equivalent to the area under the Receiver Operating Characteristic curve for binary outcomes); Cr, serum creatinine; CRS, Civil Registration System; CT, computerized tomography; CV, cardiovascular; CVD, CV disease; CV drugs, typically include antiplatelet drugs, anticoagulant drugs, ACEI, ARB, beta-blockers, CCB, diuretics, nitrates, and statins; CVD, CV disease; **D** | DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction (including 24 CV and non-CV comorbidities); dBP, diastolic BP; DDD, defined daily doses; DVT, deep vein thrombosis; DK, Denmark; DM, diabetes mellitus; DNDRP, Danish National Database of Reimbursed Prescriptions; DNPR, Danish National Patient Registry; **E** | ECI, Elixhauser Comorbidity Index (including 30 CV and non-CV comorbidities); eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; **H** | HES, UK Hospital Episode Statistics database; HF, heart failure; HR, hazard ratio; HRT, hormone replacement therapy; HT, hyperthyroidism; HTN, Hypertension; Hx, years of hospital record history (Hx5/10/15= 5-,10-, and 15-year histories, Hx1977=history since 1977); **I** | IBD, inflammatory bowel disease; IDI, integrated discrimination improvement (integrates the NRI over all possible cut-offs for the probability of an outcome, and it is the difference between the predicted probabilities of those +/- outcomes); IE, infective endocarditis; IMD, UK Index of Multiple Deprivation; In, inpatient diagnosis; In+Out, in- or outpatient diagnoses; IS, ischemic stroke; ITT, intention-to-treat; **F** | FU, follow-up; **G** | GP, general practitioners; **K** | K, serum potassium; **L** | LABKA, Clinical Laboratory Information System Research Database; **M** | M, million; MACE, major adverse cardiovascular events (composite of secondary outcomes); MI, myocardial infarction; MORT, NZ National Mortality Collection (vital status); MRI, magnetic resonance imaging; **N** | N/A, not applicable; NHISR, National Health Insurance Service Registry; NMDS, NZ National Minimum Dataset (hospital inpatient data); NPC, NZ National Pharmaceutical Collection (dispensed prescriptions); NPR, Danish National Prescription Registry; NRI, continuous Net Reclassification Index; NSAID, non-aspirin nonsteroidal anti-inflammatory drug; nsNSAIDs, non-selective NSAIDs; NZ, New Zealand; **O** | OA, osteoarthritis; OP, osteoporosis; OTC, Over-the-counter; **P** | PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; PS, propensity score; Px, years of prescription history; **R** | RA, rheumatoid arthritis; RAS, Renin–angiotensin system**;** RCD, Registry of Causes of Death; rDANCAMI, DANCAMI restricted to non-CV comorbidities; R^2, modified version of Nagelkerke's R^2 (measures overall performance with explained variation); **S** | SAP, stabile angina pectoris; sBP, systolic BP; SCTD, systemic connective tissue disease; SCZ, schizophrenia; SES, socioeconomic status; SSRI, selective serotonin reuptake inhibitors; SD, standardized difference; **T** | TCP, thrombocytopenia; TLR, target lesion revascularization; TTE, transthoracic echocardiography; **U** | unprovoked, no pregnancy, major trauma, fracture, or surgery within 3 months preceding a VTE, and no pre-existing cancer or a new cancer diagnosis within 3 months after a VTE; **U** | UGIB, upper gastrointestinal bleeding; **V** | VHD, valvular heart disease; VKA, vitamin K antagonists; VTE, venous thromboembolism; **W** | WDHR, Western Denmark Heart Registry

*****Modified and abbreviated for summary purposes

3. Methods

3.1. Data sources

Table 1 provides an overview of the study methods. The studies were based on routinely collected healthcare data from Denmark, New Zealand, and the UK, as outlined in Table 2. All countries have tax-supported healthcare, which guarantees no-cost, equal access to general practitioners and hospitals and partial reimbursement for prescribed medications, including NSAIDs.[182]

The Danish data sources included the Danish National Patient Registry (nationwide in- and outpatient hospital data),[183] the Danish National Prescription Registry (nationwide data on dispensed prescriptions),[184] the Aarhus University Prescription Database (regional data on dispensed prescriptions),[185] the Danish National Database of Reimbursed Prescriptions (nationwide data on reimbursed prescriptions),[186] the Danish online drug use statistics (nationwide aggregated data on dispensed prescriptions and OTC drug sales),[187] the Clinical Laboratory Information System Research Database (regional laboratory data),[188] the Danish National Health Insurance Service Registry (nationwide data on general practice contacts),[189] the Western Denmark Heart Registry (semi-national, detailed patient and procedure data),[190] the Danish Registry of Causes of Death (nationwide cause-of-death data),[191] and the Civil Registration System (nationwide mortality and migration data).[192]

The New Zealand data sources included the National Minimum Dataset (nationwide hospital inpatient data),[193] the National Mortality Collection (nationwide vital status),[194] and the National Pharmaceutical Collection (nationwide dispensed prescriptions).[195]

The UK data sources included the Clinical Practice Research Datalink (CPRD).[196] The CPRD contains primary care electronic health records from 7% of the UK population. These data include patient demographics, the location of the general practice, medical diagnoses, all-cause mortality, drug prescriptions, and routine laboratory test results.[196] Other UK data sources included the Hospital Episode Statistics (HES) database (nationwide inpatient hospital data in England),[197] and the Index of Multiple Deprivation (data on socioeconomic status based on area of residence).[198]

The Danish Civil Registration System and New Zealand National Mortality Collection are population registries, because they include all the inhabitants of a country;[199] in contrast, the other population-based registries include members of the populations with some defining combination of medical data.[199]

3.2. Data linkage

Personal identifiers were used to link databases at the individual level in Denmark and New Zealand. In Denmark, the ten-digit Civil Personal Registry (CPR) number is assigned to all Danish residents at birth and to residents upon immigration.[192] In New Zealand, the National Health Index (NHI) number is assigned to persons at entry into the public health system (>98% of the population).[193]

Table 2 | Sources for the different types of electronic healthcare data used in each country

Applied data types	Denmark	New Zealand	The United Kingdom
Hospital data			
Inpatient diagnoses	√[183]	√[193]	√[197]
Outpatient diagnoses	√[183]	n.a.	n.a.
Cardiac procedure data	√[183,190]	n.a.	n.a.
General practice data			
Contacts	√[189]	n.a.	√[196]
Diagnoses	n.a.	n.a.	√[196]
Laboratory data	√[188]	n.a.	√[196]
Drug data			
Prescription data (individual-level)	√[184-186]	√[88]	√[196]
Issued	n.a.	n.a.	√[196]
Filled	√[184-186]	√[88]	n.a.
Over-the-counter data (aggregated)	√[187]	n.a.	n.a.
Socioeconomic data	n.a.	n.a.	√[198]
Ethnicity data	n.a.	√[193]	n.a.
Mortality data			
All-cause mortality	√[192]	√[194]	√[196]
Causes of death	√[191]	n.a.	n.a.
Migration data	√[192]	n.a.	√[196]

In the UK, there is no unique personal identifier. However, a large subset of English general practices (currently 75%, representing 58% of all UK CPRD practices) have consented to participate in the CPRD linkage scheme. Thus, patient-level data are linked via a trusted third party (the Health and Social Care Information Centre) to other data sources, including HES (hospitalization data), Office for National Statistics (all-cause and cause-specific mortality), Index of Multiple Deprivation and Townsend scores (deprivation data), and various disease registries.[196]

3.3. Study designs

We conducted 11 cohort studies (I–X and XIII) and two case-control studies (XI and XII). The majority of studies (all, except IX and XI–XIII) represent prognosis research.[200] Prognosis research seeks to understand and improve future outcomes in patients with cardiovascular disease. The remaining (risk) studies examined the risk for developing cardiovascular disease in individuals from the general population, according to drug exposure. In accordance, we defined prognostic factors as variables associated with the outcome of a disease and risk factors as variables associated with the risk of a disease. Of note, there was some overlap between the risk and prognosis studies, because several of the risk studies also stratified the results by subgroups of patients, and hence investigated the outcome as part of the prognosis for these subgroups.

According to the Prognosis research strategy (PROGRESS) framework,[200] the prognosis studies could be further classified into the following subcategories: (1) fundamental prognosis research,[200] which examined the course of health-related conditions, in the context of the nature and quality of current care (studies I–III);

(2) prognostic factor research,[201] which examined specific factors associated with prognosis (studies I–IV, VI–IX, and XIII); and (3) prognostic model research,[202] which developed, validated, and determined the impact of statistical models that predicted the individual risk of a future outcome (study V). The methods are detailed in the original publications and summarized in Table 1. The sections below elaborate on key aspects related to comorbidity, drug use, and the statistical approach.

Table 3 | Comorbidities included in the DANish Comorbidity index for Acute Myocardial Infarction, Charlson Comorbidity Index, and Elixhauser Comorbidity Index

Disease categories	**DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI)**	**Charlson Comorbidity Index (CCI)**	**Elixhauser Comorbidity Index (ECI)**
Cardiovascular disease	Heart failure	Congestive heart failure	Congestive heart failure
	Intermittent arterial claudication	Peripheral vascular disease	Peripheral vascular disorder
	Stroke	Cerebrovascular disease	Hypertension
	Hypertension	Myocardial infarction†	Valvular disease
	Aortic disease		Cardiac arrhythmias
	Valvular heart disease		Pulmonary circulation disorders
Kidney disease	Chronic kidney disease	Moderate to severe renal disease	Renal failure
Endocrine disease	Diabetes uncomplicated	Diabetes	Diabetes uncomplicated
	Diabetes with end-organ damage	Diabetes with end-organ damage	Diabetes complicated
			Obesity
			Hypothyroidism
			Fluid and electrolyte disorders
			Weight loss
Cancer	High-risk cancer*	Any tumor	Solid tumor without metastasis
	Low-risk cancer*	Metastatic solid tumor	Metastatic cancer
		Lymphoma	Lymphoma
		Leukemia	
Hematologic disease	Coagulopathy*	AIDS	Coagulopathy
			AIDS/HIV
			Blood-loss anemia
			Deficiency anemia
Psychiatric disease	Schizophrenia*		Psychosis
	Affective disorder*		Depression
	Alcohol and drug abuse*		Alcohol abuse
			Drug abuse
Neurologic disease	Hemiplegia*	Hemiplegia	Paralysis
	Dementia*	Dementia	Neurodegenerative disorders
	Neurodegenerative disorder*		
	Epilepsy*		
Pulmonary disease	Chronic pulmonary disease*	Chronic pulmonary disease	Chronic pulmonary disease
Gastrointestinal disease	Ulcer disease*	Ulcer disease	Peptic ulcer disease, no bleeding
	Mild liver disease*	Mild liver disease	
	Moderate to severe liver disease*	Moderate or severe liver disease	Liver disease
	Chronic pancreatitis*		
Rheumatic disease		Connective tissue disease	Rheumatoid arthritis/collagen vascular disease

From Albertsen LW *et al.* Clin Epidemiol 2020[5]
*rDANCAMI is restricted to the asterisk (*)-marked non-cardiovascular comorbidities plus obesity and connective tissue disease
†Myocardial infarction was not included in the estimated Charlson Comorbidity Index score in study V

3.4. Exposures

3.4.1. Cardiac and non-cardiac comorbidities

We assessed comorbidity to characterize the study populations (prevalence, studies I–XIII), adjust for confounding (studies I–IV and VI–XIII), identify predictors (for MI mortality in study V and NSAID initiation in study XII), examine associated mortality (studies I–III), and investigate effects in patient subgroups (effect measure modification, studies I–IV and VI–XIII). We obtained information on cardiovascular and non-cardiovascular comorbidities from records on inpatient and outpatient diagnoses,[183] procedures,[183] and comedications, with a look-back period ranging from 5 to 15 years (Table 1).[184-186] When possible, we combined prescription, discharge, and laboratory data to increase the completeness of comorbidities, such as diabetes, chronic pulmonary disease, and hypertension.[183]

In addition to identifying individual comorbidities, we categorized the severity of comorbidity burden, based on comorbidity indices (Table 3). In studies prior to the study V where we developed comorbidity indices, we computed the CCI,[67] based on in- and outpatient hospital diagnoses, for periods of 5–15 years prior to the index date.[183] We computed the total CCI score for each patient, omitting index diseases when relevant (*e.g.*, MI,[1] heart failure,[2] and cerebrovascular disease[3]), and we defined four categories of comorbidity (Table 1).

3.4.2. Cardiac and non-cardiac comedications

We used prescription registries to identify prescriptions for cardiac and non-cardiac drugs that were filled by the study populations.[184-186] The cohort-defined use of ACEI/ARB (studies VI–VII) was ascertained from the CPRD.[196] Except for some NSAIDs, all drugs studied were available by prescription only.

The recommended maintenance dose of clopidogrel for tertiary prevention of ischemic vascular events in Denmark was 75 mg (one tablet), daily, for up to 12 months. Thus, for study purposes, the number of days supplied from a dispensed clopidogrel prescription corresponded to the number of tablets per package. Packages available on the Danish market contained 28 or 84 tablets. We computed the number of days exposed by adding 7 days to the number of days supplied. This buffer allowed a 7-day gap to occur between prescription refills, before we considered that a patient had discontinued the medication. Similarly, we computed the number of days exposed to PPIs. At any given point in time, we defined current users of each drug, based on when the most recent prescription was filled. Thus, in a time-varying manner, each patient contributed to the time-at-risk as either a current or non-user of each drug.

There were special issues related to NSAID use, due to the variety of NSAID subtypes, the OTC availability, the variability in clinical instructions for use/dosing, and the complexity of exposure modeling in the individual study designs. We classified NSAIDs, according to their COX-selectivity (Figure 3), as non-selective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid), older COX-2 inhibitors (diclofenac, etodolac, meloxicam, and nabumeton), or coxibs (celecoxib, rofecoxib, and etoricoxib).[116] We identified NSAID use according to the individual study designs: study X evaluated the yearly prevalence (prescription users/1000 inhabitants); studies XI–XIII evaluated pre-admission use; and study IX evaluated use at baseline (IX). We modeled the time-at-risk, based on prescription filling and

discontinuation patterns.[203] Some side effects may arise shortly after therapy initiation; thus, the inclusion of long-term users, who are more likely to tolerate the drug, may lead to an underestimation of NSAID-associated risks.[204] Therefore, we divided current users into new users and long-term users (studies XI–XIII),[204] and focused on patients that initiated NSAIDs in the emulated trial design (study IX). This approach increased the internal study validity by reducing potential confounding. In addition, it was clinically relevant, because NSAIDs are most often prescribed for use in one distinct treatment interval, for a short period of time (inter-quartile range: 9–66 days),[205] and with a median number of prescriptions within one year at around four.[10] This prescribing behavior underlines the need to understand short-term effects, and it challenges previous unfounded assumptions that patients experience a short-term, risk-neutral treatment period. In contrast to long-term drug regimens (*e.g.*, statin treatment), short-term use poses a challenge, because data on the exposure window and daily dose are not directly available from the prescription registries and they cannot be estimated from the average time between prior consecutive prescription fills. Therefore, we defined the exposure window as 30 or 60 days, which was supported by sensitivity analyses with 15 and 45 days. With this approach, we captured most current NSAID users.[205] We used the pill dose as a proxy for the daily dose, and we distinguished between low- and high-dose treatments. We defined non-users as individuals that did not fill a prescription within a 6-month period.

3.4.3. Prescriber responsibility

We assessed which healthcare units were responsible for NSAID prescriptions for patients with cardiac diseases, by identifying the prescriber variable in the prescription registries (study X).[206] The prescriber variable is a unique identifier that designates a 'provider number' to prescriber practices and 'hospital department numbers' to different hospital departments. The prescriber number does not necessarily refer to a single prescriber; instead, it refers to a single-practice unit, such as a general practitioner, a private specialist practice, or a hospital department. The identity of the single-practice unit can be retrieved by linking the prescriber number to prescriber identifiers from other sources (*e.g.*, the Registry of Health Providers and the SHAK classification).[206]

3.4.4. Renal function

All creatinine test results were extracted from the general practice records of the study population, based on creatinine-specific codes in the CPRD (studies VI–VII).[196] Then, we cross-referenced to the creatinine test results identified from a broad Read code search. Any irrelevant codes were excluded. Renal function testing in the UK included creatinine and potassium measurements; thus, we inferred that the testing frequencies were similar for creatinine and potassium. For analyses related to potassium levels, we repeated the procedure used for identifying creatinine levels to identify potassium test results.

3.5. Outcomes

We used discharge diagnoses in the Danish National Patient Registry[183,207] and the CPRD[196] to identify MI, heart failure, stroke, atrial fibrillation/flutter, VTE, and end stage renal disease, as individual cardiovascular outcomes. Moreover, we used the Western Denmark Heart Registry[190] to assess stent thrombosis and target lesion revascularization as procedure-specific outcomes, after a PCI (study VIII). Based on reviews of original medical records and catheterization angiograms, a cardiac specialist committee, blinded to the medication use history, adjudicated the occurrence of definite stent thrombosis, based on the definition established by the Academic Research Consortium.[190] A target lesion revascularization was defined as a repeated PCI or coronary artery bypass graft of the index lesion.[190]

All-cause mortality was obtained from the Danish Civil Registration System, in Denmark,[192] the National Mortality Collection, in New Zealand,[194] and the CPRD, in the UK.[196] Cause-specific deaths in Denmark were obtained from the Danish Registry of Causes of Death.[191] Furthermore, in the drug-drug interaction study (study VIII), the cardiac specialist committee reviewed the underlying cause listed on the original death certificate and classified it as either cardiac or noncardiac.[190] Cardiac death was defined as an evident cardiac death, unwitnessed death, or death from unknown causes.[208]

In studies VIII and IX, we defined MACE as the composite of a first occurrence of either (1) MI, ischemic stroke, stent thrombosis, target lesion revascularization, and cardiac death (study VIII) or (2) MI, ischemic stroke, heart failure, atrial fibrillation/flutter, and cardiac death (study IX).

3.6. Statistical analysis

We initially created contingency tables for the main study variables.[209] In the time-to-event analyses, we followed all patients until the date of a non-fatal outcome, death, emigration, or the end of follow-up, whichever came first. We performed Poisson regressions (study VII) to calculate incidence rates and incidence rate ratios (IRRs). Alternatively, we performed Cox proportional-hazards regressions (studies I–V, VIII, IX, and XII), with the time from cohort entry as the underlying time scale, to calculate HRs as a measure of the IRR. We performed log-log plots to verify the proportional hazards assumption graphically. We performed logistic regression to compute odds ratios (ORs) of potential predictors of NSAID initiation (study X), the effect estimates in case-control analyses (studies XI and XII), and propensity scores (PS) (studies IX and XIII).[210] Because we used risk-set sampling of controls (studies XI and XII), the ORs provided unbiased estimates of the IRRs.[211] In calculating the PS, the logistic regression included potential confounders and risk factors, but not factors associated exclusively with NSAID use.[212] With a greedy matching algorithm,[213] we matched each NSAID user with the comparator (non-user or paracetamol user), based on the closest PS.[213] We performed the PS matching without replacement, within a maximum matching PS range (caliper width) of ±0.025. PS matching was performed separately for each class and each individual type of NSAID.[213] We calculated 95% confidence intervals (CIs) for all estimates; *i.e.*, upon repeated sampling, 95% of the intervals

constructed in the same way would be expected to cover the true parameter, assuming no bias or prior knowledge.

In the etiological models (studies I–IV and VI–XIII), we applied various strategies to control for confounding (Table 1). In the design phase, we applied restriction and matching. In the analysis phase, we applied standardization, multivariable adjustment, stratification, and quantitative bias analyses.[214] We selected potential confounders, based on a clinical evaluation of the expected associations with both exposure and outcome.[215] We stratified the results into clinically relevant subgroups of patients, including covariables that could indicate underlying mechanisms for an association (*e.g.*, chronic kidney disease in study XIII and baseline cardiovascular risk in study IX). We performed a range of sensitivity analyses to examine the extent to which our results were sensitive to changes in analytical assumptions or variable definitions (Table 1).[216]

In addition to these well-established statistical methods, we applied the five novel methods below. These methods were related to the development and validation of comorbidity indices (study V) and the application of advanced study designs, to model the disease-disease interaction (study IV), drug-drug interaction (study VIII), renal function, based on a model of laboratory data (studies VI and VII), and the emulated trial design (study IX).

3.6.1. Comorbidity index

To develop the novel DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) (study V), we included 41 cardiovascular and non-cardiovascular comorbidities in a multivariable Cox model with sex and age. Through backwards selection, we then eliminated comorbidities that had HRs <1.10 or a 95% CI that overlapped 1. Then, we fitted the revised models with the remaining comorbidities, sex, and age. We repeated this stepwise approach, until the model included only comorbidities with HRs ≥1.10 (Table 4). We tested the proportionality assumption with the global test, based on scaled Schoenfeld residuals and log-log plots for variables that appeared non-proportional. We assigned weights to each comorbidity in the final index by multiplying the beta coefficient from the multivariable models by ten and rounding to the nearest integer. The total DANCAMI score for each patient was determined by summing the weights for his/her comorbidities (Table 4). Restricting to non-cardiovascular comorbidities, we repeated the above steps to develop the rDANCAMI. In addition to the continuous comorbidity scores, we categorized the scores into low risk (score=0), medium risk (scores=1–3), high risk (scores=4–5), and very high risk (scores≥6). This categorization was based on the survival curves for the individual DANCAMI/rDANCAMI scores (Figure 5).

We evaluated the performance of the continuous and categorical scores in MI cohorts from Denmark (internal validation) and New Zealand (external validation) with standard performance measures, including Nagelkerke's R^2, Harrell's C-statistic, the integrated discrimination improvement (IDI), and the continuous Net Reclassification Index (Table 1).[217] We intended the DANCAMI to be used for research, rather than clinical applications; therefore, we focused the performance measurements on its discriminatory ability. Subsequently, we compared the performance of the DANCAMI with that of existing comorbidity indices (CCI and ECI) by estimating nonparametric correlations.

The standard model performance measures were largely developed for assessing the performance of dichotomous diagnostic tests; thus, their application to risk prediction scores is debatable. Moreover, these metrics are insensitive to the addition of important predictors.[218] Therefore, we also tested the significance of the novel DANCAMI variables, which were not included in the CCI, by including them in a model containing the CCI variables. In this model, significant HRs for the novel DANCAMI variables would support the conclusion that the DANCAMI was superior to the CCI in the ability to predict 1-year all-cause mortality.

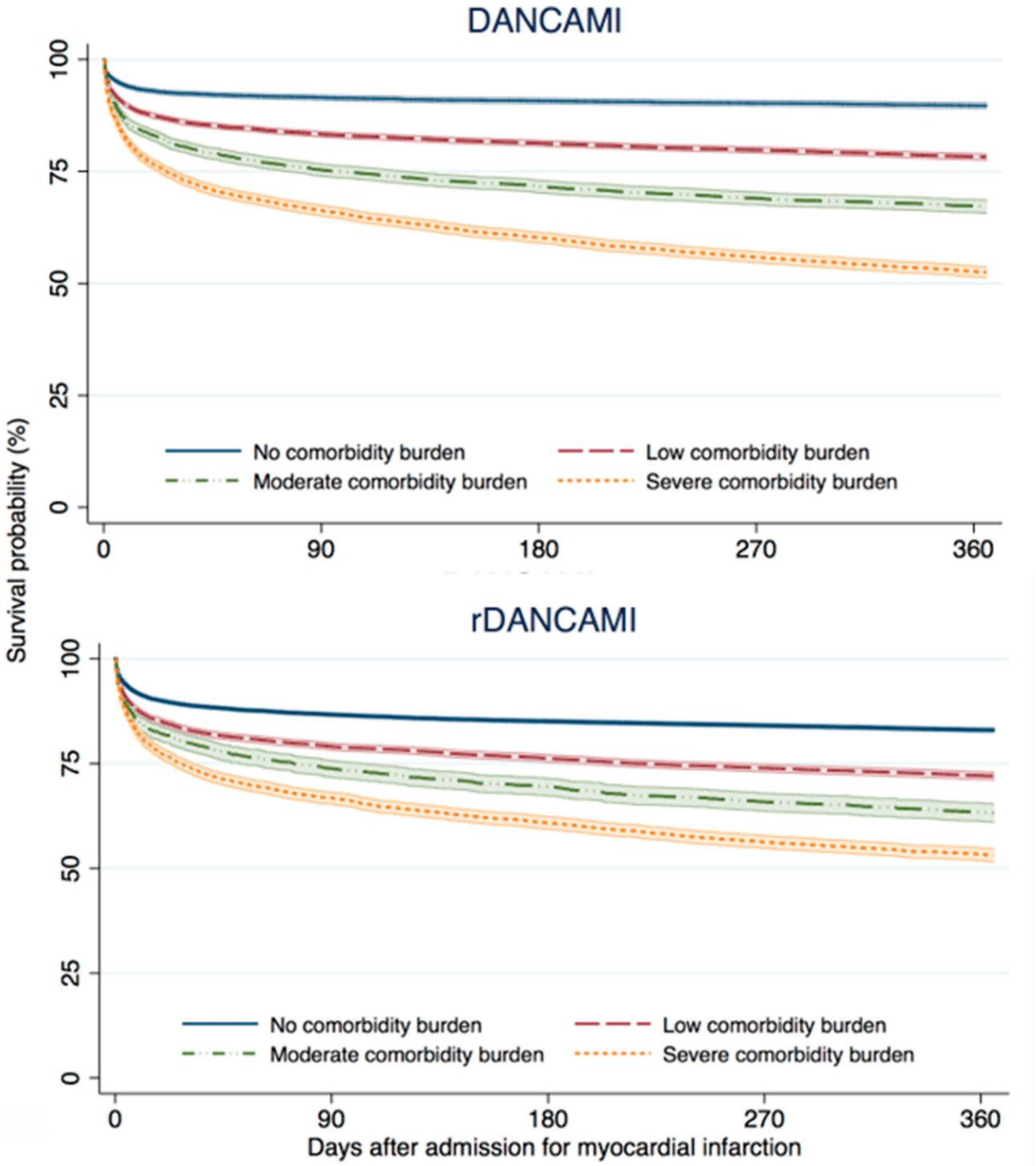


Figure 5 | Survival according to the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) categories of comorbidity burden with 95% confidence intervals. Abbreviations: DANCAMI, DANCAMI restricted to non-cardiovascular comorbidities. Modified from Albertsen LW *et al*. Clin Epidemiol 2020[5]

Table 4 | Development of the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI)

Covariables	β	SE	HR (95% CI)	Weight
DANCAMI*				
Heart failure	0.320	0.037	1.38 (1.28–1.48)	3
Intermittent arterial claudication	0.229	0. 055	1.26 (1.13–1.40)	2
Aortic disease	0.209	0. 082	1.23 (1.05–1.45)	2
Valvular heart disease	0.233	0.042	1.26 (1.16–1.37)	2
Stroke	0.254	0.042	1.29 (1.19–1.40)	3
Hypertension	0.121	0.025	1.13 (1.08–1.18)	1
High-risk cancer	1.043	0.053	2.84 (2.56–3.15)	10
Low-risk cancer	0.190	0.036	1.21 (1.13–1.30)	2
Coagulopathy	0.127	0.037	1.14 (1.06–1.22)	1
Diabetes uncomplicated	0.183	0.034	1.20 (1.12–1.28)	2
Diabetes with end-organ damage	0.315	0.040	1.37 (1.27–1.48)	3
Dementia	0.327	0.063	1.39 (1.23–1.57)	3
Alcohol and drug abuse	0.302	0.080	1.35 (1.16–1.58)	3
Schizophrenia	0.464	0.048	1.59 (1.45–1.75)	5
Affective disorder	0.255	0.027	1.29 (1.22–1.36)	3
Epilepsy	0.287	0.090	1.33 (1.12–1.59)	3
Neurodegenerative disorder	0.286	0.085	1.33 (1.13–1.57)	3
Hemiplegia	0.577	0.183	1.78 (1.24–2.55)	6
Chronic kidney disease	0.373	0.047	1.45 (1.32–1.59)	4
Chronic pulmonary disease	0.226	0.024	1.25 (1.20–1.31)	2
Ulcer disease	0.176	0.048	1.19 (1.08–1.31)	2
Mild liver disease	0.286	0.129	1.33 (1.03–1.71)	3
Moderate-to-severe liver disease	0.664	0.190	1.94 (1.34–2.82)	7
Chronic pancreatitis	0.500	0.207	1.65 (1.10–2.47)	5
rDANCAMI†				
High-risk cancer	1.041	0.053	2.83 (2.55–3.14)	10
Low-risk cancer	0.193	0.036	1.21 (1.13–1.30)	2
Coagulopathy	0.260	0.037	1.30 (1.21–1.39)	3
Obesity	0.248	0.085	1.28 (1.09–1.51)	2
Dementia	0.362	0.063	1.44 (1.27–1.62)	4
Alcohol and drug abuse	0.336	0.080	1.40 (1.20–1.64)	3
Schizophrenia	0.470	0.048	1.60 (1.46–1.76)	5
Affective disorder	0.299	0.027	1.35 (1.28–1.42)	3
Epilepsy	0.392	0.090	1.48 (1.24–1.76)	4
Neurodegenerative disorder	0.295	0.085	1.34 (1.14–1.59)	3
Hemiplegia	0.637	0.183	1.89 (1.32–2.71)	6
Chronic pulmonary disease	0.265	0.024	1.30 (1.24–1.36)	3
Ulcer disease	0.247	0.048	1.28 (1.16–1.41)	2
Mild liver disease	0.359	0.130	1.43 (1.11–1.85)	4
Moderate-to-severe liver disease	0.554	0.191	1.74 (1.20–2.53)	6
Chronic pancreatitis	0.643	0.207	1.90 (1.27–2.85)	6
Connective tissue disease	0.105	0.533	1.11 (1.00–1.23)	1

From Albertsen LW *et al.* Clin Epidemiol 2020[5]

Abbreviations: β, beta coefficient; CI, confidence interval; HR, hazard ratio; rDANCAMI, DANCAMI restricted to non-cardiovascular comorbidities; SE, standard error

*Includes both cardiovascular and non-cardiovascular comorbidities

†Restricted to non-cardiovascular comorbidities

3.6.2. Disease-disease interaction

We examined disease-disease interactions (study IV) on the additive scale, by calculating *interaction contrasts* (Figure 6).[57,58] The interaction contrast is the difference in rate differences and measures the excess or deficit mortality rate, above or below the mortality that could be explained by: (1) the baseline mortality rate among individuals without an MI or comorbidity, (2) the comorbidity-associated mortality rate, and (3) the MI-associated mortality rate. We calculated interaction contrasts for 30-day, 31–365-day, and 1–5-year MI mortality rates for different CCI categories and for individual comorbidities.

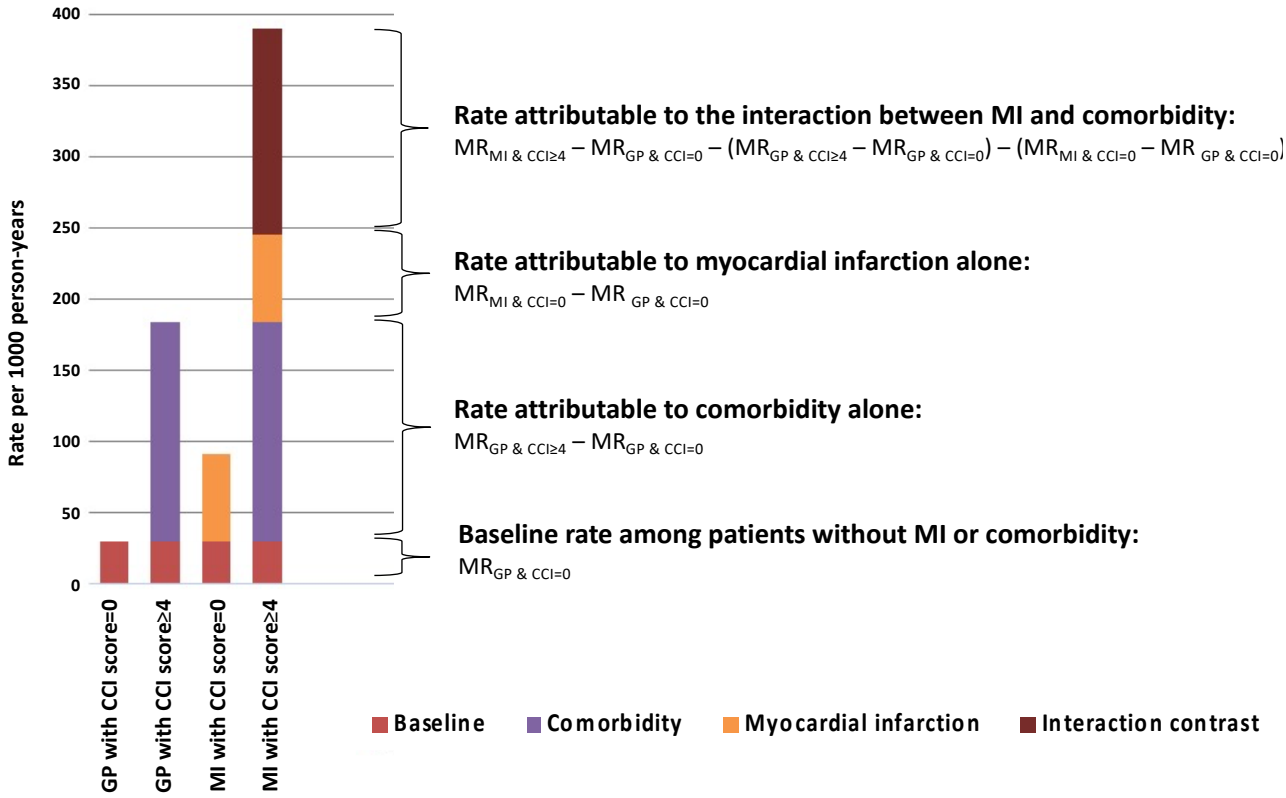


Figure 6 | Proportions of the 31–365-day mortality rate attributable to myocardial infarction, comorbidity, and their interaction. Abbreviations: CCI: Charlson Comorbidity Index; GP, General population; MI, Myocardial infarction; MR, mortality rate. Modified from Schmidt M *et al.* Int J Cardiol 2020[4]

3.6.3. Drug-drug interaction

In the drug-drug interaction study (VIII), we modeled drug exposure with a time-varying approach. That is, we allowed patients to be exposed to different combinations of medication over time. We considered the following combinations: clopidogrel plus PPI, clopidogrel without PPI, PPI without clopidogrel, and no clopidogrel or PPI. With this approach, we could compare the frequency of MACE per cumulated time-at-risk, associated with each of the four exposure categories. We then examined whether PPIs, as a class, could modify the association between clopidogrel and MACE, by comparing the current use of clopidogrel to non-use, in subgroups of patients with or without concomitant PPI use, and vice versa.

The choices of scale and interaction measures comprise an issue of debate. Drug-drug interactions may also be studied on the additive scale, with interaction contrasts or surrogate interaction measures, such as the relative excess risk due to interaction (RERI), the attributable proportion due to interaction, or the synergy index.[219,220] Studying drug-drug interactions on an additive scale is most appropriate for assessing public health importance and biological interactions.[57] However, we aimed in this study to provide an explanation for the previous clinical outcome studies, which examined the relative risk of MACE among clopidogrel users that did or did not use PPIs. We therefore estimated the 'interaction effect' on the multiplicative scale, and expressed it as the exponentiated coefficient of the interaction term in a Cox proportional-hazards regression model, that is, the ratio of the stratum-specific HRs.[108] The interaction effect on the multiplicative scale estimates the relative rate increase (or decrease) in patients that use both clopidogrel and a PPI, beyond that expected from the independent effects of each drug alone.[108] An interaction effect other than 1.0 suggests that the concomitant PPI use has modified any protective effect of clopidogrel. We used the Wald chi^2 test to assess the null hypothesis of no interaction.

3.6.4. Renal function modeling based on laboratory data

To analyze changes in renal function after ACEI/ARB initiation (studies VI and VII), we categorized ACEI/ARB users according to the level of creatinine monitoring, as follows: no baseline or follow-up monitoring, baseline monitoring only, follow-up monitoring only, and both baseline and follow-up monitoring. Baseline monitoring was defined as a test performed on the date of drug initiation or within either 12 months prior (wide interval) or 1 month prior (narrow interval) to initiation. Monitoring one month prior to initiation was a more ideal interval, and it was assumed to be driven by the ACEI/ARB initiation plan. The post-initiation monitoring interval was based on previous trial data; thus, we defined follow-up monitoring as a test performed within the first 2 months after drug initiation.[89] We then computed the proportion of individuals with both baseline and initial follow-up monitoring, where the latter was performed within the guideline-recommended interval of 2 weeks after drug initiation.

We repeated the analyses for continuing users to examine adherence to the stricter guideline recommendations for ongoing monitoring (*i.e.*, monitoring within 1, 3, 6, and 12 months after the first retest).[221] Continuation was defined as ACEI/ARB use beyond 30 days after the first monitoring date (to allow for drug stockpiling). The end date of each prescription was calculated by adding the prescription duration (total number of tablets prescribed divided by the specified number of tablets per day) to the date that the prescription was filled.

We analyzed the subcohort of patients with both pre-initiation (within 12 months prior) and post-initiation (within two months after) creatinine measurements to: (1) calculate the proportion of patients with severe declines in renal function at the first follow-up monitoring; a severe decline was defined as a creatinine increase ≥30% or a potassium level >6 mmol/L; (2) calculate the proportion of patients that continued treatment, despite contraindications for use; (3) identify patient characteristics associated with a severe decline in renal function and compare those characteristics to the characteristics associated with receiving post-initiation follow-up monitoring within 2 weeks; and (4) categorize the relative creatinine increase, according

to the guideline recommended cut-off levels of ≥30% *vs.* <30%, and according to 10% incremental increases (<10%, 10–19%, 20–29%, 30–39%, and ≥40%).

All new ACEI/ARB users that showed a change in creatinine concentration between baseline and the date of the first follow-up test were followed until the occurrence of an outcome, death, withdrawal from the general practice, or the end of the follow-up period (31 March 2014), whichever occurred first. We performed Poisson regressions to compute rates and IRRs for determining whether different categories of percentage creatinine increase were associated with cardiorenal outcomes. We calculated robust standard errors to account for clustering of general practices. We performed cause-specific hazards analyses to account for competing risks.[222,223]

3.6.5. Emulated trial design

We designed an emulated trial to study the cardiovascular risks associated with diclofenac (study IX). We used the Danish population-based registries to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a RCT.[121,224] Eligible individuals were ≥18 years with (1) at least one year of continuous prescription records prior to date of study entry, (2) no exclusion criteria, and (3) no NSAID prescriptions in the 12-month washout period before enrolment. Exclusion criteria were previous cardiovascular disease, chronic kidney disease, chronic liver disease, other alcoholism-related diseases, ulcer disease, malignancy, schizophrenia (or use of antipsychotic drugs), or dementia. Among eligible individuals, we identified all those that initiated (1) diclofenac; (2) ibuprofen or naproxen (active NSAID comparators); (3) paracetamol (active non-NSAID comparators); or (4) did not initiate NSAID treatment (NSAID non-initiators). The two latter comparison groups were PS-score matched among health-care seeking individuals that had contacted a general practice within the trial month.

In all trials, we followed enrolled individuals from baseline (*i.e.*, the date of prescription) until the first occurrence of MACE, death, loss to follow-up, or the 30-day follow-up, whichever occurred first. To increase the number of initiators and events, we applied the enrolment approach in every month between January 1996 and December 2016. Thus, we created a series of emulated 'trials' (n=252), each with a one-month enrollment period (Figure 7). We estimated an observational analogue of the intention-to-treat HR, as a measure of the IRR, by fitting a Cox proportional-hazards model, using time since baseline as the time scale and a time-independent covariable for the treatment assignment. All individual trials were pooled into a single model. We adjusted for baseline covariables in the analyses with active NSAID comparators.

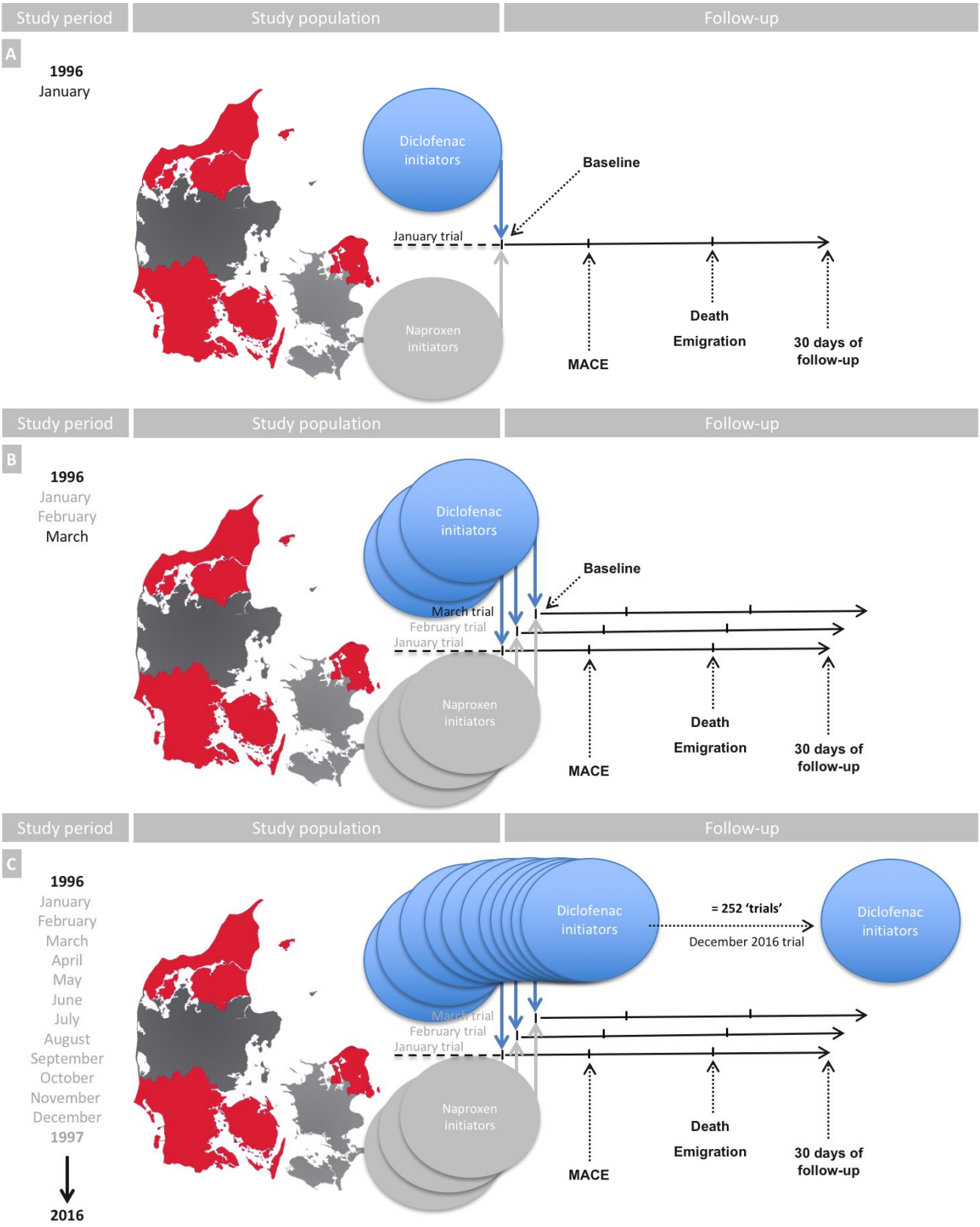


Figure 7 | The emulated trial design. Individual-level linkage among nationwide population-based registries was performed to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical trial. Panel A shows how all initiators of diclofenac and naproxen were identified during the month of January 1996. Each person was followed until a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up. This enrollment protocol was repeated for the months of February and March (Panel B), and subsequently, the protocol was performed for every month from January 1996 through December 2016 (Panel C). The series of 252 emulated 'trials' were then pooled into one model, which generated a sample size of 1,370,832 diclofenac initiators and 291,490 naproxen initiators. A similar approach was used to identify ibuprofen initiators (n=3,878,454) and propensity-score matched paracetamol initiators (n=764,781) and NSAID non-initiators (n=1,303,209). Modified from Schmidt M *et al*. BMJ 2018[9]

4. Results

Here, we summarize the main findings of all thirteen studies. The findings are presented according to content, rather than publications; therefore, some studies are described collectively. The comorbidity summary focuses primarily on MI as the index disease, rather than all individual cardiovascular diseases, to prioritize aspects of comorbidity. The non-cardiac comedication summary focuses on individual NSAIDs, rather than combined classes, to increase the clinical relevance. The figures are presented as published or slightly modified, and the original tables are modified, collapsed, and/or presented graphically to improve the overview.

4.1. Comorbidity

4.1.1. Trends in prevalence of comorbidity at first-time cardiovascular disease

Over the last 2–3 decades, the burden of comorbidity increased at first-time hospitalization of an MI. Thus, the prevalence of patients with an MI, but without a comorbidity, fell from 76% to 64%, during 1984–2008. Concomitantly, the percentages of patients with low, moderate, and severe comorbidity burden increased from 13% to 16%, from 7.4% to 11%, and from 3.9% to 10%, respectively. The most prevalent individual comorbidities in MI patients were diabetes (7.0%), stroke (7.0%), heart failure (5.8%), chronic pulmonary disease (5.8%), peripheral vascular disease (5.3%), cancer (5.4%), ulcer disease (2.5%), connective tissue disease (2.1%), and severe renal disease (1.6%).

4.1.2. Association between comorbidity and cardiovascular mortality

The 30-day and 31–365-day mortality risks were strongly associated with the comorbidity burden. To examine this association, we evaluated the age- and sex-adjusted mortality rate ratio (MRR), with no comorbidity as the reference group (study period: 2004–2008). Patients with low comorbidity had MRRs of 1.35 (95% CI: 1.26–1.45) within 30 days, and 1.83 (95% CI: 1.68–2.00) within 31–365 days (Figure 8). For patients with severe comorbidity, the adjusted MRRs were 1.96 (95% CI: 1.83–2.11) within 30 days and 3.89 (95% CI: 3.58–4.24) within 31–365 days. The mortality rate increased in association with the increasing level of comorbidity consistently across calendar periods. Moreover, consistent with the principle that effect estimates are higher among those at lower baseline risk, we found that patient age could modify the MRR associated with each comorbidity category. Indeed, we found higher effect estimates in younger age groups.

Among the individual non-malignant comorbidities, we found that mild liver disease, moderate-to-severe liver disease, and dementia were each associated with an approximately two-fold increase in the mortality rate within 30 days after an MI, compared to patients without comorbidity (Figure 8). Within 31–365 days after an MI, we also observed two-fold increases in MRRs among patients with moderate-to-severe liver or renal diseases. Heart failure, peripheral vascular disease, cerebrovascular vascular disease, chronic pulmonary disease, and ulcer disease were associated with 1.2- to 1.3-fold increases in MRR within 30 days; furthermore, these fold-increases rose to 1.5-fold within 31–365 days. Diabetes with end-organ damage was associated with a 1.3-fold increase in the short- and long-term mortality rates, but connective tissue disease did not affect mortality.

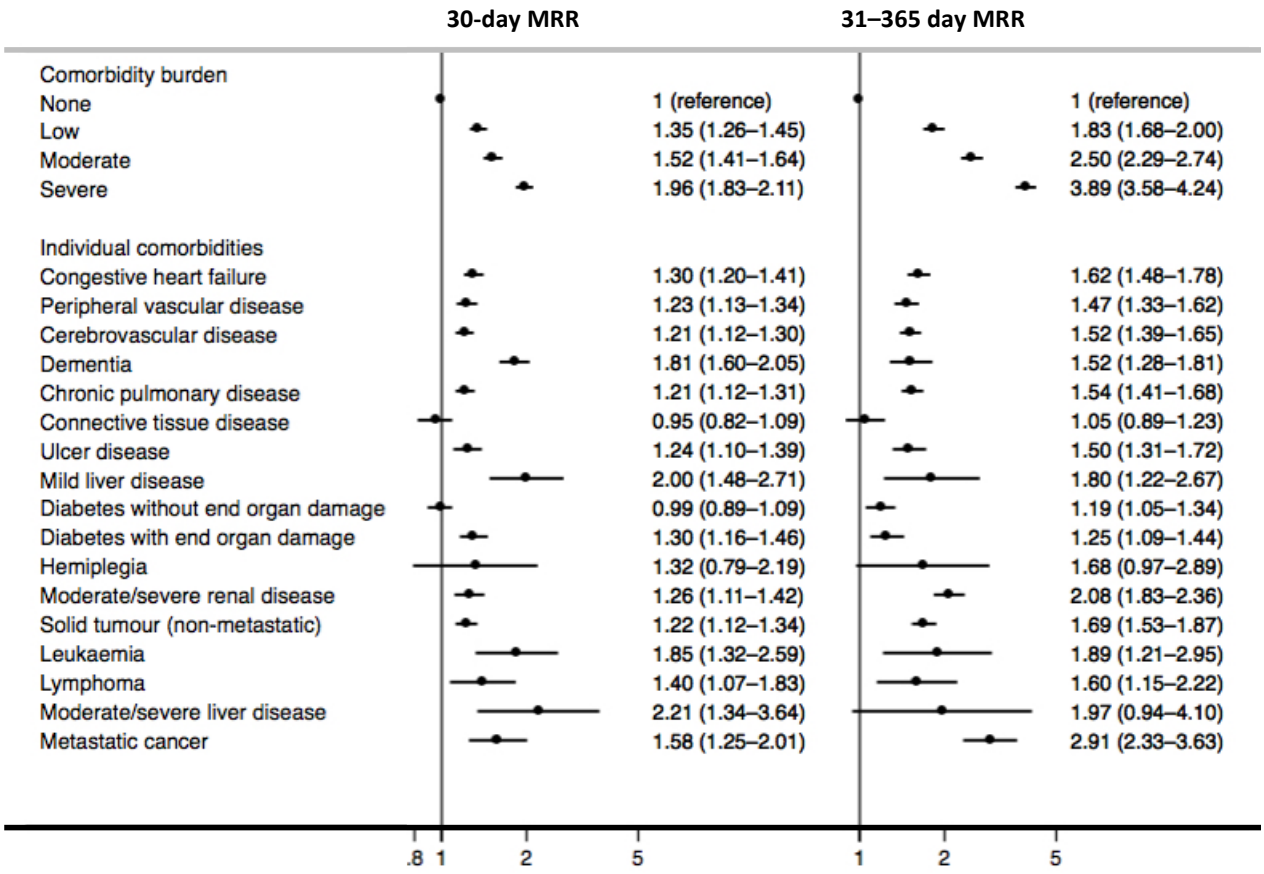


Figure 8 | 30-day and 31–365-day adjusted mortality rate ratios (MRRs) after a first-time hospitalization for myocardial infarction in Denmark, between 2004 and 2008, associated with the severity of individual comorbidities. Modified from Schmidt M *et al*. BMJ 2012[1]

4.1.3. Effect modification by comorbidity on cardiovascular mortality trends

The standardized 30-day and 31–365-day mortality risks after a first-time MI were similar for men and women, and the risks decreased comparably, between 1984 and 2008 (Figure 9). From the first calendar period (1984–1988) to the last period (2004–2008), the 30-day mortality declined from 31% to 15%, and the 31–365-day mortality declined from 16% to 11%. After adjusting for age- and comorbidity, the decline in mortality over time was above 50% (MRRs were 0.37, 95% CI: 0.35–0.38, within 30 days, and 0.48, 95% CI: 0.47–0.51 within 31–365 days). Importantly, the improvement in mortality was observed for all patients, in all age groups, and independent of their comorbidity burden (Figure 10).

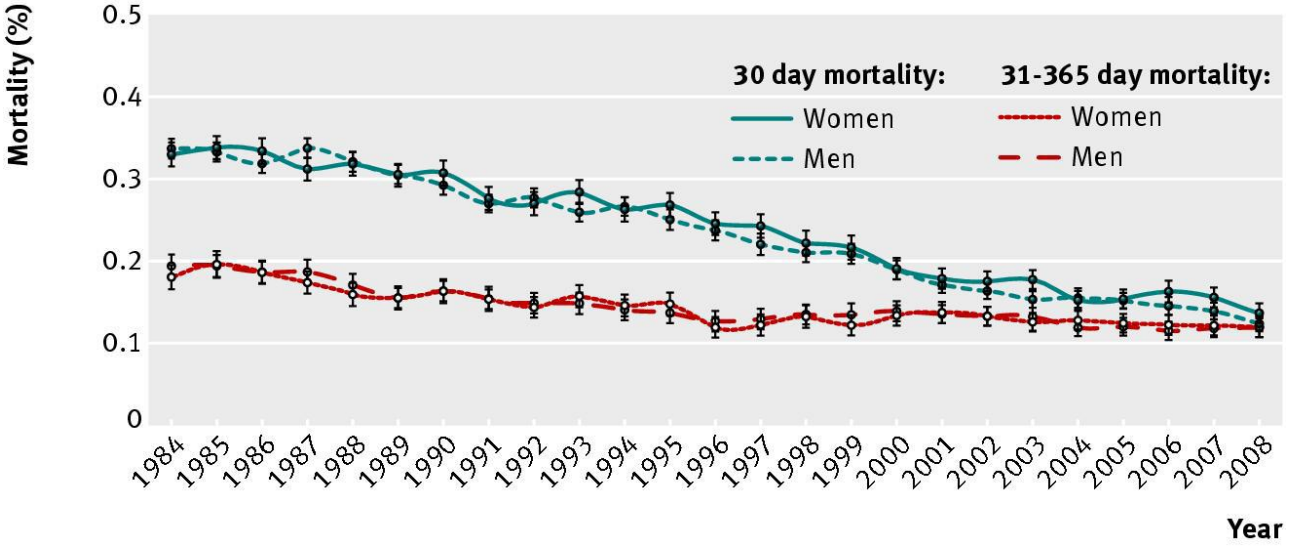


Figure 9 | Standardized rates of 30-day and 31–365 day mortality after a first-time hospitalization for myocardial infarction, among men and women, between 1984 and 2008. From Schmidt M *et al*. BMJ 2012[1]

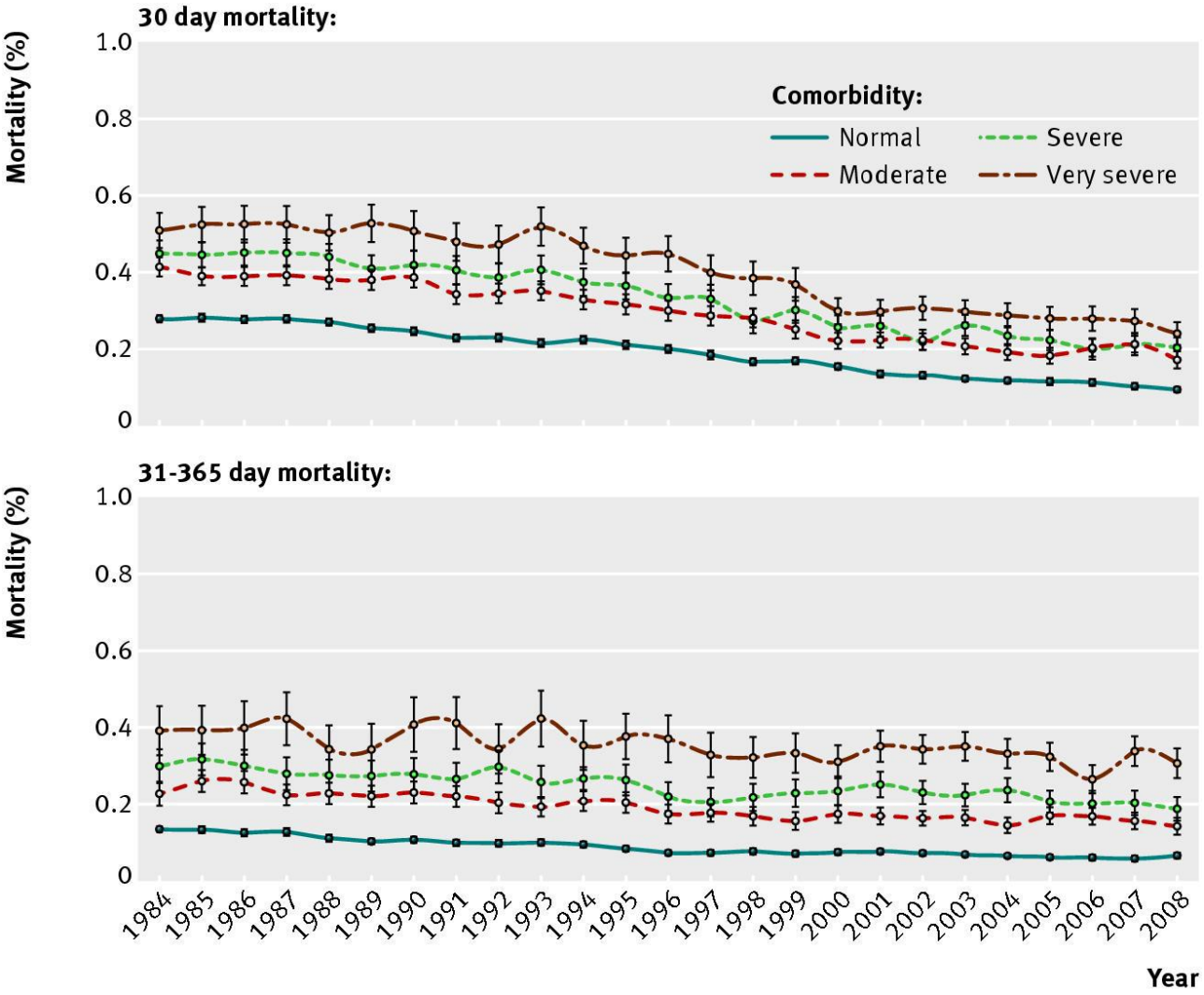


Figure 10 | 30-day and 31–365-day mortality after a first-time hospitalization for myocardial infarction, between 1984 and 2008, according to the severity of comorbidity burden. From Schmidt M *et al*. BMJ 2012[1]

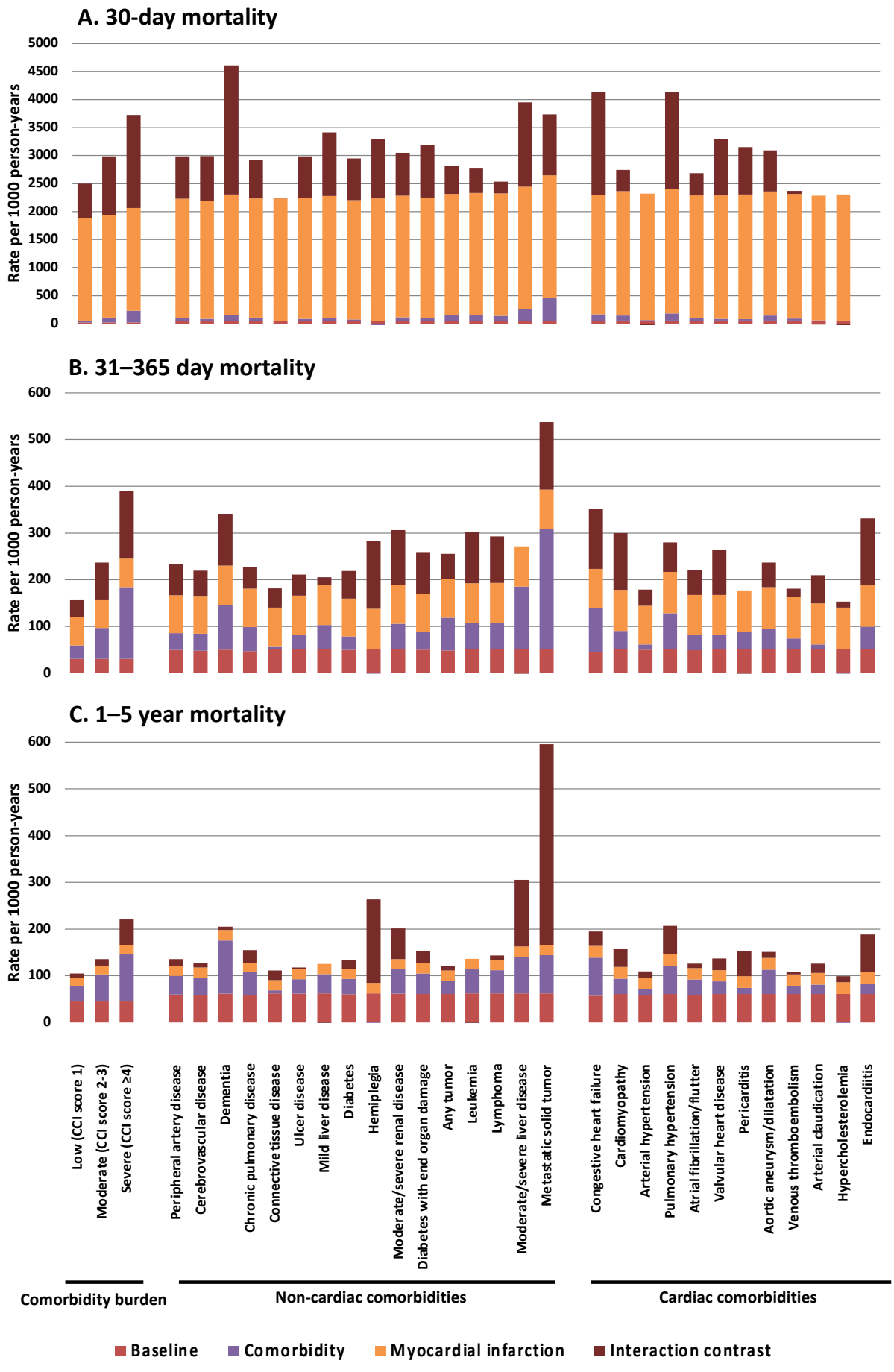


Figure 11 | Proportion of the total mortality rate attributable to myocardial infarction, individual comorbidities, and their interaction during (A) 30 days, (B) 31–365 days, and (C) >1–5 years of follow-up. Modified from Schmidt M *et al*. Int J Cardiol 2020[4]

4.1.4. Interaction effect of comorbidity on cardiovascular mortality

Among individuals without comorbidity, the 30-day mortality rates (per 1000 person-years) were 1851 (95% CI: 1818–1884) for patients with an MI and 22 (95% CI: 21–24) for the comparison cohort (*i.e.*, the rate difference=1829). For individuals with a low comorbidity burden, the baseline mortality rates were 2498 (95% CI: 2436–2560) in the MI cohort and 54 (95% CI: 50–57) in the comparison cohort (rate difference=2444). The corresponding interaction contrast (2444–1829=616) indicated that an interaction between comorbidity and MI accounted for 25% (616/2498) of the total 30-day mortality rate in patients with MI and a low comorbidity burden. This interaction increased further for patients with moderate (35%) and severe (45%) comorbidity levels. Absolute and relative interaction effects were largest within the first 30 days and inversely related to age. Dose-response relationships between the comorbidity burdens and the mortality rates were also observed during the 31–365-day and 1–5-year follow-ups (p-values for trends <0.002). The interaction strengths depended on the types of cardiac and non-cardiac comorbidities (Figure 11).

4.1.5. Prediction of cardiovascular mortality using comorbidity indices

The model development resulted in the inclusion of 24 comorbidities in the DANCAMI and 17 in the rDANCAMI (Table 4). High-risk cancer received the highest severity weight (weight=10) in both indices. Other comorbidities with high severity weights (weights ≥5) were: schizophrenia, hemiplegia, moderate/severe liver disease, and chronic pancreatitis (Table 4).

The model performance (discrimination) measures showed that the explained variance (R^2) was significantly higher in the prediction model that included age, sex, and the DANCAMI (R^2=0.33, 95% CI: 0.32–0.34), compared to the R^2 in the baseline model, which included only age and sex (R^2=0.28, 95% CI: 0.27–0.29) (Table 5). Similarly, the discrimination of DANCAMI was better than that of the baseline model (C-statistic: 0.75 *vs.* 0.73). Adding the DANCAMI score to the baseline model improved its discrimination (IDI=0.054) compared to the baseline model alone. Similarly, improved discrimination was evidenced by a total Net Reclassification Index of 0.52, where 77% of non-events and 49% of events received a better prediction of the probability of 1-year mortality. The DANCAMI score categories performed almost as well in the R^2 and C-statistics as the continuous DANCAMI score (Table 5).

A comparison between the DANCAMI and existing comorbidity indices showed that both the continuous and categorical DANCAMIs performed slightly better than the CCI and the ECI for all four performance measures. The superiority of the DANCAMI over the CCI was strongly supported by the finding that each of the eight novel variables included in the DANCAMI (*i.e.*, those that did not overlap with the CCI variables) predicted 1-year mortality, even after adjusting for the CCI variables. These novel variables included valvular heart disease (HR for 1-year mortality=1.25, 95% CI: 1.14–1.35), coagulopathy (1.13, 95% CI: 1.05–1.22), alcohol and drug abuse (1.35, 95% CI: 1.15–1.58), schizophrenia (1.60, 95% CI: 1.46–1.76), affective disorder (1.29, 95% CI: 1.22–1.36), epilepsy (1.26, 95% CI: 1.05–1.50), neurodegenerative disorder (1.30, 95% CI: 1.10–1.54) and chronic pancreatitis (1.71, 95% CI: 1.14–2.56). Finally, the external validation showed

that the DANCAMI performed as well as the CCI and the ECI in predicting 1-year mortality in the New Zealand MI population, based on the standard performance measures.

Table 5 | Performance of the continuous and categorical scores of DANCAMI and other comorbidity indices in the Danish (development) and New Zealand (validation) cohorts with a first-time myocardial infarction

Discrimination measures	**Continuous DANCAMI score**				**Categorical DANCAMI score**			
	Danish cohort		New Zealand cohort		Danish cohort		New Zealand cohort	
R^2								
Baseline*	0.28 (0.27–0.29)	ref.	0.28 (0.28–0.29)	ref.	0.28 (0.27–0.29)	ref.	0.28 (0.28–0.29)	ref.
DANCAMI†	0.33 (0.32–0.34)	1.20‡	0.37 (0.37–0.38)	1.32‡	0.32 (0.31–0.33)	1.14‡	0.36 (0.35–0.37)	1.29‡
rDANCAMI†	0.32 (0.31–0.33)	1.15‡	0.36 (0.35–0.37)	1.28‡	0.31 (0.30–0.32)	1.11‡	0.35 (0.34–0.36)	1.25‡
CCI†	0.32 (0.31–0.33)	1.14‡	0.37 (0.37–0.38)	1.32‡	0.31 (0.30–0.32)	1.11‡	0.36 (0.36–0.37)	1.29‡
ECI†	0.31 (0.30–0.32)	1.13‡	0.38 (0.37–0.38)	1.33‡	0.31 (0.30–0.32)	1.11‡	0.38 (0.37–0.39)	1.36‡
Harrell's C								
Baseline*	0.73 (0.72–0.73)	ref.	0.73 (0.72–0.73)	ref.	0.73 (0.72–0.73)	ref.	0.73 (0.72–0.73)	ref.
DANCAMI†	0.75 (0.75–0.76)	1.04§	0.77 (0.77–0.78)	1.07§	0.75 (0.74–0.75)	1.03§	0.77 (0.76–0.77)	1.05§
rDANCAMI†	0.75 (0.74–0.75)	1.03§	0.77 (0.76–0.77)	1.05§	0.74 (0.74–0.75)	1.01§	076. (0.76–0.77)	1.04§
CCI†	0.74 (0.74–0.75)	1.03§	0.77 (0.77–0.78)	1.07§	0.74 (0.74–0.75)	1.01§	0.77 (0.77–0.77)	1.05§
ECI†	0.74 (0.74–0.75)	1.02§	0.77 (0.77–0.78)	1.07§	0.74 (0.74–0.75)	1.01§	0.78 (0.77–0.78)	1.07§
IDI								
Baseline* *vs.* DANCAMI†	0.054	-	0.079	-	0.044	-	0.061	-
Baseline* *vs.* rDANCAMI†	0.038	-	0.068	-	0.033	-	0.057	-
Baseline* *vs.* CCI†	0.038	-	0.077	-	0.034	-	0.066	-
Baseline* *vs.* ECI†	0.029	-	0.081	-	0.029	-	0.081	-
NRI								
Baseline* *vs.* DANCAMI†	0.52	-	0.68	-	0.55	-	0.72	-
Baseline* *vs.* rDANCAMI†	0.43	-	0.57	-	0.41	-	0.53	-
Baseline* *vs.* CCI†	0.41	-	0.58	-	0.46	-	0.71	-
Baseline* *vs.* ECI†	0.40	-	0.68	-	0.47	-	0.69	-

From Albertsen LW *et al.* Clin Epidemiol 2020[5]
Abbreviations: CCI, Charlson Comorbidity Index; DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhauser Comorbidity Index; rDANCAMI, DANCAMI restricted to non-cardiovascular comorbidities
*Baseline model was a Cox model that included sex and age
†Model performance was examined in a Cox model that included sex, age, and individual model scores/categories
‡Difference in R^2 relative to the baseline model
§Difference in Harrell's C relative to the baseline model

4.2. Cardiac comedication

4.2.1. Adverse drug events

4.2.1.1. Adherence to renal function monitoring and discontinuation rules after RAS blockade

Among patients that initiated an ACEI/ARB treatment, creatinine levels were not monitored in 10%, either at baseline (*i.e.*, within 12 months before initiation) or during follow-up (*i.e.*, 2 months after initiation). Moreover, 28% were monitored only at baseline, 15% were monitored only during follow-up, and 47% were monitored both at baseline and during follow-up. The median period between the most recent baseline monitoring event and drug initiation was 40 days (inter-quartile range: 12–125 days). Among the 34% of patients that had baseline creatinine monitoring within one month before initiating therapy, less than 10% also had the guideline-recommended follow-up test recorded within two weeks. One in 15 patients started ACEI/ARBs, despite a baseline potassium level above the recommended level; elevated baseline potassium was also shown

to be a strong predictor of severe post-initiation hyperkalemia. Among the monitored patients, nearly 1.5% experienced a ≥30% creatinine increase or a >6 mmol/L potassium level, and most (80%) did not discontinue therapy, despite guidelines that recommended discontinuation. Although patients with a prior MI, hypertension, or baseline potassium >5 mmol/L were at an increased risk of sudden decline in kidney function after ACEI/ARB initiation, there was no evidence that these patient groups were monitored more frequently during initiation.

4.2.1.2. Creatinine elevation after RAS blockade and cardiorenal risks

Among the 1.7% of individuals with ≥30% increases in creatinine, a higher proportion were female, older, had cardiorenal comorbidity, and used NSAIDs, loop diuretics, or potassium-sparing diuretics, compared to those with <30% increases. Creatinine increases ≥30% were associated with an increased adjusted IRR for all outcomes, compared to creatinine increases <30%. The adjusted IRRs were 3.43 (95% CI: 2.40–4.91) for end-stage renal disease, 1.46 (95% CI: 1.16–1.84) for MI, 1.37 (95% CI: 1.14–1.65) for heart failure, and 1.84 (95% CI: 1.65–2.05) for death. Examining the interaction with time since drug initiation (Figure 12), we found that the risks were highest in the first year after starting ACEI/ARB treatment, and they declined within 2 years, but residual risks of end stage renal disease, MI, and death were sustained for up to 10 years.

A more detailed categorization of creatinine increases revealed graduated effects for all outcomes, as illustrated by the survival function (Figure 13A). This function also provided the absolute 1-, 5-, and 10-year risks of death for each group. This 'dose-response' relationship also held for all outcomes, after adjusting for possible confounders (all p-values for trends <0.001; Figure 13B). Notably, creatinine increases <30% were also associated with increased IRRs for all outcomes. The IRRs of death were 1.15 (95% CI: 1.09–1.22) for increases of 10%–19%, and 1.35 (95% CI: 1.23–1.49) for increases of 20%–29%, when <10% was used as the reference. Results were consistent across calendar periods and patient subgroups, and for continuing users.

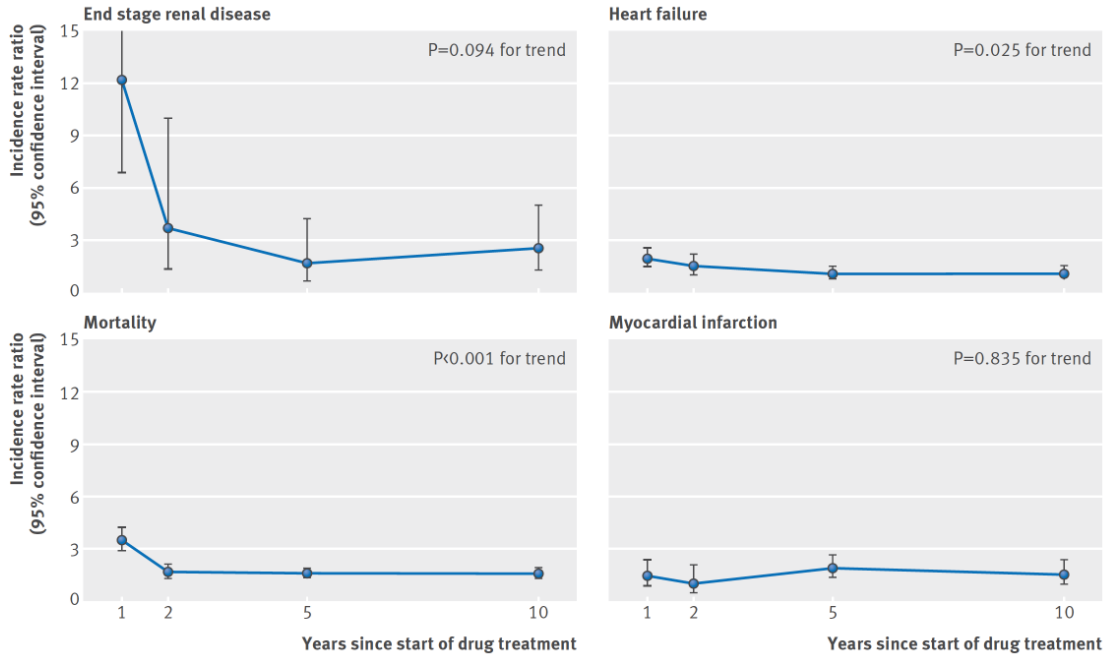


Figure 12 | Time-dependent cardiorenal risks associated with creatinine increases ≥30% after renin-angiotensin system blockade. Modified from Schmidt M *et al.* BMJ 2017[7]

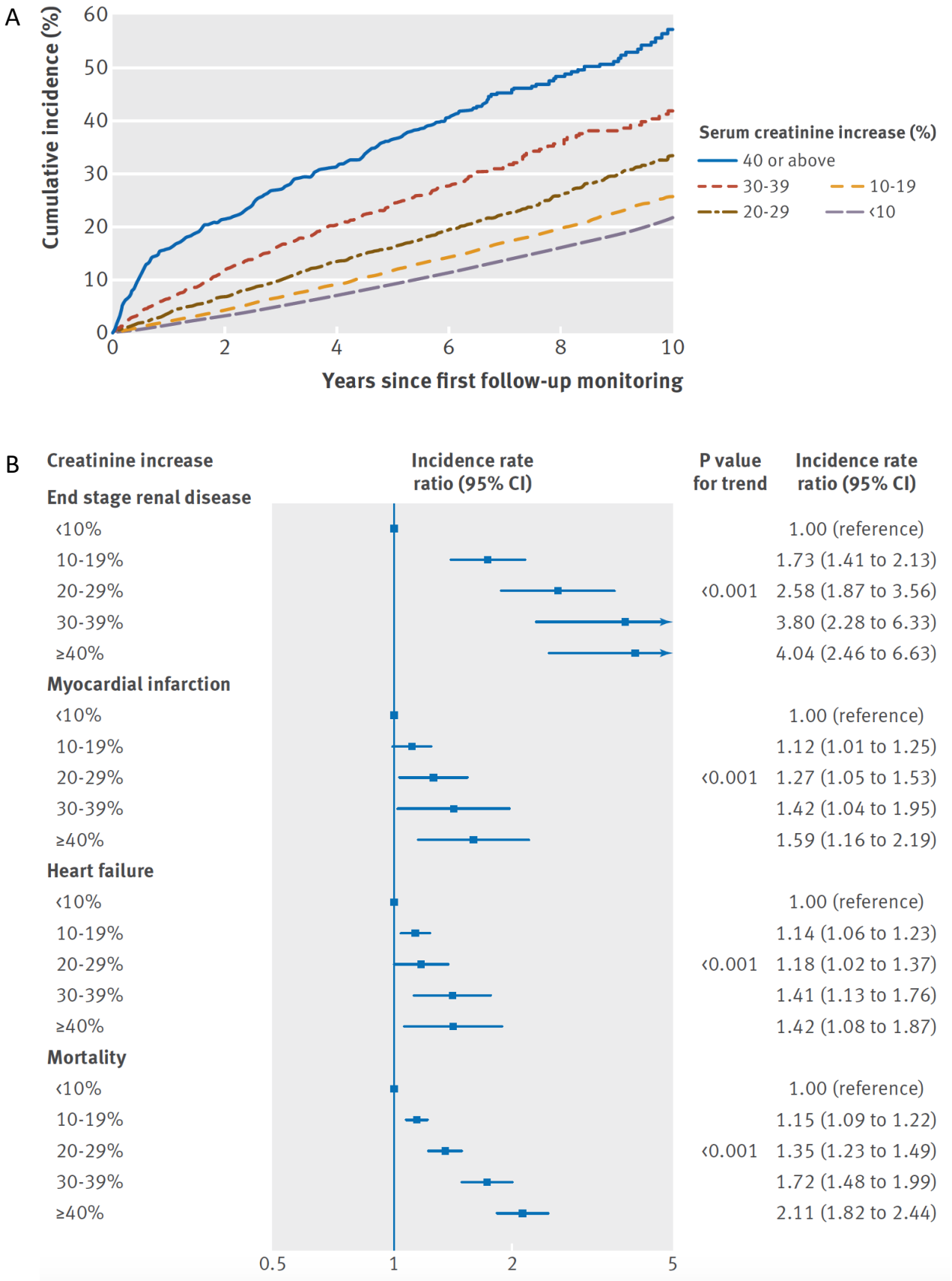


Figure 13 | Effects of creatinine increases after renin-angiotensin system blockade on (A) cumulative mortality and (B) the incidence rate ratios for the associated cardiorenal risks. Modified from Schmidt M *et al*. BMJ 2017[7]

4.2.2. Drug-drug interactions

Within 12 months after a PCI with stent implantation, 91% of patients filled prescriptions for clopidogrel and 21% filled prescriptions for PPIs. Clopidogrel use was associated with a markedly reduced rate of MACE within 12 months after a coronary stent implantation, independent of PPI use (Table 6). The use of PPIs, individually or as a class, did not substantially modify the protective effect of clopidogrel. However, PPI use was associated with an increased rate of MACE, particularly among long-term users. Thus, when PPI use was compared to non-use, the adjusted HR for MACE was 1.40 (95% CI: 1.17–1.68) among clopidogrel users and 1.16 (95% CI: 0.95–1.43) among clopidogrel non-users. Conversely, when clopidogrel use was compared to non-use, the adjusted HR for MACE was 0.57 (95% CI: 0.44–0.74) among PPI users and 0.47 (95% CI: 0.42–0.53) among PPI non-users. Thus, the relative interaction effect was 1.20 (95% CI: 0.91–1.58). Among patients that used PPIs before the PCI, the MACE rate increased by 25% compared to patients that did not previously use PPIs, independent of clopidogrel use (adjusted HR=1.24, 95% CI: 0.97–1.58 for clopidogrel users and 1.26, 95% CI: 0.97–1.63 for clopidogrel non-users). We observed similar results for other outcomes, including MI, target lesion revascularization, and cardiac death. These overall results were similar to the results observed in patient subgroups and for individual PPIs.

Table 6 | Hazard ratios for major adverse cardiovascular events* associated with clopidogrel use, compared to non-use, with (+) or without (-) concomitant use of proton pump inhibitors

Proton pump inhibitors		**Clopidogrel use**				**Unadjusted hazard ratio (95% CI)**	**Adjusted hazard ratio‡ (95% CI)**	**Interaction effect§ (95% CI)**	***p*‖**
		Number†		**Rates†**					
		Non-use	Use	Non-use	Use				
Any type¶	-	973	677	263	104	0.38 (0.34–0.42)	0.47 (0.42–0.53)		
	+	102	138	267	154	0.48 (0.37–0.63)	0.57 (0.44–0.74)	1.20 (0.91–1.58)	0.19
Esomeprazole	-	1039	759	264	108	0.39 (0.35–0.43)	0.39 (0.35–0.43)		
	+	36	56	238	153	0.50 (0.33–0.77)	0.51 (0.34–0.78)	1.32 (0.86–2.03)	0.20
Lansoprazole	-	1050	787	263	109	0.39 (0.35–0.44)	0.39 (0.35–0.44)		
	+	25	28	289	138	0.41 (0.24–0.71)	0.43 (0.25–0.74)	1.09 (0.63–1.89)	0.75
Omeprazole	-	1053	796	263	110	0.39 (0.35–0.44)	0.39 (0.36–0.44)		
	+	22	19	288	145	0.40 (0.21–0.73)	0.40 (0.21–0.73)	1.00 (0.54–1.87)	0.99
Pantoprazole	-	1056	782	264	109	0.39 (0.35–0.43)	0.39 (0.35–0.43)		
	+	19	33	254	154	0.56 (0.32–0.99)	0.57 (0.32–1.01)	1.47 (0.83–2.60)	0.19

From Schmidt M *et al*. Aliment Pharmacother. 2011[8]

*Composite of myocardial infarction, ischemic stroke, stent thrombosis, target lesion revascularization, and cardiac death, within 12 months after a coronary stent implantation.

†Numbers reflect exposure status at the time of outcome. Rates are the number of events per 1000 person years.

‡Adjusted for age, sex, diabetes, hypertension, obesity, and time-varying use of aspirin, calcium channel blockers, and statins.

§The ratio of the stratum-specific hazard ratios, which estimates the increase in hazard ratio associated with concomitant use of clopidogrel and proton pump inhibitors, beyond that expected from the independent effects of these drugs alone.

‖Based on the Wald χ^2 test for detecting "no interaction" in the model.

¶Any use of esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole.

4.3. Non-cardiac comedication

4.3.1. Diclofenac

4.3.1.1. Cardiovascular risks

Among patients that initiated diclofenac, the rate of MACE within 30 days increased by 50% compared to patients that did not initiate NSAIDs, 20% compared to those that initiated paracetamol and ibuprofen, and 30% compared to those that initiated naproxen (Figure 14A). Diclofenac initiators also showed rate increases in all MACE components, including a 20% increase in atrial fibrillations/flutters, a 60% increase in ischemic strokes, a 70% increase in heart failures and cardiac deaths, and a 90% increase in MIs, compared to NSAID non-initiators. The risk increases were similar among men and women of all ages. The IRR was more pronounced for high-dose than for low-dose diclofenac pills (although the CIs overlapped); nevertheless, the IRR also increased consistently for low-dose pills (Figure 14C).

The additional absolute annual number of MACE per 1000 patients that initiated diclofenac (the adjusted incidence rate difference) increased with the baseline risk. Thus, for patients at low, moderate, and high

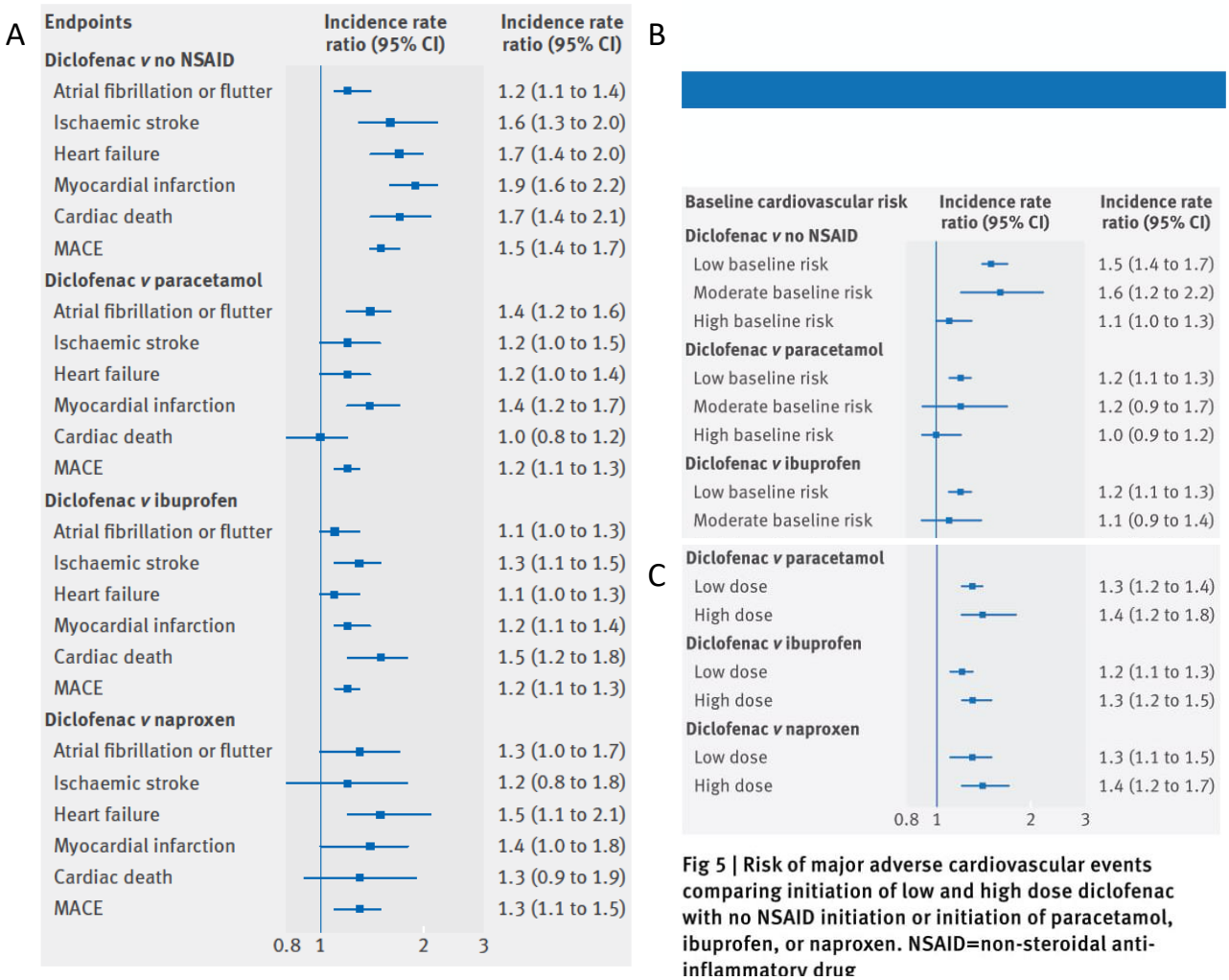


Fig 5 | Risk of major adverse cardiovascular events comparing initiation of low and high dose diclofenac with no NSAID initiation or initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug

Figure 14 | Incidence rate ratios for major adverse cardiovascular events (MACE) within 30 days after diclofenac initiation. Diclofenac is compared to paracetamol, ibuprofen, naproxen, and NSAID non-initiators, both (A) overall and according to (B) baseline cardiovascular risk and (C) pill dose. Modified from Schmidt M *et al.* BMJ 2018[9]

baseline risk, the additional MACE observed were, respectively, 1, 7, and 16, compared to those that initiated ibuprofen, 1, 7, and 10 compared to those that initiated naproxen, 3, 8, and 1 compared to those that initiated paracetamol, and 4, 14, and 39 compared to NSAID non-initiators. Although the absolute risk of MACE was highest among individuals with high baseline risk, the relative risk was highest among individuals with low or moderate baseline risk (Figure 14B). In addition, the risk of upper gastrointestinal bleeding associated with diclofenac initiation was increased by 4.5-fold compared to NSAID non-initiation, increased by 2.5-fold compared to ibuprofen and paracetamol initiation, and similar to the risk associated with naproxen initiation.

4.3.1.2. Trends and predictors of contraindicated use

The yearly prevalence of NSAID initiation after a first-time diagnosis of cardiovascular disease increased by 3.4%, from 1996 (19.4%) to 2001 (22.7%), and it declined by 2.7% from 2002 to 2017 (13.5%) (Figure 15). These trends were independent of age, sex, and the subtype of cardiovascular disease, although after 2002, larger annual declines occurred among patients with heart failure (3.9%) and ischemic heart disease (3.5%).

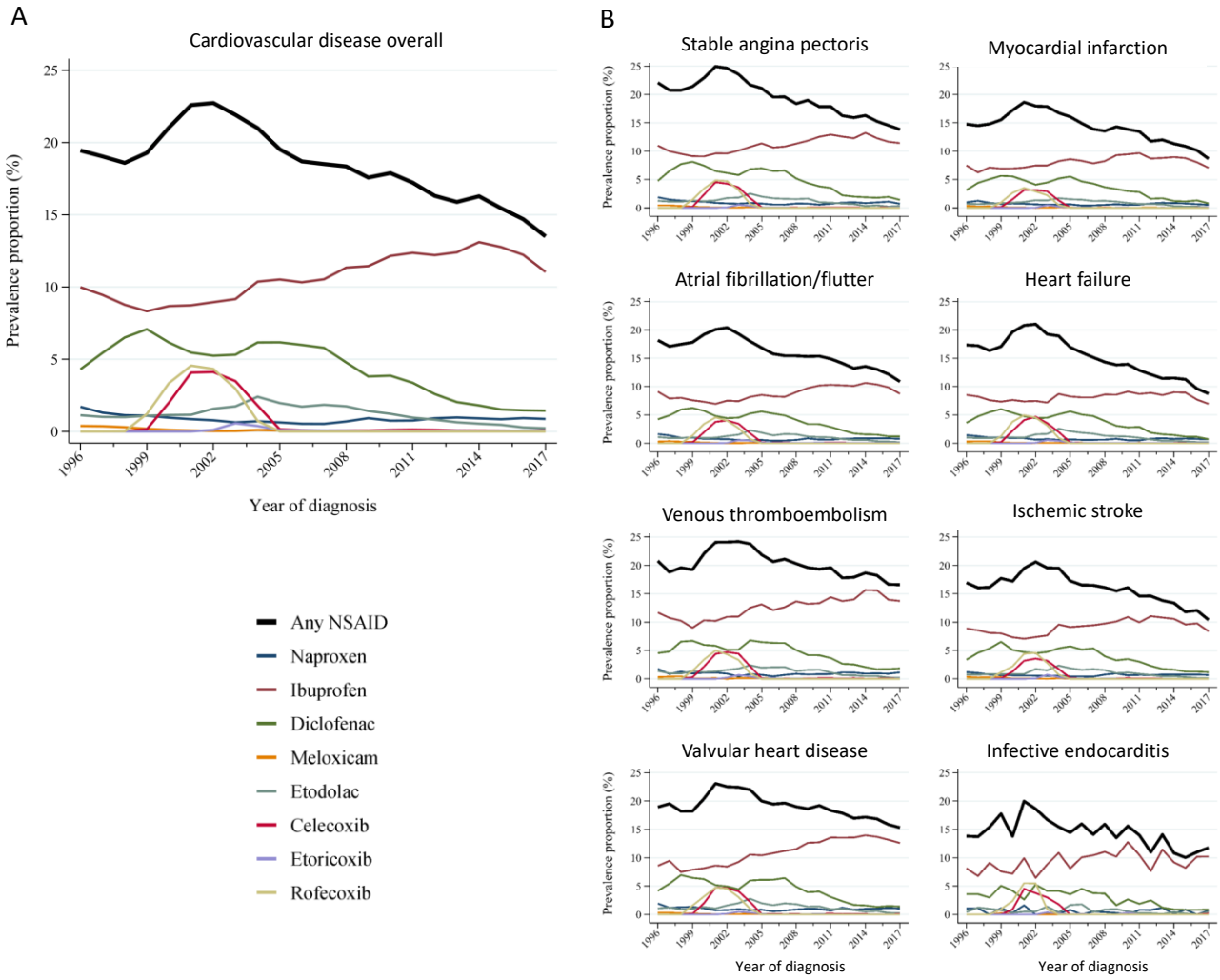


Figure 15 | Temporal trends in the one-year prevalence of non-aspirin NSAID use after a first-time diagnosis of cardiovascular disease in Denmark (1996–2017). The trends for each type of NSAID are shown for (A) cardiovascular diseases overall and (B) subgroups of patients with different cardiovascular diseases. Modified from Schmidt M *et al.* Eur Heart J Cardiovasc Pharmacother 2020[10]

In 2017, the one-year prevalence was highest among patients with VTE (16.6%) and angina (13.8%), and it was lowest among patients with ST-segment elevation MI (7.0%) and heart failure (8.8%). Patients that initiated NSAIDs were predominantly prescribed ibuprofen (59%), diclofenac (23%), and etodolac (6%). However, diclofenac and coxib use declined, and ibuprofen and naproxen use increased over time. The median prescribed dose of ibuprofen declined after 2008, from a moderate/high dose (600 mg/pill) to a low dose (400 mg/pill). The treatment duration also declined for all NSAIDs, except for celecoxib. NSAID initiation was most strongly predicted by the presence of rheumatic diseases, obesity, and pain-related conditions.

4.3.1.3. Prescriber responsibility for contraindicated use

Within one year after a first-time diagnosis of cardiovascular disease (1996–2017), 86–91% of all NSAID prescriptions were issued by general practitioners, 7.3–12% were issued by hospital prescribers, and ≤1.1% were issued by private practice specialists (Figure 16). Despite minor variations, the percentages of NSAIDs prescribed by general practitioners were consistently high for ibuprofen (84–89%), naproxen (90–93%), diclofenac (87–93%), meloxicam (77–100%), etodolac (94–97%), celecoxib (56–90%), and etoricoxib (93–100%).

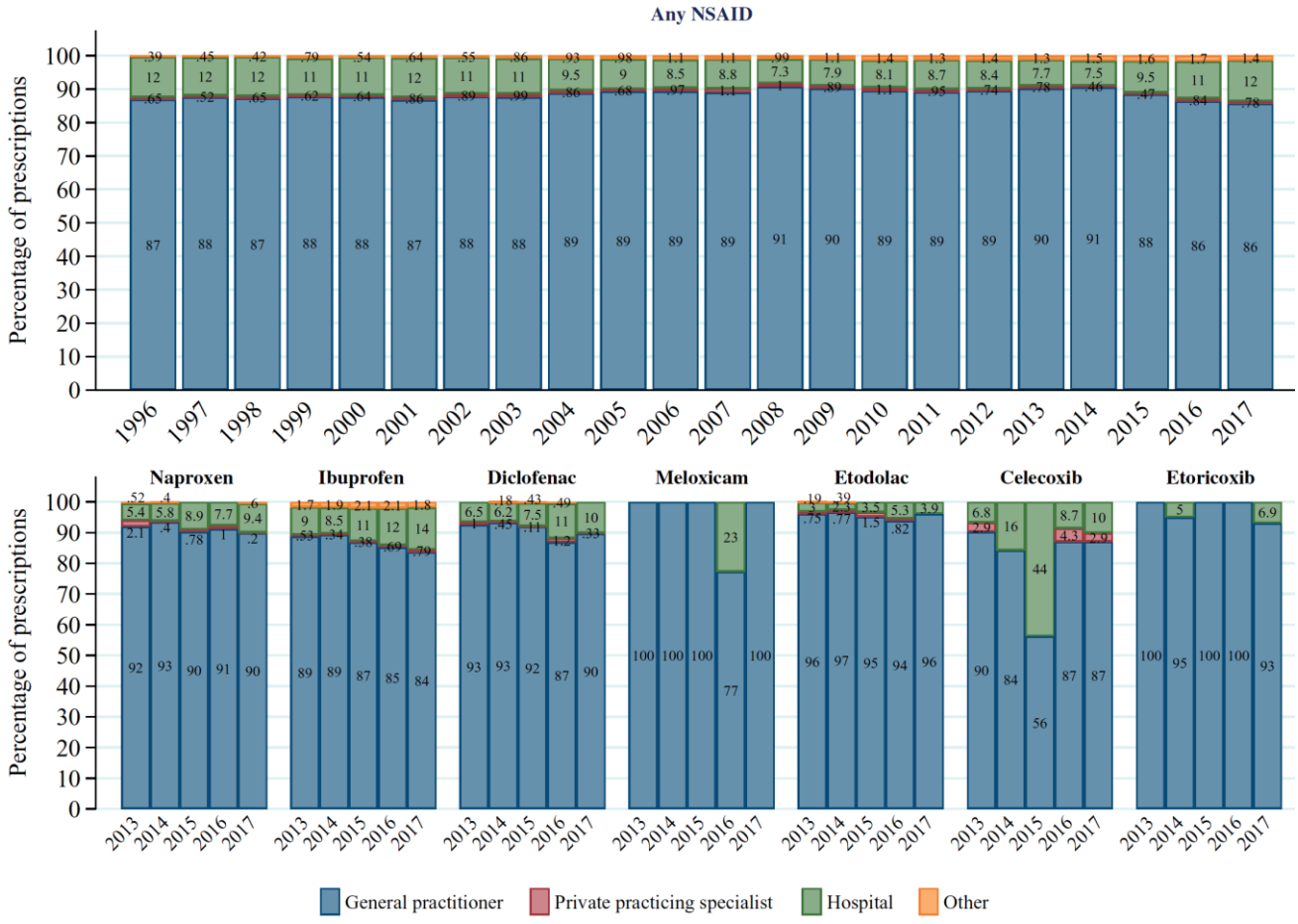


Figure 16 | Prescriber responsibility for initiating non-aspirin NSAIDs within one year after a first-time diagnosis of cardiovascular disease in Denmark (1996–2017). (*Top*) Percentage of NSAID prescriptions issued from different providers from 1996 to 2017; (*bottom*) Percentages of each type of NSAID issued by different providers from 2013 to 2017. From Schmidt M *et al*. Eur Heart J Cardiovasc Pharmacother 2020[10]

4.3.2. Novel cardiovascular risks

4.3.2.1. Atrial fibrillation/flutter

NSAID use was associated with an increased risk of atrial fibrillation/flutter (Figure 17). Notably, COX-2 inhibitors were associated with a greater increase in the risks of atrial fibrillation/flutter (adjusted IRR=1.27, 95% CI: 1.20–1.34) than non-selective NSAIDs (1.17, 95% CI: 1.10–1.24). This finding indicated a potential important pharmacological role of COX-2 inhibition. Older COX-2 inhibitors and coxibs had similar effect estimates, although diclofenac had the highest estimated effect (1.38, 95% CI: 1.27–1.50). The association between NSAID use and atrial fibrillation/flutter was strongest among new users, who showed a 40–70% relative risk increase. The IRRs among new users were lowest for non-selective NSAIDs (1.46, 95% CI: 1.33–1.62) and highest for COX-2 inhibitors (1.71, 95% CI: 1.56–1.88). The IRRs were highest among older individuals and patients with chronic kidney disease or rheumatoid arthritis. The results were robust when the evaluation was restricted to patients without systemic inflammatory conditions. The increased risks were consistent for both high-dose and low-dose pills of all individual NSAIDs. However, the effect was greater for high-dose than for low-dose pills of ibuprofen, naproxen, and diclofenac. In a direct drug comparison, with ibuprofen as reference, no NSAID had a lower associated risk than ibuprofen, and in particular, diclofenac conferred a higher risk than ibuprofen (1.19, 95% CI: 1.00–1.40).

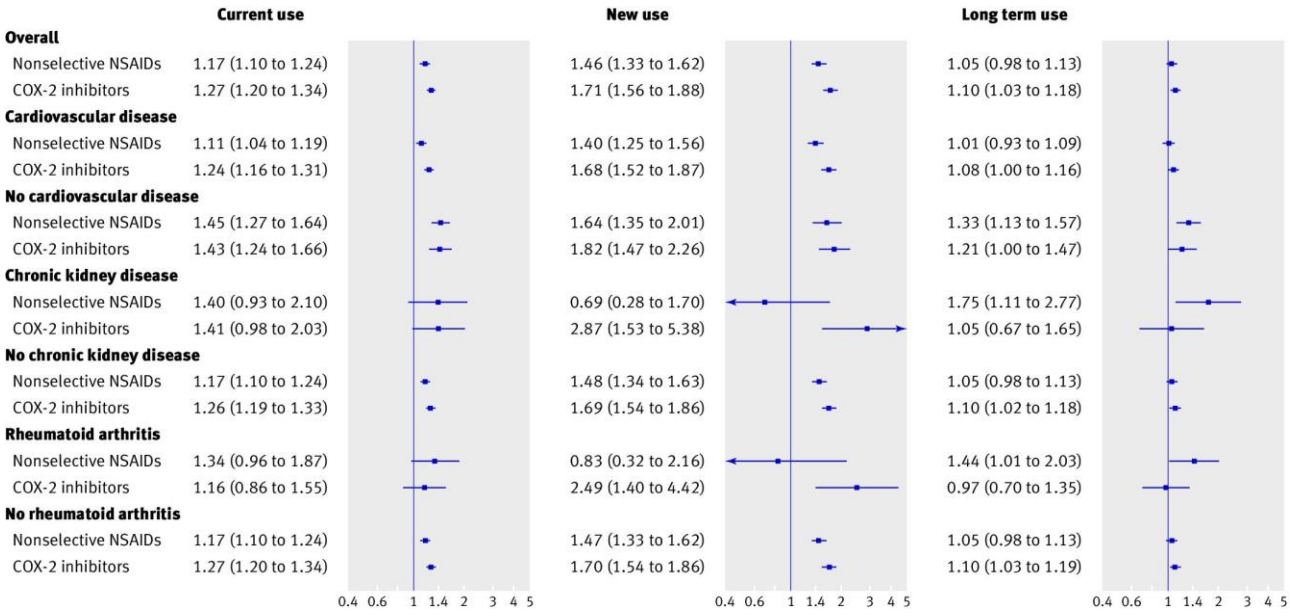


Figure 17 | Adjusted incidence rate ratios for the association between NSAID use and atrial fibrillation/flutter in patients with or without cardiovascular disease, chronic kidney disease, or rheumatoid arthritis. From Schmidt M *et al.* BMJ 2011[11]

4.3.2.2. Venous thromboembolism

NSAID use was associated with an increased rate of VTE. The adjusted IRRs for the association between non-selective NSAIDs and VTE were 2.51 (95% CI: 2.29–2.76) for current users, 4.56 (95% CI: 3.85–5.40) for new users, and 2.06 (95% CI: 1.85–2.29) for long-term users. The adjusted IRRs for the association between COX-2 inhibitors and VTE were 2.19 (95% CI: 1.99–2.41) for current users, 3.23 (95% CI: 2.69–3.89) for new users, and 1.92 (95% CI: 1.72–2.15) for long-term users. Former use of non-selective NSAIDs (IRR: 1.44,

95% CI: 1.33–1.56) and COX-2 inhibitors (IRR: 1.41, 95% CI: 1.30–1.54) were also moderately associated with an increased VTE risk. The results were consistent in subgroup analyses of the exposure (individual NSAIDs, and low-dose and high-dose pills) and outcome (unprovoked VTE, deep vein thrombosis, and pulmonary embolism). A sensitivity analysis of different exposure windows indicated that our estimates might have underestimated the true risk. Finally, we estimated that, if no increased risk between NSAIDs and VTE actually existed, our findings could only be fully explained by an unmeasured confounder that was highly prevalent (30%), that occurred four times more frequently among COX-2 inhibitor users than among non-users, and that increased the risk of VTE by a factor of 17 or more. Moreover, an even stronger confounder would be needed to explain our findings for current users of non-selective NSAIDs or for new users of either NSAID subclass.

4.3.2.3. Stroke mortality

Pre-admission use of COX-2 inhibitors was associated with an increase in the 30-day mortality following an ischemic stroke, but not a hemorrhagic stroke. Thus, the 30-day MRR for ischemic stroke was 1.14 (95% CI: 1.03–1.27) for current users of COX-2 inhibitors, and among these it was highest for new users (1.31, 95% CI: 1.13–1.52). The PS-matched analysis yielded similar results, with MRRs of 1.16 (95% CI: 1.01–1.34) for current users and 1.28 (95% CI: 1.07–1.54) for new users.

When we compared the initiation of different types of COX-2 inhibitors, we found that the increased MRR was driven by older COX-2 inhibitors (1.30, 95% CI: 1.12–1.52). Among those, the MRRs were 1.51 (95% CI: 1.16–1.98) for etodolac and 1.21 (95% CI: 1.01–1.45) for diclofenac. We observed no association between a former use of COX-2 inhibitors and ischemic stroke mortality. Moreover, the use of non-selective NSAIDs was not associated with 30-day mortality following ischemic stroke.

5. Discussion

5.1. Summary

The studies described in this dissertation examined the importance of multimorbidity — focusing on comorbidity and comedication — in relation to the risk, prognosis, and prediction of cardiovascular disease. We showed how the prevalence of comorbidity at a first-time MI, heart failure, or stroke has increased over the last three decades. In that same period, the mortality associated with these conditions declined, independent of the comorbidity burden. Nevertheless, the comorbidity burden was a strong prognostic factor for both short- and long-term mortality. We found that cardiac and non-cardiac comorbidities increased short- and long-term MI mortality beyond that explained by their additive effects. This synergistic effect suggested that these conditions interacted biologically. The interaction was dose-dependent and its magnitude was clinically important. We developed novel, contemporary comorbidity indices (DANCAMI and rDANCAMI) to assess, adjust for, and predict the impact of comorbidity on mortality, in patients with a first-time MI. The DANCAMI outperformed existing comorbidity indices, and was generalizable to MI patients in New Zealand.

The dissertation studies also examined ADEs related to common cardiac comedications. ACEIs/ARBs are common comedications in this patient group. However, an important ADE of RAS blockade is kidney impairment. Consequently, kidney function must be routinely monitored. We found that only a minority (10%) of patients received serum creatinine monitoring before and after ACEI/ARB initiation, according to unambiguous guidelines for detecting sudden renal impairment. Moreover, the vast majority (>80%) of patients with ≥30% increases in creatinine levels or a potassium level >6 mmol/L at follow-up did not discontinue treatment, according to recommendations.[225] Adding concern to this non-adherence to guidelines, we found that patients in routine clinical care that had started ACEI/ARB treatment and displayed a ≥30% increase in creatinine at the first follow-up represented a high-risk group for cardiorenal outcomes and death, compared to patients with more stable creatinine levels at follow-up.

Our studies also examined drug-drug interactions for common cardiac comedications. Clopidogrel and PPIs are medications that are commonly co-prescribed in patients with ischemic heart disease. Among patients that underwent PCI with coronary stent implantations, we found no evidence of clinically relevant drug-drug interactions between clopidogrel and PPIs.

NSAIDs are among the most commonly used classes of non-cardiac comedications. Therefore, we elucidated the cardiovascular risks associated with NSAID use. First, we outlined the cardiovascular risks associated with the most frequently prescribed older COX-2 inhibitor — diclofenac. We showed that diclofenac use increased these risks compared to non-use and also compared to the use of two active comparator drug classes, paracetamol and non-selective NSAIDs (ibuprofen and naproxen). Although NSAID use is declining, we found that it is frequently prescribed to patients after their first cardiovascular diagnosis. This finding emphasized the importance of raising the awareness of appropriate use, particularly among general practitioners, who issued 90% of NSAID prescriptions in these patients. Finally, our data suggested that the initiation of NSAIDs, particularly COX-2 inhibitors, was associated with cardiovascular risks that were not previously recognized, namely atrial fibrillation/flutter, VTE, and stroke mortality.

5.2. Internal validity

Internal validity depends on random and systematic errors.[226] By random error (or chance), we refer to the precision of the estimates.[227] By systematic errors, we refer to selection bias, information bias, and confounding.[226] Selection and information biases arise during data collection or in the study design; therefore, these biases are often difficult to correct for with statistical approaches.[226] In contrast, confounding can be controlled for by both the study design (randomization, restriction, and matching) and statistical approaches (standardization, stratification, adjustment, and quantitative bias analyses) (Table 1).[226] We discussed internal validity systematically in each publication described in this dissertation (Appendices I–X), but we will also summarize the internal validity of our studies here.

5.2.1. Random error

The precision of the associations was evaluated by the width of the CIs.[227] We interpreted the CI as a quantitative measure that indicated the magnitude of the effect and the degree of precision, rather than as a surrogate for significance tests. Thus, according to recommendations,[228] we consistently reported and discussed the point estimates (even when the CIs were wide), taking into account both the lower and upper limits of the CIs. We aimed to avoid overconfidence in the estimates, despite the high precision often achieved, by emphasizing potential systematic errors that were of concern. We deliberately chose not to dichotomize results based on statistical significance. In the exceptions, when we reported p-values (typically in tests for trends),[229] we provided sensible precision, omitted all kinds of adornments to denote statistical significance, and avoided binary inequalities, such as P <0.05 or >0.05. However, in general, we chose not to report p-values, because they are redundant for data interpretation, and they increase the risk of misinterpretation by the readers.[228]

An example of the misinterpretation of a significance test was experienced in response to study XI.[230] In that study, we reported that the use of newer COX-2 inhibitors was associated with a relative risk of 1.20 (95% CI: 1.09–1.33) for atrial fibrillation/flutter. A subsequent study by Chao *et al.*[231] reported the same association, with a relative risk of 1.20 (95% CI: 0.97–1.48). In apparent contrast to our interpretation, Chao *et al.*[231] concluded that the use of selective COX-2 inhibitors was not associated with the risk of atrial fibrillation. They further speculated on the biological mechanisms, and they mentioned that the discrepancy between our results and theirs was due to our inclusion of both atrial fibrillation and flutter, because "their detailed pathogeneses are different".[231] Nonetheless, as previously mentioned, atrial fibrillation and flutter share risk factors and some pathophysiology,[232] and our results were mainly driven by cases of atrial fibrillation (>90%). Most importantly, however, the results from the two studies did not differ materially; Chao *et al.*[231] simply misinterpreted their data by relying on statistical significance testing to make inferences. As such, a comparison of the p-value functions[227] for the associations from the two studies (Figure 18) demonstrated that the only real difference between the results of the two studies was that our data provided greater precision, which was reflected in the narrower CIs and the narrower p-value function (Figure 18). Thus, the data from Chao *et al.*[231] did not contradict our findings, but actually supported them, as shown in the meta-analysis of the two study results (Figure 18).[230]

For our primary analyses, the large number of outcomes and cases in the Danish, New Zealand, and UK cohorts ensured statistically precise estimates.[227] In general, the sample sizes were also sufficiently large to allow subgroup analyses, *e.g.*, for individual comorbidities and comedications. However, despite the unprecedented large sample sizes in some studies (*e.g.*, study IX), we had to categorize some variables (*e.g.*, NSAID tablet dose) into broader classes than preferable. Similarly, despite our large PCI cohort (n=13,001) in our drug-drug interaction study (study VIII), compared to cohorts in other studies, the precision of the estimated effects on one-year MACE did not allow us to make firm conclusions about PPI subtypes.

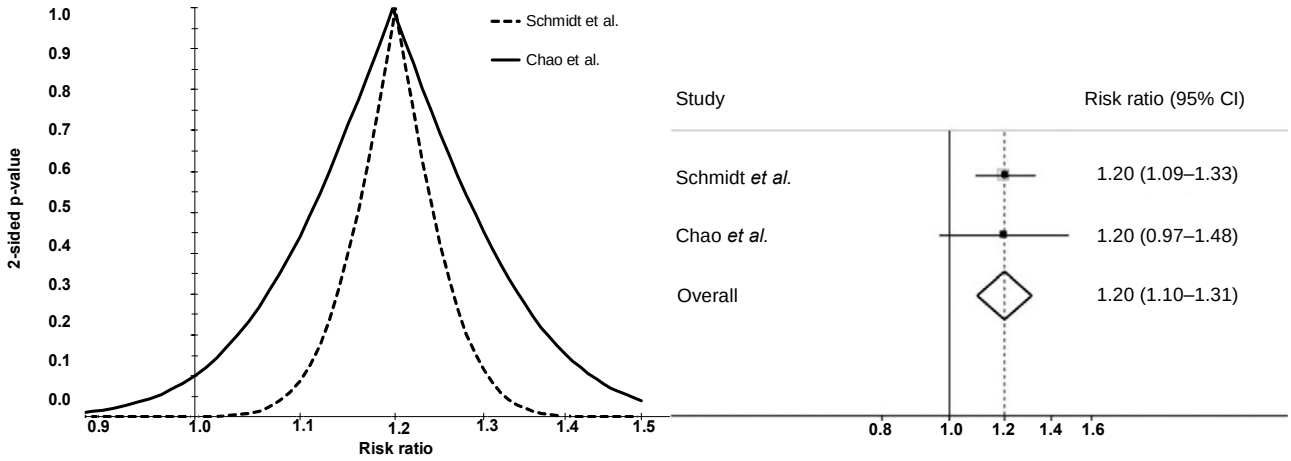


Figure 18 | P-value function and meta-analysis of the association between the use of COX-2 inhibitors and atrial fibrillation, as reported by Schmidt *et al.* BMJ. 2011[11] and Chao *et al*. Int J Cardiol. 2013.[231] (*Left*) The p-value function describes the function most compatible with the data and shows the probability of observing risk ratios at least as extreme as the results actually observed, assuming that the null hypothesis is true. (*Right*) The results of the meta-analysis show the corresponding risk ratios and summary estimate with 95% confidence intervals (CIs). Modified from Schmidt M and Rothman KJ. Int J Cardiol 2014[230]

We defined the primary outcome MACE in studies VIII–IX as a composite of several individual outcomes, because the absolute risk of some outcomes was expected to be low, due to the short follow-up period (*e.g.*, 30 days in study IX), and because there was no preferred single outcome of interest. In clinical trials, MACE is often used to increase statistical efficiency,[233] because it increases the event rate in the control group, which reduces the required sample size and the cost of a trial.[234] The inherent trade-off in using MACE as an effect estimate is that the increased precision comes at the expense of greater uncertainty in interpreting the results.[235] It is generally recommended that composite outcomes include components that are similar in severity, frequency (particularly among the most and least severe components), and treatment effect (*i.e.*, no substantial variability across components).[235] In practice, all these criteria are rarely met.[233] In our emulated trial (study IX), atrial fibrillation/flutter was a less severe, but more frequent complication than ischemic stroke and cardiac death. Composite outcomes are particularly problematic, when only one component of the composite outcome is affected, or when the direction of the effect differs across the individual components.[233] In addition to reducing the precision, in the latter scenario, a strong association with one component might be attenuated by a less strong association with another, more frequent, component.[233] Therefore, in the interest of transparency, we reported on the individual components separately and found no evidence that the null result

was due to heterogeneous treatment effects. Of note, we defined MACE as major adverse *cardiovascular* events and not solely *cardiac* events. Thus, we included ischemic stroke in the definition to acknowledge its importance as a thromboembolic complication of therapy. Our definition of MACE therefore corresponded well to another frequently used term: major adverse cardiac and cerebral events (MACCE).

5.2.2. Systematic errors

5.2.2.1. Selection bias

We evaluated selection bias in terms of the systematic error associated with the selection of study participants according to exposure status, in cohort studies, or according to case or control status, in case-control studies.[226] A selection bias arises when the association between exposure and outcome is different between study participants and non-participants.[226] However, this association among non-participants is rarely known; consequently, selection bias cannot be observed, it must be inferred.[226]

In the setting of the tax-supported universal healthcare systems in Denmark, New Zealand, and the UK, our population-based study designs largely removed selection biases that stemmed from the selective inclusion of specific hospitals, health insurance systems, or age groups.[182] We had nationwide coverage in New Zealand (study V) and either nationwide (studies I–IV, IX, X, and XIII) or representative regional[236] (studies V, XI, and XII) coverage in Denmark. Although the CPRD only covered 7% of the UK population, patients included in the CPRD (studies VI and VII) were largely representative of the UK population, in terms of age, sex, and ethnicity.[196] Of note, a potential limitation was that the Danish National Patient Registry did not include patients that experienced a sudden cardiac death outside a hospital or an ambulance, or patients that did not receive a resuscitation attempt in the emergency room.[182] To address this limitation, we performed a time-course comparison of the proportion of patients with an MI recorded as the cause of death in the Danish Registry of Causes of Death to the proportion of patients without a previous MI recorded in the Danish National Patient Registry.[1] This supplementary analysis revealed that the proportion of MIs missing from the Danish National Patient Registry could not account for the observed incidence and mortality trends.[1] We could accurately account for censoring, due to death or emigration, in Denmark, through the Danish Civil Registration System,[192] in New Zealand, through the National Mortality Collection,[194] and in the UK, through the CPRD.[196] In the UK, emigration was addressed by censoring at withdrawal from the general practice unit.[237]

5.2.2.2. Information bias

Information bias occurs when exposure or outcome data are measured erroneously (misclassified).[226] Differential misclassification occurs when misclassified exposure or outcome data depends on the presence of its counterpart. The direction of bias due to differential misclassification is particularly concerning, because it is less predictable.[226] Because information on hospital diagnoses, drug use, and confounding factors were collected prospectively, we avoided reliance upon self-reporting, which reduced the potential of differential misclassification due to recall bias.[226]

Misclassification of exposure is non-differential, when it is independent of the outcome (and vice versa). Non-differential misclassification most often biases the results towards the null hypothesis.[226] However, when the misclassification depends on misclassification of other variables, or when the exposure or disease variable

has more than two levels, then non-differential misclassification might introduce bias against the null hypothesis.[226] Overall, it was unlikely that coding errors in hospital diagnoses and death had an important influence on our results. For example, non-differential misclassification of coding errors could not explain results that were not neutral.

Below, we discuss the potential for misclassifications of drug use (exposure in studies VI–XIII), laboratory data (studies VI and VII), hospital diagnoses (study cohorts in studies I–V, X, and XIII; exposures in studies I–V; and outcomes in studies VII–XII), cardiac death (outcome in studies VIII and IX), and all-cause mortality (a censoring event in all studies, and outcome in studies I–V, VII, and XIII).

Misclassification of drug use

The data in Denmark's prescription databases are virtually complete; they only lack in-hospital and OTC medication use.[184] Because the prescription data were prospectively recorded, any misclassifications of cardiac and noncardiac comedication use, due to 'as-needed' prescriptions, non-adherence, or OTC use, were likely non-differential. This implies that the effect estimates for current users may be underestimates.[111] However, in the studies on *novel cardiovascular risks*, we categorized NSAID use into three exposure levels (non-use, former use, and current use); consequently, a non-differential misclassification between current and former NSAID use could potentially have introduced a bias in the effect estimates for former users against the null hypothesis.[226]

Drug use was identified from actual pharmacy dispensations, for which patients paid a portion of the cost; thus, we did not rely on written prescriptions alone (except in the UK). Although we used prescriptions as a proxy for actual use, the intended beneficial effects of cardiac drugs, PPIs, and NSAIDs on a wide range of symptoms increased the likelihood of adherence among chronic users.

In the drug-drug interaction study (study VIII), we computed the number of days exposed, based on the number of days a medication supply lasted (these drugs were typically prescribed as one pill per day). This approach increased the accuracy of exposure information. We also accounted for variations in patient adherence behavior by allowing up to 7-day gaps between prescription refills.[238] Finally, with our time-varying drug assessment, we avoided the assumption that patients adhered to the medication for the entire recommended treatment period. These methods of defining exposure reduced the likelihood of nondifferential misclassification.[239]

We lacked information on the OTC use of NSAIDs. The only OTC non-aspirin NSAIDs available in Denmark were diclofenac, which was available during a short period (July 16, 2007 to December 14, 2008), and ibuprofen, which was supplied in 200-mg pills (since 27 March 1989).[111] Moreover, OTC sales of ibuprofen have been restricted over time; they were only available to individuals aged ≥18 years (since 2011), at a maximum of one package per person per day (since 2011), and package sizes could only contain a maximum of 20 pills (since 2013).[111] Due to these OTC restrictions and the reimbursement scheme for prescriptions through the Danish National Health Service's insurance program, regular NSAID users were motivated, both through practical and economic incentives, to obtain these drugs by prescription. Indeed, OTC use has been far less common in Denmark than in many other countries.[111] Therefore, the potential for identifying NSAID use based on Danish prescription registries was relatively high: we captured 66–70% of

the total ibuprofen sales during 2000–2013, and that proportion increased to 85% in 2018; moreover, we captured virtually all sales of other NSAIDs.[111] Finally, we previously showed that the magnitude of misclassification bias due to OTC ibuprofen use could not substantially impact the relative risk estimate, unless the relative risk estimate was very high, which was not the case in any of our studies.[111]

Misclassification of cardiovascular diagnoses and procedures

The hospital registries include discharge diagnoses, not admission diagnoses. However, the positive predictive values (PPVs) of cardiovascular diagnoses, examinations, procedures, and surgeries registered in the Danish National Patient Registry were previously validated and found adequate, with medical record review as the reference. The PPVs were approximately 92–100% for MI,[183,207] 75–90% for VTE,[183,207] 93–97% for atrial fibrillation,[183,207] 97% for ischemic stroke,[240] 74% for intracerebral hemorrhage,[240] 98% for examinations,[241] 98% for procedures,[241] and 99% for cardiac surgery.[241] We classified unspecified strokes as ischemic strokes, which inevitably misclassified some intracerebral hemorrhages (approximately 6%) as ischemic strokes.[240] Given the lack of association between NSAID use and mortality due to intracerebral hemorrhage, this misclassification would only bias the results for ischemic stroke towards the null hypothesis, and thus, it could not explain our findings. Misclassification were also unavoidable in studies IX–XI, due to their inability to distinguish among paroxysmal, persistent, and permanent atrial fibrillation. However, in study XI, we restricted atrial fibrillation cases to patients treated with cardioversion within one year after a first diagnosis; thus, to some extent, NSAID use was related to disease severity. In study VIII, the individual components of MACE, including cardiac death, were adjudicated by a specialist committee and considered accurate.[242,243] Cardiac death diagnoses based on the Danish Registry of Causes of Death[191] lacked adjudication (study IX), and thus, they were considered less valid. However, that misclassification was unlikely to be associated with prior NSAID use, and hence, it was considered nondifferential. The all-cause mortality data were accurate.[192]

In New Zealand, validation studies are rare. A validation study from 1987 reported a sensitivity of 86% and a PPV of 67% for an MI in discharge diagnosis data.[244] A recent validation study, based on the All New Zealand Acute Coronary Syndrome Quality Improvement (ANZACS-QI) as reference, also supported the validity and completeness of MI discharge diagnosis data.[245] The universal tax-supported healthcare systems ensured that MI treatment was organized at public hospitals; this was an important reason for the high completeness of MI diagnoses in all three countries.[182,244,246] Moreover, the mortality data were considered accurate and complete.[247]

In the UK, the validity of MI diagnoses was also consistently high, with PPVs of 92–93%, in both the CPRD and HES.[246,248] Heart failure, end-stage renal disease, and mortality have not been validated individually in the UK. However, the diagnoses recorded in the CPRD, particularly in the domains assessed by the Quality and Outcomes Framework,[249,250] were generally considered to be adequately valid for research purposes; the overall median proportion of cases with a confirmed diagnosis was 89%.[237,251]

Misclassification of comorbidity

The overall PPV was 98% for the comorbidities included in the CCI.[252] As suggested for patients with stable angina pectoris,[73] the CCI could be even more appropriate for patients with MI by assigning greater weights

to some diseases (*e.g.*, liver and renal disease) and omitting others that lacked prognostic significance (*e.g.*, connective tissue disease) or showed low prevalence (*e.g.*, hemiplegia, leukemia, and AIDS) among patients with MIs.[73,253] Despite these limitations, we used the CCI (prior to our development of the DANCAMI), because it was proven acceptable for measuring the prognostic impact of the total comorbidity burden in patients with ischemic heart disease, heart failure, and stroke.[61] In contrast to a full hospital discharge history, our fixed look-back periods, between 5–15 years, eliminated the risk of left-censoring before 1977 and reduced nondifferential misclassification by ensuring similar comorbidity histories between the comparison groups.[254] To avoid including complications caused by the index diseases (studies I–III), we excluded secondary diagnoses that were coded during the index admission.

The sensitivity of the comorbidity burden measured with the CCI has not been examined, but it is expected to be lower than its specificity. In developing the DANCAMI, we examined a larger spectrum of potential predictive comorbidities for inclusion in our comorbidity index, including psychiatric diseases. Therefore, the DANCAMI is likely to show higher sensitivity than the CCI in a contemporary cohort of Danish patients with MI.

5.2.2.3. Confounding

We defined confounding as the lack of exchangeability, which arises in situations where the effect of the exposure disease/drug is mixed with the effect of another variable.[255] A confounder must be an independent cause or a proxy/marker for the cause, imbalanced across exposure categories, and not on the causal pathway between exposure and the study outcomes.[226] As previously mentioned, we aimed to reduce potential confounding in both the design and analysis phases of our etiological study designs. Individual study approaches that we implemented to deal with confounding are summarized in Table 1. Due to the non-randomized designs, we note that potential residual confounding (due to imperfect measurement) and unmeasured confounding could not be excluded. Here, we discuss issues of particular concern.

In studies I–V, we identified individual comorbidities, and categorized comorbidity burden using comorbidity indices. We did not have data to compute patient complexity measures.[43,44] In particular, we did not have data on socioeconomic status. Socioeconomic status is a well-established risk factor for multimorbidity[256] and mortality.[37] Whether it could have influenced the association or interaction between comorbidity and cardiovascular mortality in studies I–IV remains to be investigated.

In study VII, patients that showed the greatest falls in renal function after starting ACEI/ARB treatment had a higher proportion of comorbidities and used more concurrent drugs that were associated with adverse renal outcomes. However, our findings were robust, after adjusting for a range of potential confounders, including comorbidity, comedication use, lifestyle factors, and socioeconomic status. Among the potential unmeasured confounders, we could not adjust for proteinuria, due to incomplete recording. However, to explain our results, the degree of proteinuria would have had to be positively associated with the degree that creatinine concentrations increased after starting ACEI/ARB treatment. We found no evidence of this association. In addition, the effect estimates were similar in analyses restricted to patients with diabetes, a disease associated with substantial urinary protein excretion. Nevertheless, residual or unmeasured confounding could not be excluded. This concern was also reflected in responses to our paper,[257,258] and why

we stressed that it was not clear whether increases in creatinine values after the start of ACEI/ARB treatment were due to pathophysiological processes, representing a biomarker of increased risk, or whether a direct causal relation exists between reduced renal function and adverse outcomes.[7] Therefore, the results identified a group of patients at high risk of adverse outcomes, but they did not necessarily support the discontinuation of ACEI/ARB treatment.[7] The concern of premature discontinuation related particularly to patients with heart failure with reduced ejection fraction. In these patients, ACEI/ARB therapy has a well-documented, life-prolonging effect, and declines in renal function might actually be caused by decompensated heart failure due to venous congestion and fluid overload.[259] Thus, the adverse outcomes associated with creatinine elevations among patients that initiated ACEI/ARB require further investigation. Optimally, RCTs should enroll patient populations that are more generalizable to clinical practice to facilitate a separation between drug effects and patient frailty.

In study VIII, confounding may have played an important role in identifying PPI-associated cardiovascular risks. The apparent increase in risk associated with PPI use was likely due to the characteristics of the patients studied.[260] In Denmark, PPIs are prescribed mainly for clear indications, such as peptic ulcer disease or gastroesophageal reflux disease. They are not routinely prescribed in combination with dual antiplatelet therapy. However, previous studies have shown that PPI users tended to be more obese, smoke more frequently, and have more comorbidities than PPI nonusers.[261] Therefore, the identified PPI-associated risks may reflect confounding, due to unmeasured variables (such as smoking, alcohol use, body mass index, or other cardiovascular risk factors that are not routinely recorded in registry data), or residual confounding, due to imperfectly measured variables (such as diabetes, hypertension, or obesity). Thus, it is important to note that the cardiovascular risks associated with PPI use most likely do not reflect a direct drug effect.

In all our NSAID studies (studies IX–XIII), we adjusted indirectly for unmeasured lifestyle factors, by controlling for hospital-diagnosed chronic obstructive pulmonary disease, obesity, and ischemic heart disease. Additionally, the quantitative bias analyses in studies XI and XII indicated that the results could not easily be explained by a single unmeasured confounder, even if it had a strong effect. Moreover, the prescription registries did not contain information on indications for NSAID use; therefore, confounding by indication was a general concern in all our NSAID studies. We addressed confounding by indication, as outlined below, using active NSAID comparators, comparing effect estimates of current *vs*. former use, and excluding patients with inflammatory diseases of particular concern in sensitivity analyses.[262]

In study IX, the fairly equal distribution of measured covariables among the NSAID groups increased the likelihood that unmeasured variables would also be equally distributed. Confounding by indication was not a concern in the active NSAID comparisons, due to the shared indications for the use of traditional NSAIDs. This was a major strength of our emulated trial design. Moreover, the consistency in both direction and magnitude between our point estimates and those of previous meta-analyses of both trial and observational data was reassuring,[117,127] not least, because our precision was also higher than the precision of those studies.[117] Thus, the Coxib and traditional NSAID Trialists' Collaboration meta-analysis of diclofenac use *vs.* placebo or no use found IRRs of 1.85 (95% CI: 1.17–2.94) for heart failure (in our study 1.7, 95% CI: 1.4–2.0), 1.70 (95% CI: 1.19–2.41) for MI (in our study 1.9, 95% CI: 1.6–2.2), 1.65 (95% CI: 0.95–2.85) for cardiac death (in our study 1.7, 95% CI: 1.4–2.1), and 1.41 (95% CI: 1.12–1.78) for MACE (in our study 1.5, 95% CI: 1.4–1.7).[117]

In study XI, we lacked data on underlying inflammatory conditions that could lead to NSAID use. These conditions could increase the risk of atrial fibrillation; therefore, we could not rule out the possibility that new users might have had more severe underlying inflammatory conditions, compared to long-term users (*i.e.*, confounding by indication). However, former use (a marker of confounding by indication) was not associated with the outcome, which indicated that the effect was due to current use. Moreover, the effect estimates did not change, when we excluded patients with systemic inflammatory conditions, *e.g.*, rheumatoid arthritis.

In study XII, we lacked data on the use of oral contraceptives, body size, and immobilization.[263] Because NSAID use was associated with VTE among both men and women, oral contraceptives were unlikely to have confounded the effect estimates substantially. We found an association between former use and VTE occurrence, but the association was much weaker than the association between current use and VTE, which indicated an actual drug effect of current use. The direct comparisons between VTE risk and the individual NSAIDs, with ibuprofen as the reference, likely reduced confounding by indication. The increased risk among long-term users was of particular importance, because the longer use period should have eliminated any protopathic bias, *i.e.* the association between new NSAID use and prodromal symptoms related to an incipient VTE occurrence.[264] It remains unclear to what extent our results might have been influenced by physical limitations in mobility, due to, for example, lower back pain or chronic disease.

In study XIII, we observed a balance in the measured variables between users and nonusers, after PS matching.[213] Slight differences in the estimates between the PS-matched analyses and the multivariable outcome model might have been influenced, in part, by the exclusions due to matching and any potential treatment heterogeneity (the PS-matched analysis estimated the average treatment effect in the treated group).[265] It should be noted that matching on the PS could result in an imbalance of unmeasured variables, such as smoking or body weight, between treated and untreated subjects (for variables unrelated to the covariables included in the PS calculation).[213] Nevertheless, the agreement between these two approaches supported the robustness of our findings.

5.3. External validity

Assuming that systematic and random errors were negligible, our results would most likely be generalizable to similar populations. We note that representativeness is not a prerequisite for generalizability.[266,267] Thus, valid scientific generalization does not require study subjects to constitute a representative sample of a target population.[266,267] However, a different distribution of potential effect modifiers (*e.g.*, lifestyle, socioeconomic status, and treatment regimens) in other target populations might limit extrapolation of our results. The Danish population is homogenous, regarding ethnicity: the vast majority of the population is of Scandinavian and European ancestry. Therefore, our relative estimates of association are likely to be applicable to similar ethnic groups; however, to the extent that ethnicity acts as an effect modifier (as observed in DANCAMI), they might not be applicable to non-European ethnicities.

5.4. Contributions to the advancement of science

Validated measures that quantify the overall contributions made to the advancement of science by a dissertation are lacking. The 2019 Journal Impact Factor ranged between 2.3 and 30 for the studies in this dissertation (average=14). Quantitative measures, however, have limitations. For example, because the studies described in this dissertation were published over a 10-year period (2011–2020), cumulated paper citations would underestimate the influence of recent work. As a consequence, a more qualitative assessment is needed.

Table 7 | Contributions to the advancement of science

Impact on research methodology	• Development and validation of new comorbidity indices o DANCAMI (including cardiovascular and non-cardiovascular comorbidities) o rDANCAMI (restricted to non-cardiovascular comorbidities) • Application of new study designs in cardiovascular epidemiology o Disease-disease interaction models (additive scale) o Renal function models (based on laboratory data) o Drug-drug interaction models (multiplicative scale) o Emulated trial design (based on Danish population-based data) o Prescriber responsibility (based on prescription data) • Application of new statistical methods in cardiovascular epidemiology o Rule-out approach to quantify the influence of an unmeasured confounder o Probabilistic bias analysis to control for an unmeasured confounder o Interpretation of significance testing • Underlying methodological advances o Registry reviews (research potential of key Danish registries) o Variable validation (cardiovascular diagnoses, examinations, and procedures)
Impact on clinical practice	• Insights into how multimorbidity affects cardiovascular disease o Comorbidity: Prognostic impact of comorbidity on cardiovascular diseases o Cardiac comedication: Adverse drug events and drug-drug interactions o Non-aspirin NSAIDs: Trends in use, prescriber responsibility, predictors for initiation, and associated cardiovascular risks • Medical education o Textbook curriculum in medical school in Denmark • Clinical guidelines o National and international guidelines o Position papers from the Danish and European Societies of Cardiology
Impact on regulatory actions	• Actions against drugs with adverse cardiovascular side effects o Withdrawal of over-the-counter diclofenac in Sweden in 2020 o Withdrawal of over-the-counter diclofenac in Norway in 2020

Abbreviations: DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction; NSAID, nonsteroidal anti-inflammatory drug

Contributions to science can be made at different levels. At the research level, advances in research methodology are important for the field of research in general. At the patient level, the importance of the individual study findings are reflected by their impact on clinical recommendations. Finally, at the population level, health authority regulations indicate study findings of not only clinical, but also public health importance. The following sections will summarize how I, through the studies described in this dissertation, have contributed to the advancement of science. This contribution will be detailed according to its impact on research methodology, clinical practice, and regulatory actions (Table 7).

5.4.1. Impact on research methodology

Studies I–V contributed important insights into the adverse prognostic effect of comorbidity in patients with cardiovascular disease by covering 3 out of 4 of the PROGRESS framework classification of prognostic studies (Figure 1).[200] Studies IV and V were particularly innovative. Study IV pioneered, by its design, in the estimation of biological interaction between comorbidity and MI. The development of the DANCAMI in study V represented af turning point away from older, one-fits-all comorbididty indices, towards contemporary comorbidity indices developed specifically for cardiovascular disease with clinical-influenced variable selection. The external validation in New Zealand supported the generalizability of DANCAMI to MI patients in other countries as well. Improving the measure of comorbidity burden in patients with MI by using the DANCAMI indices will provide better adjustments for cardiovascular and/or non-cardiovascular comorbidities in future MI prognosis studies. The methods developed in studies I–V have overall paved the way for future studies on risk, interaction, and prediction of comorbidity-associated cardiovascular mortality.

Studies VI–VII established renal function models based on laboratory data from general practices in the UK. The format of the laboratory data (*e.g.*, repeated measurements) necessitated new statistical approaches. The lack of general practice data and limited laboratory data at the time prevented the studies from being conducted in Denmark.

Study VIII provided the first adequately-designed study to examine the potential drug-drug interaction between clopidogrel and PPI. With this study design, the one major limitation of all previous studies was adressed,[268-276] *i.e.*, the inability to quantify the isolated interaction effect on clinical outcomes. Although well-described in the epidemiological literature,[219] this approach to interaction was unknown to most clinical journals; thus, the majority of the studies on the clopidogrel-PPI interaction, including meta-analyses, had limited validity.[277] The finding that PPI use *vs.* no PPI use was associated with an increased rate of MACE among clopidogrel users confirmed previous findings,[278-280] but important evidence was added to show that the cardiovascular risks associated with PPI use were independent of clopidogrel use. Other methodological advances in this study included the use of probabilistic bias analysis to control for unmeasured confounders in summary estimates of the PPI-clopidogrel association[281] The developed methodology was subsequently also applied to investigate the potential interactions between clopidogrel and calcium channel blockers[282] and between clopidogrel and lipophilic statins.[283]

Study IX introduced the emulated trial design in Denmark and was as such considered cutting edge. Moreover, the refinement of the emulated trial design to include active drug comparisons, particularly between

different NSAID types, was clinically important.[9] This design may undergo further refinement in the future, but in general, it is applicable to a vast number of pharmaco-epidemiological studies on both short- and long-term drug effects in Denmark.

Study X was the first to examine temporal trends in the use and dosing of NSAIDs in patients with cardiovascular disease. The potential use of prescriber variables in the prescription registries remains unknown to most pharmacoepidemiologists in Denmark.[206] This study was the first to use this information to shed light on the clinically important aspect of prescriber responsibility for contraindicated NSAID use.

Studies XI–XIII were among the first in the field of cardiovascular epidemiology to apply a rule-out approach to quantify the influence of unmeasured confounding.[214] Based on study XI, I also demonstrated how misinterpretation of significance tests can lead to faulty statistical inference.[230] Although this example is only one of many on this topic since 1978,[284] it nonetheless served as the key example in a Nature commentary entitled "Retire statistical significance",[228] which received unprecedented attention in the research society (Almetric score >12,900). Thus, this contribution helped convey the important message of how to interpret significance testing and p-values.

Finally, although studies I–XIII represent the core work of this dissertation, it should be acknowledged that underlying methodological studies, such as registry reviews[18,111,182-184,186,187,190,192,285,286] and validation studies,[158,190,207,241,286-290] also indirectly contributed to the methodological advances arising from this dissertation.

5.4.2. Impact on clinical practice

Guidelines for managing comorbidity according to the cardiovascular index disease are rare. The importance of comorbidity is acknowledged and, to some degree, included in the European Society of Cardiology guidelines on acute and chronic heart failure.[291] However, comorbidity is only sparsely mentioned in the guidelines for acute coronary syndromes[292] and is highlighted as a knowledge gap for chronic coronary syndromes.[293] Studies I–V added evidence to the influence of comorbidities on cardiovascular disease risk and prognosis. The findings highlighted the clinical importance of identifying and treating both cardiovascular and non-cardiovascular comorbidities, in addition to the index disease. The results of study I have also been included in the leading Danish textbook in internal medicine (in Danish: Medicinsk Kompendium), which forms part of the Danish medical school curriculum.

Studies VI–VII documented a concerning lack of adherence to guidelines for creatinine monitoring and treatment discontinuation after RAS blockade. These findings prompt regular follow-up monitoring to ensure the implementation of guidelines in clinical practice. The study VIII on drug-drug interactions between clopidogrel and PPIs contributed to the accumulated evidence against a clinically important interaction. Hence, there is no need to warn against the concomitant use of these drugs.

The NSAID results have been implemented in various guidelines, position papers, and reviews. Study IX has been cited in reference to the adverse cardiovascular risks of NSAIDs in UpToDate,[294] and it is expected to influence upcoming recommendations from the EMA and US Food and Drug administration.[124] The studies XI and XII are referenced in the national clinical guidelines from the Danish Society of Cardiology[295] and in

reviews published in Danish[296] and international medical journals.[118,297] Study XI has also been cited in position papers published by the Danish[298] and European[118] Societies of Cardiology, UpToDate,[294] and the Danish Pharmaceutical Information (in Danish: Dansk Lægemiddel Information).[299] Highlighting the contribution to the field overall, I also first-authored the current position papers from the Danish[298] and European[118] Societies of Cardiology and the most recent review in the Danish Medical Journal.[296] Overall, the data supported the current recommendations that selective COX-2 inhibitors, particularly diclofenac, should be contraindicated in patients with or at high risk of cardiovascular disease.[118] Study X underlined the importance of these findings and call for follow-up studies to monitor whether the prevalence of NSAID use, particularly COX-2 inhibitors, declines further in patients with cardiovascular contraindications. Study X also elucidated the role of general practitioners in inappropriate NSAID prescribing and call for attention to whether general practitioners succeed in reducing NSAID prescriptions to patients with cardiovascular disease.

Finally, it should be acknowledged that numerous follow-up papers to studies I–XIII expanded the evidence base further within the areas of comorbidity,[300-304] cardiac comedication,[158] drug-drug interactions,[282,283] NSAIDs,[111,118,126,230,298,305] cardiovascular disease trends.[19,306,307]

5.4.3. Impact on regulatory actions

Following our publications on the cardiovascular risks of diclofenac (study IX), we studied the differences in NSAID utilization among the Nordic countries.[126] Surprisingly, the use of diclofenac varied considerably across countries. Diclofenac use declined after 2008 in all countries, but in Norway, it remained the most widely prescribed NSAID in 2016 with 63 prescription users/1000 inhabitants,. Moreover, the total sales (including OTC) remained high in Iceland, Norway, and Sweden, with defined daily doses/1000 inhabitants/day of 13, 8.1, and 7.8, respectively.[126] We considered the persistent high use of diclofenac in Iceland, Norway, and Sweden and the OTC availability of diclofenac in Norway and Sweden a cardiovascular health concern. We communicated this concern to the respective medical agencies. With direct reference to study IX, the Norwegian[308] and Swedish[309] medical agencies subsequently announced the withdrawal of OTC diclofenac during 2020. In addition to these announced regulatory actions, Table 8 and Figure 4 provide updated historic timelines of OTC NSAID sales in the Nordic countries.[126]

Table 8 | Timeline of over-the-counter availability of NSAIDs in the Nordic countries and the regulatory actions instigated due to the dissertation studies (red)

	OTC drugs	Period of OTC availability	Changes in regulations
Denmark	Diclofenac 12.5 mg	July 2007–December 2008	March 2011: NSAID sales restricted to individuals aged ≥18 years
	Ibuprofen 200 mg	March 1989–present	October 2012: Sales of NSAIDs allowed from outlets other than pharmacies
			September 2013: A single sale of ibuprofen restricted to 4000 mg
Finland	Dexibuprofen 300 mg	1998–2008	1995: Each sale of ketoprofen decreased to 375 mg (from 750 mg)
	Ibuprofen 400 mg	1989–present	2008: Each sale of ibuprofen increased to 12,000 mg (from 4000 mg)
	Ketoprofen 25 mg	1992–present	
	Ketoprofen 50 mg	1992–1995	
	Naproxen 250 mg	December 2015–present	
Iceland	Diclofenac 12.5 mg	<2003*–April 2014	2011: Each sale of diclofenac increased to 500 mg (from 250 mg)
	Ibuprofen 200 mg	<2003*–present	November 2012: Each sale of ibuprofen increased to 20,000 mg (from 12,000 mg)
	Ibuprofen 400 mg	<2003*–present	
	Naproxen 250 mg	1991–present	
Norway	Diclofenac 12.5 mg	2001–2020	2003: Sales of NSAIDs allowed from outlets other than pharmacies to individuals aged ≥18 years
	Diclofenac 25 mg	2012–2020	2014: Each sale of diclofenac restricted to 250 mg
	Ibuprofen 200 mg	1989–present	2020: Withdrawal of OTC diclofenac
	Ibuprofen 400 mg	2004–present	
	Naproxen 250 mg	1997–present	
Sweden	Diclofenac 12.5 mg	2005–2020	2009: Sales of NSAIDs (excluding diclofenac) allowed from outlets other than pharmacies to individuals aged ≥18 years
	Diclofenac 25 mg	2004–2020	2020: Withdrawal of OTC diclofenac
	Diclofenac 50 mg	2004–2020	
	Ibuprofen 100 mg	2015–present	
	Ibuprofen 200 mg	1982–present	
	Ibuprofen 400 mg	1982–present	
	Naproxen 250 mg	1991–present	

Modified from Kristensen KB *et al.* Pharmacother 2019[126]
Abbreviations: NSAIDs, non-aspirin nonsteroidal anti-inflammatory drugs; OTC, over-the-counter
*OTC market entry occurred before 2003, but the exact dates were not available from the national medicine agencies.

6. Conclusions

The studies described in this dissertation added evidence to support the importance of multimorbidity in the context of cardiovascular disease. The studies covered various aspects of how comorbidity influences cardiovascular prognosis, the ADEs and drug-drug interactions related to cardiac comedications, and the cardiovascular risks associated with NSAID use. In conjunction, this dissertation has contributed to the advancement of science through its impact on research methodology, clinical guidelines, and regulatory actions against OTC availability of drugs with adverse cardiovascular side effects.

7. Summaries

7.1. English summary

Multimorbidity refers to the coexistence of two or more chronic conditions, each a non-communicable disease, a mental health disorder, or an infectious disease of long duration. Multimorbidity is a growing global health concern, but currently, the available evidence on its causes, impact, and treatment remains inadequate. This dissertation describes population-based studies focused on the importance of multimorbidity — measured in terms of comorbidity and comedication — in relation to the risk and prognosis of cardiovascular disease, based on electronic healthcare records from Denmark, New Zealand, and the UK.

The results showed how the prevalence of comorbidity at a first-time myocardial infarction, heart failure, or stroke has increased over the decades. Over the same period, the comorbidity burden did not influence the overall declining trends of mortality from these diseases, but increased the short- and long-term mortality. Moreover, cardiac and non-cardiac comorbidities interacted with myocardial infarction to increase short- and long-term mortality beyond that which could be explained by their additive effects. These interactions showed a dose-response relation with comorbidity burden and their magnitude was clinically important. We developed the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) to enable future studies to adjust for comorbidity burden.

We examined adverse drug events and drug-drug interactions of common cardiac comedications. We addressed concerns related to renal dysfunction after renin-angiotensin system blockade. We found that only 10% of patients, who initiated angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, received the recommended monitoring of serum creatinine, and 80% of these patients continued treatment despite meeting the post-initiation criteria for treatment discontinuation, based on creatinine and potassium elevations. Underlying the importance of these findings, 30% or more increases in creatinine at the first follow-up monitoring were associated with adverse cardiorenal outcomes and death. Another concern was the potential drug-drug interaction between clopidogrel and proton pump inhibitors after coronary stent implantation. We found that this interaction was not clinically important.

As an example of a non-cardiac comedication, we studied the cardiovascular risks associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). A particular focus was the risks associated with initiation of diclofenac compared to no use, paracetamol, or other traditional NSAIDs. Although declining, NSAID use has remained prevalent among patients with cardiovascular disease. Thus, awareness should be raised, particularly among general practitioners, about the appropriate use of NSAIDs. Additionally, we established novel associations between NSAID use and atrial fibrillation, venous thromboembolism, and stroke mortality.

In conclusion, the studies described in this dissertation provided evidence to support the importance of multimorbidity in the context of cardiovascular disease. The dissertation has contributed to the advancement of science through its impact on research methodology, clinical guidelines, and regulatory actions against over-the-counter availability of drugs with adverse cardiovascular side effects.

7.2. Danish summary

Multisygdom refererer til sameksistensen af to eller flere kroniske tilstande. Multisygdom er et voksende globalt sundhedsproblem. Viden om årsager til multisygdom, samt dets følger og behandling er mangelfuld. Denne doktordisputats sammenfatter forskning der ved brug af danske, newzealandske og britiske sundhedsregistre undersøgte betydningen af multisygdom hos patienter med hjertekarsygdom.

Forskningen viste at andelen af hjertepatienter med multisygdom på debuttidspunktet er steget over de sidste årtier. I samme periode faldt dødeligheden fra hjertekarsygdom for alle patienter uafhængigt af graden af deres multisygdom. Multisygdom var dog i sig selv en stærk prognostisk faktor for kort- og langtidsdødeligheden. Vi fandt også et samspil (interaktion) mellem multisygdom og hjertesygdom som påvirkede prognosen i en sådan grad at kort- og langtidsdødeligheden blev forværret ud over det, der kunne forklares fra deres indvirkninger på død hver især. Vi udviklede en statistisk model (prædiktionsmodel) der kan bruges i fremtidige studier til at beskrive forekomsten af multisygdom, tage højde for multisygdom i statistiske analyser og forudsige dødeligheden af et akut hjerteanfald ud fra sværhedsgraden af multisygdom.

Vi undersøgte også bivirkninger ved hjertemedicin, der hyppigt anvendes ved multisygdom. Resultaterne viste at kun 10% af de patienter der startede behandling med blodtryksmedicin af typen ACE-hæmmere fik den anbefalede blodprøvekontrol efter opstart. Dertil kom at hele 80% af patienterne, som opfyldte kriterierne for at stoppe behandlingen pga. faldende nyrefunktion, fortsatte behandlingen. De patienter der oplevede et stort fald i nyrefunktionen med en kreatinin-stigning over 30% efter opstart af ACE-hæmmere var desuden i højere risiko for komplikationer i form af hjertekar- og nyresygdomme. Forskningen afkræftede endvidere at samspillet (interaktionen) mellem blodfortyndende medicin (clopidogrel) og syrepumpehæmmere havde klinisk betydning hos patienter der havde fået foretaget en ballonudvidelse efter et akut hjerteanfald.

Som et eksempel på medicin der hyppigt anvendes ved andre sygdomme end hjertesygdomme undersøgte vi de hjertekarmæssige risici ved smertestillende medicin af typen non-steroide antiinflammatoriske midler (NSAID). Vi fandt brugere af NSAID-typen diclofenac havde en øget risiko for hjertekarsygdomme. Risikoen var øget sammenlignet med intet brug, men også i forhold til brug af andre NSAID og paracetamol. Selvom om forbruget af NSAID hos hjertepatienter faldt over tid så var det stadig højt i 2017 (14%). Størstedelen af recepterne på NSAID til hjertepatienter blev udskrevet i almen praksis (90%). Sammen med resultaterne fra en forudgående ph.d.-afhandling, viste forskningen endvidere nye sammenhænge mellem NSAID og forskellige hjertekarsygdomme, heriblandt en øget risiko for at udvikle forkammerflimren, blodpropper i ben og lunger og for at dø af et slagtilfælde.

Disputatsen bidrager samlet set med viden om hvordan multisygdom påvirker risikoen og prognosen ved hjertekarsygdom. Der belyses mange aspekter af multisygdom, heriblandt dets forekomst blandt hjertepatienter, indvirkning på prognosen af hjertesygdom, samt evne til at forudsige død af hjertesygdom. Derudover belyses bivirkninger ved hjertemedicin samt hjertekarmæssige risici ved NSAID. Forskningen har bidraget til videnskabens fremme gennem dets indvirkning på nye forskningsmetoder, kliniske retningslinjer og lovgivningsmæssige indgreb mod håndkøbsmedicin med alvorlige hjertekarmæssige bivirkninger.

8. Supplementary material

Table S1 | Overview of literature analyzed for this dissertation on novel cardiovascular risks associated with NSAID use (studies XI–XIII)*

XI: Atrial fibrillation/flutter			
Author / journal / year	**Design / setting / registries / period**	**Population / exposure / outcome / controls**	**Results / limitations**
Chokesuwattanaskul R *et al.*[310] - QJM - 2020	- Meta-analysis (observational studies) - 4 case-control[11,143,231,311] + 4 cohort studies[9,312-314] - Registries described under each study[11,143,231,311-313] - Through August 2019	- Population described under each study (n=14,806,420)[11,143,231,311-313] - NSAIDs *vs.* no use - AF - See included case-control studies[11,143,231,311]	- Pooled RRs: 1.29 (1.19–1.39) for all, 1.37 (1.15–1.63) for case–control, 1.22 (1.14–1.31) for cohort studies; 1.30 (1.22–1.39) for ibuprofen, 1.44 (1.18–1.76) for naproxen, 1.37 (1.10–1.71) for diclofenac. - Between-study heterogeneity.
Schmidt *et al.*[9] - BMJ - 2018	- Emulated trial (series of 252 cohort studies) - Denmark (nationwide) - NPR, PR, CRS, RCD, NHISR - 1996–2016	- General population (source) - Diclofenac initiators (n=1,370,832) - First-time AF/AFL (within 30 days) - PS-matched paracetamol (n=764,781)/no (1,303,209), ibuprofen (3,878,454), naproxen (291,490) initiators	- aHRs=1.2 (1.1–1.4) *vs.* no NSAID use; 1.4 (1.2–1.6) *vs.* paracetamol; 1.1 (1.0–1.3) *vs.* ibuprofen; 1.3 (1.0–1.7) *vs.* naproxen - No data on AF subtypes or drug indications.
Chuang SY *et al.*[311] - Br J Clin Pharmacol - 2018	- Nested case–control study - Taiwan (nationwide) - NHIRD - 2001–2013	- General population >45 yrs old (source) - NSAID (any) *vs.* no use - AF (n=28,529) - Matched controls (n=28,529)	- aORs=1.18 (1.14–1.23) for current users, 2.18 (1.95–2.43) for new users, and 1.05 (1.01–1.10) for past users; 1.17 (1.11–1.24) for nsNSAIDs, 1.12 (1.06–1.18) for older COX-2Is, and 1.05 (0.93–1.20) for coxibs. - No data on individual NSAIDs.
Schjerning Olsen AM *et al.*[314] - Eur Heart J Cardiovasc Pharmacother. 2015	- Cohort study - Denmark (nationwide) - NPR, PR, CRS - 1997–2011	- Patients with a first-time MI >30 yrs old (n=86,496) - NSAIDs (time-varying) *vs.* no use - First-time AF/AFL	- HRs=1.27 (1.14–1.40) overall, 1.28 (1.03–1.58) for diclofenac, 1.31 (1.13–1.53) for ibuprofen, and 1.09 (0.65–1.85) for naproxen; 1.45 (1.24–1.69) for short-term (0–14 days) treatment. - Lack of non-MI group limits interpretation of MI importance.
Liu G *et al.*[315] - Am J Cardiol. - 2014	- Meta-analysis (observational studies) - 3 case-control[11,143,231] + 2 cohort studies[312,313] - Registries described under each study[11,143,231,312,313] - Through June 8, 2014	- Population described under each study[11,143,231,312,313] - NSAIDs (any) - AF - Controls described in included case-control studies[11,143,231]	- Pooled RRs: 1.18 (1.13–1.23) for current users, 1.05 (1.01–1.08) for recent users, 1.53 (1.37–1.70) for new users, 1.09 (1.04–1.14) for long-term users. - Between-study heterogeneity. Asymmetric funnel plot.
Krijthe BP *et al.*[312] - BMJ Open - 2014	- Cohort study - The Netherlands - Rotterdam Study, PR, NPR, CRS - 1990–2009 (interval follow-up)	- Participants >55 yrs old without AF (n=8,423) - NSAIDs (any) (time-varying) *vs.* no use - AF (from ECG or medical record) (n=857)	- aHRs=1.76 (1.07–2.88) for current users, 1.84 (1.34–2.51) for recent past users (<30 days after discontinuation), 1.00 (0.77–1.29) for past users (31–180 days after discontinuation), 1.04 (0.88–1.22) for distant past users (>180.days after discontinuation) - No data on individual NSAIDs/indications; limited sample size.
Chao T *et al.*[230,231] - Int J Cardiol - 2013	- Case-control study - Taiwan (nationwide) - NHIRD - 2000–2009	- General population (source) - tNSAIDs, coxibs *vs.* no use - First-time AF ≥18 yrs old (n=7,280) - Matched controls (n=72,800)	- aORs (tNSAIDs or coxibs)=1.14 (1.06–1.23) overall, 1.65 (1.38–1.97) for new users, 1.92 (1.49–2.48) for new users with HF; aORs (coxibs)=1.20 (0.95–1.28) overall, 1.66 (1.14–2.41) for users with CKD, 1.71 (1.20–2.42) for users with COPD; aOR(tNSAIDs *vs.* coxibs)=1.39 (1.18–1.64) overall - Imprecise coxib estimates.
Bäck M *et al.*[313] - Eur Heart J - 2012	- Population-based cohort study - Sweden (nationwide) - NPR, PR, RCD, CRS, other - 2005–2008	- General population >18 yrs old (n=6,991,645) - tNSAIDs, coxibs (time-varying) *vs.* no use - First-time AF (n=139,323)	- aHRs=1.11 (1.09–1.13) for tNSAIDs, 1.35 (1.19–1.54) for etoricoxib, 0.94 (0.79–1.11) for celecoxib, and 1.16 (1.05–1.29) for coxibs combined. - No data on AF subtypes or individual tNSAIDs.
Schmidt M *et al.*[11,230] - BMJ - 2011	- Population-based case-control study - Northern Denmark - NPR, PR, CRS - 1999–2008	- General population (source) - nsNSAIDs, older COXIs, coxibs - First-time AF or AFL (n=32,602) - Matched controls (n=325,918)	- aORs (nsNSAIDs)=1.17 (1.10–1.24) overall, 1.46 (1.33–1.62) for new users. ORs (COX-2Is)=1.27 (1.20–1.34) overall, 1.71 (1.56–1.88) for new users. OR (older COX-2Is)=1.31 (1.22–1.40); aOR (coxibs)=1.20 (1.09–1.33). COX-2I risk highest CKD or RA - No data on AF subtypes or drug indications.
De Caterina R *et al.*[143] - Arch Intern Med	- Case-control study - UK	- General population (source) - tNSAIDs	- aORs: chronic AF (>1 week)=1.44 (1.08–1.91) for current users, 1.80 (1.20–2.72) for long-term users (>1 yr). aORs for paroxysmal

- 2010	- GPRD - 1996	- Paroxysmal and chronic AF (n=525/1035) - Matched controls 40–89 yrs old (n=10,000)	AF (≤1 week)=1.18 (0.85–1.66) for current users, 1.74 (1.11–2.71) for long-term users. - Imprecise estimates for individual NSAIDs.
Zhang J *et al.*[144] - JAMA - 2006	- Meta-analysis	- 116,094 participants in 114 RCTs - Coxibs - Arrhythmias (any) (n=286)	- aRRs=2.90 (1.07–7.88) for rofecoxib, 0.84 (0.45–1.57) for celecoxib, 0.78 (0.62–1.01) for valdecoxib/parecoxib, and 1.16 (0.40–3.38) for etoricoxib. - Imprecise estimates and AF not examined.

XII: Venous thromboembolism

Author, journal, year	Design, setting, registries, period	Population, exposure, outcome, controls	Results, limitations
Lee T *et al.*[316] - Rheumatology - 2016	- Nested case-control study - UK - The Health Improvement Network (THIN) - 1995–2013	- Patients with knee OA, 18–90 yrs old (n=24,079) - Individual NSAIDs *vs.* no use - VTE (n=4,020) - Matched controls (n=20,059)	aORs: 1.43 (1.36–1.49) overall, 1.49 (1.38–1.62) for ibuprofen, 1.00 (0.89–1.12) for naproxen, 1.63 (1.53–1.74) for diclofenac, 1.29 (1.11–1.50) for meloxicam, 1.30 (1.11–1.51) for celecoxib, and 1.44 (1.18–1.76) for rofecoxib. 1.38 (1.32–1.44) for recent users.
Ungprasert P *et al*.[317] - Rheumatology - 2015	- Meta-analysis (6 observational studies) - 5 case-control[12,166,167,318,319] and 1 cohort studies[168] - Registries described under each study[12,166-168,318,319] - Through December 2013	- Population described under each study[12,166-168,318,319] - NSAID use *vs.* no use - VTE (n=21,401) - Controls described under each study[12,166,167,318,319]	- Pooled RRs: 1.80 (1.28–2.52) overall and 1.99 (1.44–2.75) for COX-2Is. - Asymmetric Funnel plot. Between-study heterogeneity
Goy J *et al.*[320] - Thromb Res - 2014	- Meta-analysis (trials) - 15 trials - N/A - 1980–2011	- Trial participants - Rofecoxib (n=15,160) *vs.* placebo (n=13,147) - VTE (not primary endpoints)	- Number: 8 *vs.* 9 events; Rate: 86.8 *vs.* 99.1 per 100,000 person-yrs; RR=0.87 (0.29–2.56). - Sparse data. Short duration trials (~12 weeks). Between-study heterogeneity
Bergendal A *et al*.[318] - Pharmacoepidemiol Drug Saf - 2013	- Case-control study - Sweden (nationwide) - Thrombo Embolism Hormone Study - 2003–2009	- Females, aged 18–64 yrs - Propionic-, acetic acid derivatives, coxibs - First-time VTE (n=1,433) - Matched population controls (n=1,402)	- aORs: 0.88 (0.72–1.10) for propionic acid derivatives (92% ibuprofen), 1.18 (0.82–1.70) for acetic acid derivatives (97% diclofenac), and 1.76 (0.73–4.27) for coxibs (53% celecoxib, 29% rofecoxib, 15% etoricoxib). aORs increased with cumulative dose for diclofenac/coxibs. - No data on duration of use. Limited precision on coxib estimates.
Biere-Rafi S *et al.*[319] - Pharmacoepidemiol Drug Saf - 2011	- Case-control study - The Netherlands - PHARMO Record Linkage System - 1990–2006	- General population >18 yrs old (source) - NSAIDs, paracetamol, tramadol - First-time PE (n=4,433) - Matched controls (n=16,802)	- aORs (any NSAIDs): 2.39 (2.06–2.77) for current users, 1.23 (1.14–1.34) for past users, 4.77 (3.92–5.81) for new users, 2.14 (1.48–3.09) for long-term users. aORs highest for tNSAIDs (3.19, 2.73–3.72), diclofenac any dose (3.85, 3.09–4.81), and diclofenac >150 mg (6.64, 3.56–12.4). ORs=1.74 (1.42–2.14) for paracetamol, 4.07 (2.86–5.75) for tramadol. - Concerns of confounding by underlying pain indication.
Schmidt M *et al.*[12] - J Thromb Haemost - 2011	- Population-based case-control study - Northern Denmark - NPR, PR, CRS - 1999–2006	- General population (source) - nsNSAIDs, older COXIs, coxibs - First-time DVT/PE (n=8,368) - Matched controls (n=82,218)	- aORs (nsNSAIDs)=2.51 (2.29–2.76) overall and 2.06 (1.85–2.29) for long-term users. aORs (COX-2Is)=2.19 (1.99–2.41) overall and 1.92 (1.72–2.15) for long-term users. Similarly, increased risks were found for unprovoked VTE, DVT, PE, and individual NSAIDs. - Unmeasured confounding could not be excluded.
Sundström *et al.*[165] - BJOG - 2008	- Nested case-control study - UK - GPRD - 1992–1998	- Women, 15–49 yrs old with menorrhagia - Mefenamic acid (prescription ≤90 days) - DVT/PE (n=134) - Matched controls (n=552)	- aOR: 5.54 (2.13–14.40). - Small sample size (10 exposed cases and 12 exposed controls), only mefenamic acid examined.
Lacut K *et al.*[167] - Haematologica - 2008	- Case-control study - France - The EDITH study - 2000–2004	- General population >18 yrs old (source) - NSAIDs - Unprovoked, first-time VTE (n=402) - Matched controls	- aOR: 0.93 (0.44–1.98). - Small sample size and no data on individual NSAIDs or duration of use.
Nagai N *et al*.[321] - Thromb Res - 2008	- Animal experimental study - Belgium - 2008	- Murine venous thrombosis model - Rofecoxib (4 weeks) - VTE	- Enhanced prothrombotic effect detected in lean mice. - Not population-based or clinical setting, only rofecoxib examined.
Huerta C *et al.*[166]	- Nested case-control study	- General population (source)	- aORs=1.86 (1.65–2.10) for VTE, 2.17 (1.89–2.50) for DVT, 1.60

- Arch Intern Med - 2007	- UK - GPRD - 1994–2000	- tNSAIDs (drugs not specified) - VTE (DVT/PE) (n=6,550) - Matched controls (n=10,000)	(1.37–1.87) for PE. OR for VTE=2.82 (2.35–3.39) within 0–30 days, 1.68 (1.39–2.04) within 31–365 days, 1.26 (1.04–1.54) >1 yr. No association for long-term users with OA (estimates not provided). - No data on individual NSAIDs. No subgroups other than OA.
Westgate EJ *et al.*[322] - PLoS Med - 2005	- Case report - US	- 25 y old woman: >3 yrs of oral contraceptive use, non-smoker, no risk factors, vigorously athletic - Valdecoxib (40 mg/day) due to neck pain - DVT/PE	- DVT and bilateral and multiple PEs 1 month after drug initiation. - Risk of chance or confounding from oral contraceptives (despite 3–yr period of apparent tolerance) or prolonged stasis due to a 6–h car trip (despite having taken similar trips on multiple occasions).
Chan AL *et al.*[323] - Ann Pharmacother - 2005	- Case report - Taiwan - 2003	- 52 y old man with gout, no thrombosis history, previously prescribed indomethacin - Celecoxib 200 mg/day - DVT	- DVT 5 days after drug initiation. Other causes were ruled out, except celecoxib. The adverse reaction was determined as probable, according to the Naranjo probability scale. - Risk of chance and confounding could not be ruled out.
Layton D *et al.*[163] - Rheumatology (Oxford) - 2003	- Cohort study - England - NHS PR, GP-questionnaires - 1996–1997 (for meloxicam); 1999 (for rofecoxib)	- GP-treated general population cohort - Rofecoxib *vs.* meloxicam (reference) - Thromboembolic (cardiovascular, VTE, or cerebrovascular) events within 9 months	- Number of VTEs=6/15,268 (0.05%) for rofecoxib and 20/19,087 (0.10%) for meloxicam. aRR for VTE=0.29 (0.11–0.78). - COX-2I reference group made comparison to non-users difficult. No data on other NSAIDs. Risk of non-response bias.
Tsai AW *et al.*[168] - Arch Intern Med - 2002	- Cohort study - US (6 communities) - The ARIC and CHS studies - 1987–1998	- General population (n=9,293) - tNSAIDs (drugs not specified) - First-time VTE (n=215)	aHR=1.44 (1.03–2.02). No association (estimate not provided) after further adjustment for BMI and diabetes. - No data on individual NSAIDs or new/long-term use. Unclear if null association reflected mistaken inference of significance test
Bombardier *et al.*[162] - New Engl J Med - 2000	- RCT (VIGOR) - 301 centers in 22 countries - Randomization - 1999	- Patients with RA (n=8,076) - Naproxen (500 mg twice/day) *vs.* rofecoxib (50 mg/day) - Peripheral vascular events (VTE)	- aRR for peripheral vascular events=0.17 (0.00–1.37), with rofecoxib as reference.[114,163,164] - Not powered to detect differences among individual thromboembolic events. VTE results not part of original study.
Crofford LJ *et al.*[324] - Arthritis Rheum - 2000	- Case report - US - 1999	- 56 y old woman with systemic sclerosis and lupus, taking anticoagulant - Celecoxib (200 mg/day) for leg pain	- PE two days after drug initiation. - Although temporal relationship, risk of chance and confounding could not be ruled out. Risk of protopathic bias.

XIII: Stroke mortality

Author, journal, year	Design, setting, registries, period	Population, exposure, outcome, controls	Results, limitations
Rist PM *et al.*[181] - Eur J Intern Med - 2014	- Cohort study - US - Women's Healthy Study - Since 1993	- 39,860 women ≥45 yrs old without NSAID use - NSAIDs (any) - Functional outcome after first-time TIA (n=702) or ischemic stroke (n=292)	- aHRs=1.00 (0.77–1.29) for TIA, 1.48 (1.04–2.10) for mRS scores 0–1, 0.83 (0.52–1.33) for mRS scores 2–3, and 1.33 (0.68–2.59) for mRS scores 4–6. - Self reported NSAID use (≥11 days in the past month) *vs.* non-use (<11 days in the past month). No data on individual NSAIDs.
Schmidt M *et al.*[13] - Neurology - 2014	- Population-based cohort study - Denmark (nationwide) - NPR, PR, CRS - 2004–2012	- Patients with first-time stroke (n=100,043) - nsNSAIDs, older COXIs, coxibs - 30-day all-cause mortality	aHR for ischemic stroke: Current/new users: nsNSAIDs=1.00 (0.87–1.15)/1.04 (0.85–1.26); COX-2Is=1.19 (1.02–1.38)/1.42 (1.14–1.77); older COX-2Is=1.20 (1.03–1.40)/1.42 (1.14–1.78), including 1.53 (1.02–2.28) for etodolac and 1.28 (0.98–1.68) for diclofenac. - No data on ICH, stroke-specific mortality, functional outcomes, former users. Imprecise estimates for coxibs.

Abbreviations: **A** | aHR, adjusted HR; aOR, adjusted OR; aRR, adjusted RR; AF, atrial fibrillation; AFL, atrial flutter; ARIC, The Atherosclerosis Risk In Communities; **B** | BMI, body mass index; **C** |CHS, The Cardiovascular Health Study; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; COX-2Is, COX-2 selective inhibitors; coxibs, newer COX-2 inhibitors; CRS, Civil Registration System or similar mortality/migration registry; **D** | DVT, deep vein thrombosis; **G** | GP, general practitioner; GPRD, General Practice Research Database; **H** |HF, heart failure; HR, hazard ratio; **I** | ICH, intracerebral hemorrhage; **M** | MI, myocardial infarction; mRS, modified Rankin Scale; **N** | N/A, not applicable; NHIRD, National Health Insurance Research Database; NHISR, National Health Insurance Service Registry; NSAID, non-aspirin non-steroidal anti-inflammatory drug; nsNSAIDs, nonselective NSAIDs; NPR, National Patient Registry; **O** | OA, osteoarthritis; OR, odds ratio; **P** | PE, pulmonary embolism; PR, Prescription registry (various); **R** | RA, rheumatoid arthritis; RCD, Registry of Causes of Death; RCT, randomized controlled trial; RR, relative risk; **T** | TIA, transient ischemic attacks; tNSAIDs, traditional NSAIDs (*i.e.*, nsNSAIDs or older COX-2Is); **U** | UK, United Kingdom; US, United States; **Y** | yr(s), year(s)

Medline search algorithms for studies XI–XIII: (1) relevant Medline hits (of total hits) + (2) relevant citing papers (Web of Science) + (3) relevant CoCites[325] + other relevant papers = total number of relevant papers:

- XI: ("Anti-Inflammatory Agents, Non-Steroidal"[Majr]) AND ("Arrhythmias, Cardiac"[Majr]): 3 (48) + 6 + 0 + 2 = 11 total papers
- XII: (("Anti-Inflammatory Agents, Non-Steroidal"[Majr]) AND ("Venous Thrombosis"[Mesh] OR "Pulmonary Embolism"[Majr] OR "Venous Thromboembolism"[Majr])): (86) + 3 + 0 + 9 = 16 total papers
- XIII: "(""Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) AND ("Stroke"[Majr] OR "Intracranial Hemorrhages"[Majr])": 2 (295) + 0 + 0 + 0 = 2 total papers

* This overview also includes post-publication studies, in accordance with Aarhus University's dissertation criteria for studies previously included in a PhD thesis.[15]

9. References

1. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344:e356.
2. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Sørensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail*. 2016;18(5):490-499.
3. Schmidt M, Jacobsen JB, Johnsen SP, Bøtker HE, Sørensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology*. 2014;82(4):340-350.
4. Schmidt M, Horvath-Puho E, Ording AG, Bøtker HE, Lash TL, Sørensen HT. The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: A nationwide cohort study. *Int J Cardiol*. 2020;308:1-8.
5. Albertsen LW, Heide-Jørgensen U, Schmidt SAJ, et al. The DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI): Development, Validation and Comparison with Existing Comorbidity Indices. *Clin Epidemiol*. 2020;12:1299-1311.
6. Schmidt M, Mansfield KE, Bhaskaran K, et al. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin–angiotensin system blockade: a UK general practice-based cohort study. *BMJ Open*. 2017;7(1):e012818.
7. Schmidt M, Mansfield KE, Bhaskaran K, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ*. 2017;356:j791.
8. Schmidt M, Johansen MB, Robertson DJ, et al. Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular events following coronary stent implantation. *Aliment Pharmacol Ther*. 2011;35(1):165-174.
9. Schmidt M, Sørensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ*. 2018:k3426–10.
10. Schmidt M, Pottegård A. Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2020;37:1015.
11. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. *BMJ*. 2011;343:d3450-d3450.
12. Schmidt M, Christiansen CF, Horvath-Puho E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. *J Thromb Haemost*. 2011;9(7):1326-1333.

13. Schmidt M, Hováth-Puhó E, Christiansen CF, Petersen KL, Bøtker HE, Sørensen HT. Preadmission use of nonaspirin nonsteroidal anti-inflammatory drugs and 30-day stroke mortality. *Neurology*. 2014;83(22):2013-2022.

14. Schmidt M. Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use. *Dan Med J*. 2015;62(3).

15. Aarhus University. Requirements for the doctoral dissertation's form, content and language. Available at https://health.au.dk/en/research/doctoral-dissertations/. Accessed on 1 November 2020.

16. World Health Organization. Cardiovascular diseases (CVDs). Available at https://www.who.int/health-topics/cardiovascular-diseases/. Accessed on 1 November 2020.

17. The Danish Health Data Authority. Cause of Death Registry Annual report 2018. Numbers and analysis.

18. Schmidt M, Andersen LV, Friis S, Juel K, Gislason G. Data Resource Profile: Danish Heart Statistics. *Int J Epidemiol*. 2017;46(5):1368–1369g.

19. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Nielsen JC, Sørensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *Int J Cardiol*. 2016;225:30-36.

20. Søgaard KK, Schmidt M, Pedersen L, Horvath-Puho E. 30-Year Mortality Following Venous Thromboembolism: A Population-Based Cohort Study. *Circulation*. 2014;130(10):829-836.

21. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005;3(3):223-228.

22. van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract*. 1996;2:65-70.

23. Nicholson K, Almirall J, Fortin M. The measurement of multimorbidity. *Health Psychol*. 2019;38(9):783-790.

24. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. *J Gerontol A Biol Sci Med Sci*. 2011;66(3):301-311.

25. Willadsen TG, Bebe A, Køster-Rasmussen R, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity - a systematic review. *Scand J Prim Health Care*. 2016;34(2):112-121.

26. Fortin M, Stewart M, Poitras M-E, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med*. 2012;10(2):142-151.

27. The Lancet. Making more of multimorbidity: an emerging priority. *Lancet*. 2018;391(10131):1637.

28. *The Academy of Medical Sciences. Multimorbidity: a Priority for Global Health Research. Available at Https://Acmedsci.Ac.Uk/Policy/Policy-Projects/Multimorbidity. Accessed on 1 November 2020*. 2018.

29. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med*. 2009;7(4):357-363.

30. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009;374(9696):1196-1208.

31. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2(1):51–12.

32. Fortin M, Soubhi H, Hudon C, Bayliss EA, van den Akker M. Multimorbidity's many challenges. *BMJ*. 2007;334(7602):1016-1017.

33. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162(20):2269-2276.

34. Glynn LG, Valderas JM, Healy P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Family Practice*. 2011;28(5):516-523.

35. Burgers JS, Voerman GE, Grol R, Faber MJ, Schneider EC. Quality and coordination of care for patients with multiple conditions: results from an international survey of patient experience. *Eval Health Prof*. 2010;33(3):343-364.

36. Skajaa N, Ording AG, Darvalics B, Horvath-Puho E, Sørensen HT. Long-term mortality in young and middle-aged adults hospitalised with chronic disease: a Danish cohort study. *BMJ Open*. 2020;10(10):e038131.

37. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. *Lancet*. 2017;389(10075):1229-1237.

38. Prior A, Fenger-Grøn M, Larsen KK, et al. The Association Between Perceived Stress and Mortality Among People With Multimorbidity: A Prospective Population-Based Cohort Study. *Am J Epidemiol*. 2016;184(3):210.

39. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis*. 1970;23(7):455-468.

40. Meghani SH, Buck HG, Dickson VV, et al. The Conceptualization and Measurement of Comorbidity: A Review of the Interprofessional Discourse. *Nursing Research and Practice*. 2013;2013(7):1-10.

41. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol*. 2003;56(3):221-229.

42. Ording A, Henrik Toft Sørensen H. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clin Epidemiol*. 2013;5:199-203.

43. Safford MM, Allison JJ, Kiefe CI. Patient complexity: more than comorbidity. the vector model of complexity. *J Gen Intern Med*. 2007;22 Suppl 3(S3):382-390.

44. Nardi R, Fiorino S, Borioni D, et al. Comprehensive complexity assessment as a key tool for the prediction of in-hospital mortality in heart failure of aged patients admitted to internal medicine wards. *Arch Gerontol Geriatr*. 2007;44 Suppl 1(SUPPL.):279-288.

45. Krumholz HM, Gross CP, Peterson ED, et al. Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-1 study. *Am Heart J*. 2003;146(5):839-847.

46. Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA*. 2007;297(11):1233-1240.

47. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J*. 2003;146(2):250-257.

48. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age and ageing*. 2013;42(1):62-69.

49. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716-724.

50. Newell MC, Henry JT, Henry TD, et al. Impact of age on treatment and outcomes in ST-elevation myocardial infarction. *Am Heart J*. 2011;161(4):664-672.

51. Hall M, Dondo TB, Yan AT, et al. Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: Latent class analysis of a nationwide population-based cohort. Lam CSP, ed. *PLoS Med*. 2018;15(3):e1002501.

52. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. 2012;366(1):54-63.

53. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. 2007;356(23):2388-2398.

54. Laing BY, Katz MH. Coronary arteries, myocardial infarction, and history. 2012;366(13):1258–9–authorreply1260.

55. Balzi D, Buiatti E, Franceschini C, et al. Effect of comorbidity on coronary reperfusion strategy and long-term mortality after acute myocardial infarction. *Am Heart J*. 2006;151(5):1094-1100.

56. Corraini P, Olsen M, Pedersen L, Dekkers O, Vandenbroucke J. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. *Clin Epidemiol*. 2017;Volume 9:331-338.

57. VanderWeele TJ. On the distinction between interaction and effect modification. *Epidemiology*. 2009;20(6):863-871.

58. VanderWeele TJ. Sufficient cause interactions and statistical interactions. *Epidemiology*. 2009;20(1):6-13.

59. Saracci R. Interaction and synergism. *Am J Epidemiol*. 1980;112(4):465-466.

60. Blot WJ, Day NE. Synergism and interaction: are they equivalent? *Am J Epidemiol*. 1979;110(1):99-100.

61. Rashid M, Kwok CS, Gale CP, et al. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes*. 2017;3(1):20-36.

62. Stirland LE, González-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ*. 2020;12:m160–12.

63. Normand SL, Morris CN, Fung KS, McNeil BJ, Epstein AM. Development and validation of a claims based index for adjusting for risk of mortality: the case of acute myocardial infarction. *J Clin Epidemiol*. 1995;48(2):229-243.

64. Qu Z, Zhao LP, Ma X, Zhan S. Building a Patient-Specific Risk Score with a Large Database of Discharge Summary Reports. *Med Sci Monit*. 2016;22:2097-2104.

65. Sanchis J, Núñez J, Bodí V, et al. Influence of Comorbid Conditions on One-Year Outcomes in Non–ST-Segment Elevation Acute Coronary Syndrome. *Mayo Clinic Proceedings*. 2011;86(4):291-296.

66. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol*. 2001;37(4):992-997.

67. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

68. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Medical care*. 2009;47(6):626-633.

69. Li P, Kim MM, Doshi JA. Comparison of the performance of the CMS Hierarchical Condition Category (CMS-HCC) risk adjuster with the Charlson and Elixhauser comorbidity measures in predicting mortality. *BMC Health Serv Res*. 2010;10(1):245.

70. Holman CDJ, Preen DB, Baynham NJ, Finn JC, Semmens JB. A multipurpose comorbidity scoring system performed better than the Charlson index. *J Clin Epidemiol*. 2005;58(10):1006-1014.

71. Jacobs DR, Kroenke C, Crow R, et al. PREDICT: A simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. *Circulation*. 1999;100(6):599-607.

72. Radovanovic D, Seifert B, Urban P, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. *Heart*. 2014;100(4):288-294.

73. Sachdev M, Sun JL, Tsiatis AA, Nelson CL, Mark DB, Jollis JG. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2004;43(4):576-582.

74. George S, Kwok CS, Martin GP, et al. The Influence of the Charlson Comorbidity Index on Procedural Characteristics, VARC-2 Endpoints and 30-Day Mortality Among Patients Who Undergo Transcatheter Aortic Valve Implantation. *Heart Lung Circ*. 2019;28(12):1827-1834.

75. Kearney L, Ord M, Buxton B, et al. Usefulness of the Charlson co-morbidity index to predict outcomes in patients >60 years old with aortic stenosis during 18 years of follow-up. *Am J Cardiol*. 2012;110(5):695-701.

76. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke*. 2004;35(8):1941-1945.

77. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging*. 2008;3(2):383-389.

78. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC medicine*. 2015;13(1):74–10.

79. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions -the need for a prediction tool. *Clin Interv Aging*. 2016;11:497-505.

80. Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol*. 2007;63(2):136-147.

81. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. *Br J Clin Pharmacol*. 2008;65(4):573-579.

82. National Institute for Health and Clinical Excellence (NICE). Hypertension in adults: diagnosis and management *(*2011). Available at https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2. Accessed on 1 April 2016.

83. National Institute for Health and Clinical Excellence (NICE). Chronic heart failure in adults: management *(*2010). Available at http://pathways.nice.org.uk/pathways/chronic-heart-failure. Accessed on 1 November 2020.

84. National Institute for Health and Clinical Excellence (NICE). Management of chronic kidney disease *(*2014). Available at http://pathways.nice.org.uk/pathways/chronic-kidney-disease#path=view%3A/pathways/chronic-kidney-disease/management-of-chronic-kidney-

disease.xml&content=view-node%3Anodes-blood-pressure-control-and-antihypertensive-treatment. Accessed on 1 November 2020.

85. National Institute for Health and Clinical Excellence (NICE). Myocardial infarction: secondary prevention *(*2013). Available at http://pathways.nice.org.uk/pathways/myocardial-infarction-secondary-prevention. Accessed on 1 November 2020.

86. Lesogor A, Cohn JN, Latini R, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. *Eur J Heart Fail*. 2014;15(11):1236-1244.

87. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Cardiovasc Ther*. 2012;30(3):e156-e166.

88. McDowell SE, Thomas SK, Coleman JJ, Aronson JK, Ferner RE. A practical guide to monitoring for adverse drug reactions during antihypertensive drug therapy. *JRSM*. 2013;106(3):87-95.

89. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160(5):685-693.

90. McDowell SE, Ferner RE. Biochemical Monitoring of Patients Treated with Antihypertensive Therapy for Adverse Drug Reactions. *Drug Saf*. 2011;34(11):1049-1059.

91. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349(9054):747-752.

92. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int.* 2006;70(11):2021-2030.

93. McFadden Ep Fau Stabile E, Stabile E Fau Regar E, Regar E Fau Cheneau E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;(1474-547X (Electronic)).

94. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. *J Am Coll Cardiol*. 2010;56(24):2051-2066.

95. Geisler T, Langer H, Wydymus M, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J*. 2006;27(20):2420-2425.

96. Gilard M, Arnaud B, Cornily J-C, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008;51(3):256-260.

97. Zuern CS, Geisler T, Lutilsky N, Winter S, Schwab M, Gawaz M. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res*. 2010;125(2):e51-e54.

98. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost*. 2009;101(4):714-719.

99. Cuisset T, Frere C, Quilici J, et al. Comparison of Omeprazole and Pantoprazole Influence on a High 150-mg Clopidogrel Maintenance Dose. *J Am Coll Cardiol*. 2009;54(13):1149-1153.

100. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metab Dispos*. 2003;31(1):53-59.

101. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation*. 2003;107(1):32-37.

102. Neubauer H, Günesdogan B, Hanefeld C, Spiecker M, Mügge A. Lipophilic statins interfere with the inhibitory effects of clopidogrel on platelet function--a flow cytometry study. *Eur Heart J*. 2003;24(19):1744-1749.

103. Mach F, Senouf D, Fontana P, et al. Not all statins interfere with clopidogrel during antiplatelet therapy. *Eur J Clin Invest*. 2005;35(8):476-481.

104. Siller-Matula J, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. *J Am Coll Cardiol*. 2008;52(19):1557-1563.

105. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Calcium-channel blockers decrease clopidogrel-mediated platelet inhibition. *Heart*. 2010;96(3):186-189.

106. Harmsze AM, Robijns K, van Werkum JW, et al. The use of amlodipine, but not of P-glycoprotein inhibiting calcium channel blockers is associated with clopidogrel poor-response. *Thromb Haemost*. 2010;103(5):920-925.

107. Hulot JS, Collet JP, Silvain J, et al. Cardiovascular Risk in Clopidogrel-Treated Patients According to Cytochrome P450 2C19*2 Loss-of-Function Allele or Proton Pump Inhibitor Coadministration. *JACC*. 2010;56(2):134-143.

108. Greenland S, Lash TL, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 71–86.

109. Willadsen TG, Siersma V, Nicolaisdóttir DR, et al. Multimorbidity and mortality: A 15-year longitudinal registry-based nationwide Danish population study. *J Comorb*. 2018;8(1):2235042X18804063.

110. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). *BMJ*. 2013;346:f3195.

111. Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other non-steroidal anti-inflammatory drugs in Denmark: Trends in utilization 1999-2012. *Clin Epidemiol*. 2014;6:155-168.

112. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf*. 2012;35(12):1127-1146.

113. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. 2005;352(1533-4406):1092-1102.

114. Grosser T, Yu Y, FitzGerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu Rev Med*. 2010;61:17-33.

115. Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J*. 2004;18(7):790-804.

116. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat*. 2007;82(1-4):85-94.

117. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779.

118. Schmidt M, Lamberts M, Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J*. 2016;37(13):1015-1023.

119. European Medicines Agency (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). Call for information on effectiveness of risk minimisation on diclofenac (Referral EMEA/H/A-31/1344). February 2017.

120. McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med*. 2013;10(2):e1001388.

121. Danaei G, Rodriguez LAG, Cantero OF, Logan R, Hernan MA. Observational data for comparative effectiveness research: An emulation of randomised trials of statins and primary prevention of coronary heart disease. *Statistical Methods in Medical Research*. 2013;22(1):70-96.

122. European Medicines Agency. Public CHMP assessment report for medicinal products containing non-selective non-steroidal anti-inflammatory drugs (NSAIDs). EMEA/H/A-5.3/800. 2006.

123. European Medicines Agency. Assessment report for diclofenac containing medicinal products (systemic formulations). EMA/544760/2013. 2013.

124. European Medicines Agency. New safety advice for diclofenac. New measures aim to minimise cardiovascular risks. EMA/592685/2013. 2013.

125. Scholle O, Kollhorst B, Haug U. Are prescribers not aware of cardiovascular contraindications for diclofenac? A claims data analysis. *J Intern Med*. 2019;345(1):433-439.

126. Kristensen KB, Karlstad Ø, Martikainen JE, et al. Nonaspirin Nonsteroidal Antiinflammatory Drug Use in the Nordic Countries from a Cardiovascular Risk Perspective, 2000-2016: A Drug Utilization Study. *Pharmacotherapy*. 2019;10(2):e1001388–11.

127. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.

128. Wilke T, Groth A, Mueller S, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace*. 2013;15(4):486-493.

129. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309.

130. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107(23):2920-2925.

131. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988.

132. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-952.

133. van der Hooft CS, Heeringa J, van Herpen G, Kors JA, Kingma JH, Stricker BHC. Drug-induced atrial fibrillation. *J Am Coll Cardiol*. 2004;44(11):2117-2124.

134. Miyazaki T, Pride HP, Zipes DP. Prostaglandins in the pericardial fluid modulate neural regulation of cardiac electrophysiological properties. *Circ Res*. 1990;66(1):163-175.

135. Miyazaki T, Zipes DP. Pericardial prostaglandin biosynthesis prevents the increased incidence of reperfusion-induced ventricular fibrillation produced by efferent sympathetic stimulation in dogs. *Circulation*. 1990;82(3):1008-1019.

136. Coker SJ, Parratt JR. The effects of prostaglandins E2, F2 alpha, prostacyclin, flurbiprofen and aspirin on arrhythmias resulting from coronary artery ligation in anaesthetized rats. *Br J Pharmacol*. 1981;74(1):155-159.

137. Wang D, Patel VV, Ricciotti E, et al. Cardiomyocyte cyclooxygenase-2 influences cardiac rhythm and function. *Proc Natl Acad Sci USA*. 2009;106(18):7548-7552.

138. Frolov RV, Berim IG, Singh S. Inhibition of delayed rectifier potassium channels and induction of arrhythmia: a novel effect of celecoxib and the mechanism underlying it. *J Biol Chem*. 2008;283(3):1518-1524.

139. Whelton A. Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2-specific inhibitors. *Am J Med*. 2001;110 Suppl 3A:33S–42S.

140. van den Hondel KE, Eijgelsheim M, Ruiter R, Witteman JCM, Hofman A, Stricker BHC. Effect of short-term NSAID use on echocardiographic parameters in elderly people: a population-based cohort study. *Heart*. 2011;97(7):540-543.

141. Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure-five more years. 2004;351(23):2437-2440.

142. Aw T-J, Haas SJ, Liew D, Krum H. Meta-analysis of Cyclooxygenase-2 Inhibitors and Their Effects on Blood Pressure. *Arch Intern Med*. 2005;165(5):490-496.

143. De Caterina R, Ruigómez A, Rodríguez LAG. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. *Arch Intern Med*. 2010;170(16):1450-1455.

144. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA*. 2006;296(13):1619-1632.

145. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363-2371.

146. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158(6):585-593.

147. Arshad N, Isaksen T, Hansen J-B, Brækkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. 2017;32(4):299-305.

148. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388(10063):3060-3073.

149. Kahn SR. The Post-Thrombotic Syndrome. *Hematology*. 2011;2010(1):216-220.

150. Piazza G, Goldhaber SZ. Chronic Thromboembolic Pulmonary Hypertension. 2011;364(4):351-360.

151. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med*. 2010;170(19):1710-1716.

152. Prandoni P. Venous and arterial thrombosis: Two aspects of the same disease? *Clin Epidemiol*. 2009;1:1-6.

153. Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. *J Clin Pathol*. 1974;27(7):517-528.

154. Sevitt S. Pathology and pathogenesis of deep vein thrombi. *Proceedings of the Royal Society of Medicine*. 1975;68(4):261.

155. Prandoni P. Venous and arterial thrombosis: two aspects of the same disease? *Eur J Intern Med*. 2009;20(6):660-661.

156. Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet*. 2007;370(9601):1773-1779.

157. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. 2012;366(21):1959-1967.

158. Schmidt M, Cannegieter SC, Johannesdottir SA, Dekkers OM, Horvath-Puho E, Sørensen HT. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study. *J Thromb Haemost*. 2014;12(8):1207-1215.

159. Bishop-Bailey D, Pepper JR, Larkin SW, Mitchell JA. Differential induction of cyclooxygenase-2 in human arterial and venous smooth muscle: role of endogenous prostanoids. *Arterioscler Thromb Vasc Biol*. 1998;18(10):1655-1661.

160. Rabausch K, Bretschneider E, Sarbia M, et al. Regulation of thrombomodulin expression in human vascular smooth muscle cells by COX-2-derived prostaglandins. *Circ Res*. 2005;96(1):e1-e6.

161. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001;345(6):433-442.

162. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343(21):1520–8, 2 p following 1528.

163. Layton D, Heeley E, Hughes K, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. *Rheumatology (Oxford)*. 2003;42(11):1342-1353.

164. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. 2006;354(11):1193.

165. Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. *BJOG*. 2008;116(1):91-97.

166. Huerta C, Johansson S, Wallander M-A, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med*. 2007;167(9):935-943.

167. Lacut K, van der Maaten J, Le Gal G, Cornily G, Mottier D, Oger E. Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study. *Haematologica*. 2008;93(7):1117-1118.

168. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162(10):1182-1189.

169. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol*. 2006;13(6):581-598.

170. Demant MN, Andersson C, Ahlehoff O, et al. Temporal trends in stroke admissions in Denmark 1997--2009. *BMC Neurology*. 2013;13(1):156.

171. Palnum KD, Petersen P, Sørensen HT, et al. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. *Age and ageing*. 2007;37(1):90-95.

172. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011;342:c7086.

173. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiol Drug Saf*. 2011;20(12):1225-1236.

174. McCullough L, Wu L, Haughey N, et al. Neuroprotective function of the PGE2 EP2 receptor in cerebral ischemia. *J Neurosci*. 2004;24(1):257-268.

175. Kim EJ, Raval AP, Hirsch N, Perez-Pinzon MA. Ischemic Preconditioning Mediates Cyclooxygenase-2 Expression Via Nuclear Factor-Kappa B Activation in Mixed Cortical Neuronal Cultures. *Transl Stroke Res*. 2010;1(1):40-47.

176. Kim E, Raval AP, Defazio RA, Perez-Pinzon MA. Ischemic preconditioning via epsilon protein kinase C activation requires cyclooxygenase-2 activation in vitro. *Neuroscience*. 2007;145(3):931-941.

177. Horiguchi T, Snipes JA, Kis B, Shimizu K, Busija DW. Cyclooxygenase-2 mediates the development of cortical spreading depression-induced tolerance to transient focal cerebral ischemia in rats. *Neuroscience*. 2006;140(2):723-730.

178. Park H-K, Lee S-H, Chu K, Roh J-K. Effects of celecoxib on volumes of hematoma and edema in patients with primary intracerebral hemorrhage. *J Neurol Sci*. 2009;279(1-2):43-46.

179. Ahmad M, Zhang Y, Liu H, Rose ME, Graham SH. Prolonged opportunity for neuroprotection in experimental stroke with selective blockade of cyclooxygenase-2 activity. *Brain Res*. 2009;1279:168-173.

180. Ayer R, Jadhav V, Sugawara T, Zhang JH. The neuroprotective effects of cyclooxygenase-2 inhibition in a mouse model of aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl*. 2011;111:145-149.

181. Rist PM, Glymour MM, Orav EJ, et al. Non-steroidal anti-inflammatory drug use and functional outcome from ischemic cerebral events among women. *Eur J Intern Med*. 2014;25(3):255-258.

182. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591.

183. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen H. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.

184. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798–798f.

185. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol*. 2010;2:273-279.

186. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol*. 2012;4:303-313.

187. Schmidt M, Hallas J, Laursen M, Friis S. Data Resource Profile: Danish online drug use statistics (MEDSTAT). *Int J Epidemiol*. 2016;45(5):1401–1402g.

188. Grann AF, Erichsen R, Nielsen AG, Frøslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol*. 2011;3:133-138.

189. Andersen JS, Olivarius NDF, Krasnik A. The Danish National Health Service Register. *Scand J Public Health*. 2011;39(7 Suppl):34-37.

190. Schmidt M, Maeng M, Madsen M, Sørensen HT, Jensen LO, Jakobsen C-J. The Western Denmark Heart Registry: Its Influence on Cardiovascular Patient Care. *J Am Coll Cardiol*. 2018;71(11):1259-1272.

191. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39(7 Suppl):26-29.

192. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549.

193. New Zealand Ministry of Health. About the National Minimum Dataset (hospital events). Available at https://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/national-minimum-dataset-hospital-events. Accessed on 1 November 2020.

194. O'Grady G. Death of the teaching autopsy. *BMJ*. 2003;327(7418):802-803.

195. New Zealand Ministry of Health. About the Pharmaceutical Collection. Available at https://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/pharmaceutical-collection. Accessed on 1 November 2020.

196. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

197. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol*. 2017;46(4):1093–1093i.

198. The English Indices of Deprivation 2010. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf. Accessed on 1 November 2020.

199. Olsen J, Basso O, Sørensen HT. What is a population-based registry? *Scand J Public Health*. 1999;27(1):78-78.

200. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ*. 2013;346(feb05 1):e5595-e5595.

201. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: Prognostic Factor Research. *PLoS Med*. 2013;10(2):e1001380.

202. Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. *PLoS Med*. 2013;10(2):e1001381.

203. Støvring H, Pottegård A, Hallas J. Determining prescription durations based on the parametric waiting time distribution. *Pharmacoepidemiol Drug Saf*. 2016;25(12):1451-1459.

204. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.

205. Fosbøl EL, Gislason GH, Jacobsen S, et al. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidem Drug Saf*. 2008;17(8):822-833.

206. Rasmussen L, Valentin J, Gesser KM, Hallas J, Pottegård A. Validity of the Prescriber Information in the Danish National Prescription Registry. *Basic Clin Pharmacol Toxicol*. 2016;119(4):376-380.

207. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11):e012832.

208. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344-2351.

209. Greenland S, Rothman KJ. *Fundamentals of Epidemiologic Data Analysis. Modern Epidemiology*. 3rd ed. (Rothman KJ, Greenland S, Lash TL, eds.). Philadelphia, PA: Lippincott Williams & Wilkins; 2008:213-237.

210. Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. 3rd ed. John Wiley & Sons; 2013.

211. Rothman KJ, Greenland S, Lash TL. *Case–Control Studies. Modern Epidemiology*. 3rd ed. (Rothman KJ, Greenland S, Lash TL, eds.). Philadelphia, PA: Lippincott Williams & Wilkins; 2008:111-127.

212. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Til S. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156.

213. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: A systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg*. 2007;134(5):1128–1135.e3.

214. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15(5):291-303.

215. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.

216. Porta M. *A Dictionary of Epidemiology*. 6 ed.; 2014.

217. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the Performance of Prediction Models. *Epidemiology*. 2010;21(1):128-138.

218. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.

219. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41(2):514-520.

220. Skrondal A. Interaction as departure from additivity in case-control studies: a cautionary note. *Am J Epidemiol*. 2003;158(3):251-258.

221. GP notebook. General Practice Notebook - a UK medical reference. Available at www.gpnotebook.co.uk. Accessed on 1 November 2020.

222. Bhaskaran K, Rachet B, Evans S, Smeeth L. Re: Helene Hartvedt Grytli, Morten Wang Fagerland, Sophie D. Fosså, Kristin Austlid Taskén. Association between use of β-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2013.01.007: beta-blockers and prostate cancer survival--interpretation of competing risks models. *Eur Urol*. 2013;64(4):e86-e87.

223. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861-870.

224. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available: Table 1. *Am J Epidemiol*. 2016;183(8):758-764.

225. National Institute for Health and Clinical Excellence (NICE). Hypertension in adults: diagnosis and management. Available at http://www.nice.org.uk/guidance/cg127/chapter/1-recommendations#choosing-antihypertensive-drug-treatment-2. Accessed on 1 November 2016.

226. Rothman KJ, Greenland S, Lash TL. *Validity in Epidemiologic Studies. Modern Epidemiology*. 3rd ed. (Rothman KJ, Greenland S, Lash TL, eds.). Philadelphia, PA: Lippincott Williams & Wilkins; 2008:128-147.

227. Rothman KJ, Greenland S, Lash TL. *Precision and Statistics in Epidemiologic Studies. Modern Epidemiology*. 3rd ed. (Rothman KJ, Greenland S, Lash TL, eds.). Philadelphia, PA: Lippincott Williams & Wilkins; 2008:147-167.

228. Amrhein V, Greenland S, Mcshane B, 2019. Retire statistical significance. Comment. *Nature*. 2019;567:305-307.

229. Rothman KJ. Writing for epidemiology. *Epidemiology*. 1998;9(3):333-337.

230. Schmidt M, Rothman KJ. Mistaken inference caused by reliance on and misinterpretation of a significance test. *Int J Cardiol*. 2014;177(3):1089-1090.

231. Chao T-F, Liu C-J, Chen S-J, et al. The association between the use of non-steroidal anti-inflammatory drugs and atrial fibrillation: A nationwide case-control study. *Int J Cardiol*. 2013;168(1):312-316.

232. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. *J Am Coll Cardiol*. 2008;51(8):779-786.

233. Tomlinson G, Detsky AS. Composite End Points in Randomized Trials: There Is No Free Lunch. *JAMA*. 2010;303(3):267-268.

234. Detsky AS. Using economic analysis to determine the resource consequences of choices made in planning clinical trials. *J Chronic Dis*. 1985;38(9):753-765.

235. Ferreira-González I, Permanyer-Miralda G, Busse JW, et al. Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *J Clin Epidemiol*. 2007;60(7):651-657.

236. Henriksen DP, Rasmussen L, Hansen MR, Hallas J, Pottegård A. Comparison of the five Danish Regions regarding demographic characteristics, healthcare utilization, and medication use—A descriptive cross-sectional study. *Plos ONE*. 2015;10(10):e0140197.

237. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4-14.

238. Schneeweiss S, Patrick AR, Til S, et al. Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results. *Medical care*. 2007;45(Suppl 2):S131-S142.

239. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol*. 2005;162(10):1016-1023.

240. Krarup L-H, Boysen G, Janjua H, Evva P, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28(3):150-154.

241. Adelborg K, Sundbøll J, Munch T, et al. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open*. 2016;6(12):e012817.

242. Maeng M, Jensen L, Rasmussen K, et al. Target lesion revascularisation in patients treated with a sirolimus-eluting or paclitaxel-eluting stent. *Heart*. 2007;93(6):694-697.

243. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol*. 2007;50(5):463-470.

244. Beaglehole R, Stewart AW, Walker P. Validation of coronary heart disease hospital discharge data. *Aust N Z J Med*. 1987;17(1):43-46.

245. Kerr AJ, Lee M, Jiang Y, et al. High level of capture of coronary intervention and associated acute coronary syndromes in the all New Zealand acute coronary syndrome quality improvement cardiac registry and excellent agreement with national administrative datasets (ANZACS-QI 25). *N Z Med J*. 2019;132(1492):19-29.

246. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346(may20 3):f2350-f2350.

247. New Zealand Ministry of Health. About the Mortality Collection. Available at https://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/mortality-collection. Accessed on 1 November 2020.

248. Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. *Pharmacoepidemiol Drug Saf*. 2008;17(12):1197-1201.

249. Doran T, Kontopantelis E, Valderas JM, et al. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. *BMJ*. 2011;342:d3590.

250. Barbour SJ, Schachter M, Er L, Djurdjev O, Levin A. A systematic review of ethnic differences in the rate of renal progression in CKD patients. *Nephrol Dial Transplant*. 2010;25(8):2422-2430.

251. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract*. 2010;60(572):e128-e136.

252. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

253. Quan H, Li B, Couris CM, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. *Am J Epidemiol*. 2011;173(6):676-682.

254. Madsen M, Ehrenstein V, Sørensen HT. Length of comorbidity lookback period and predicting one-year mortality based on registry data from Denmark. Abstract 690. Pharmacoepidemiol Drug Saf. 2015, Vol 24 (suppl. 1). *Pharmacoepidemiol Drug Saf*. February 2015:1-2.

255. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. *Int J Epidemiol*. 1986;15(3):413-419.

256. Pathirana TI, Jackson CA. Socioeconomic status and multimorbidity: a systematic review and meta-analysis. *Aust N Z J Public Health*. 2018;42(2):186-194.

257. McMurray JJV, Kalra P. Re: Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. Available at https://www.bmj.com/content/356/. bmj.j791/rr-8. Accessed on 1 November 2020. *BMJ*. 2017.

258. Olaoye OA, Mohandas R. Re: Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. Available at https://www.bmj.com/content/356/bmj.j791/rr-7. Accessed on 1 November 2020. *BMJ*. 2017.

259. Clark AL, Kalra PR, Petrie MC, Mark PB, Tomlinson LA, Tomson CR. Change in renal function associated with drug treatment in heart failure: national guidance. *Heart*. 2019;105(12):904-910.

260. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med*. 2010;153(6):378-386.

261. Hvid-Jensen F, Pedersen L, Nielsen R, et al. Lifestyle factors among proton pump inhibitor users and nonusers: a cross-sectional study in a population-based setting. *Clin Epidemiol*. 2013;5:493-499.

262. Walker AM. Confounding by indication. *Epidemiology*. 1996;7(4):335-336.

263. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379(9828):1835-1846.

264. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. *Am J Med*. 1980;68(2):255-258.

265. Brookhart MA, Wyss R, Layton JB, Til S. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):604-611.

266. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. *Int J Epidemiol*. 2013;42(4):1012-1014.

267. Rothman KJ. Six Persistent Research Misconceptions. *J Gen Intern Med*. 2014;29(7):1060-1064.

268. O'donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet*. 2030;374(9694):989-997.

269. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009;180(7):713-718.

270. Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular Outcomes and Mortality in Patients Using Clopidogrel With Proton Pump Inhibitors After Percutaneous Coronary Intervention or Acute Coronary Syndrome. *Circulation*. 2009;120(23):1-9.

271. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med*. 2010;170(8):704-710.

272. van Boxel OS, van Oijen MGH, Hagenaars MP, Smout AJPM, Siersema PD. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol*. 2010;105(11):2430-2436; quiz2437.

273. Wayne A Ray KTMMRGCPCWESKHJRDLAKCMS. Outcomes with Concurrent Use of Clopidogrel and Proton-Pump Inhibitors: A Cohort Study. *Ann Intern Med*. 2010;152(6):337-345.

274. Simon T, Verstuyft C, Drouet E, Steg PG, Ferrières J, Danchin N. Genetic determinants of response to clopidogrel and cardiovascular events. 2009;360(4):363-375.

275. Valkhoff VE, t Jong GW, Van Soest EM, Kuipers EJ, Sturkenboom MCJM. Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors. *Aliment Pharmacol Ther*. 2011;33(1):77-88.

276. Banerjee S, Weideman RA, Weideman MW, et al. Effect of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. *Am J Cardiol*. 2011;107(6):871-878.

277. Bundhun PK, Teeluck AR, Bhurtu A, Huang W-Q. Is the concomitant use of clopidogrel and Proton Pump Inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012 - 2016). *BMC cardiovascular disorders*. 2017;17(1):3-11.

278. Hulot J-S, Collet J-P, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol*. 2010;56(2):134-143.

279. Kwok CS, Loke YK. Meta-analysis: effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther*. 2010:1-14.

280. Siller-Matula JM, Jilma B, Schrör K, Christ G, Huber K. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost*. September 2010.

281. Lash TL, Schmidt M, Jensen AØ, Engebjerg MC. Methods to apply probabilistic bias analysis to summary estimates of association. *Pharmacoepidemiol Drug Saf*. 2010;19(6):638-644.

282. Schmidt M, Johansen MB, Robertson DJ, et al. Use of clopidogrel and calcium channel blockers and risk of major adverse cardiovascular events. *Eur J Clin Invest*. 2012;42(3):266-274.

283. Schmidt M, Johansen MB, Maeng M, et al. Concomitant use of clopidogrel and statins and risk of major adverse cardiovascular events following coronary stent implantation. *Br J Clin Pharmacol*. 2012;74(1):161-170.

284. Rothman KJ. A show of confidence. *N Engl J Med*. 1978;299(24):1362-1363.

285. Schmidt M, Maeng M, Jakobsen C-J, et al. Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. *Clin Epidemiol*. 2010;2:137-144.

286. Nielsen LH, Nørgaard BL, Tilsted HH, et al. The Western Denmark Cardiac Computed Tomography Registry: a review and validation study. *Clin Epidemiol*. 2015;7:53-64.

287. Østergaard L, Adelborg K, Sundbøll J, Pedersen L, Loldrup Fosbøl E, Schmidt M. Positive predictive value of infective endocarditis in the Danish National Patient Registry: a validation study. *Epidemiol Infect*. 2018;146(15):1965-1967.

288. Egholm G, Madsen M, Thim T, et al. Evaluation of algorithms for registry-based detection of acute myocardial infarction following percutaneous coronary intervention. *Clin Epidemiol*. 2016;Volume 8:415-423.

289. Lauridsen MD, Gammelager H, Schmidt M, Nielsen H, Christiansen CF. Positive predictive value of International Classification of Diseases, 10(th) revision, diagnosis codes for cardiogenic, hypovolemic, and septic shock in the Danish National Patient Registry. *BMC Med Res Methodol*. 2015;15(1):23.

290. Schmidt M, Johannesdottir SA, Lemeshow S, et al. Obesity in young men, and individual and combined risks of type 2 diabetes, cardiovascular morbidity and death before 55 years of age: a Danish 33-year follow-up study. *BMJ Open*. 2013;3(4):e002698.

291. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200.

292. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020;37:267-279.

293. Knuuti J, Wijns W, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2019;100(k504):106-171.

294. Solomon DH. NSAIDs: Adverse cardiovascular effects. *UpToDate*. February 2020. https://www.uptodate.com/contents/nsaids-adverse-cardiovascular-effects.

295. Danish Society of Cardiology. National clinical guidelines (NBV). Chapter 35.1 on NSAIDs and risk in patients with cardiovascular disease [in Danish, NSAID og risiko ved hjertekarsygdom]. Available at https://nbv.cardio.dk/farmaka. Accessed on 1 November 2020.

296. Schmidt M, Fosbøl EL, Torp-Pedersen C, Olsen A-MS, Christensen B, Gislason G. [Cardiovascular risks of non-steroidal anti-inflammatory drugs treatment]. *Ugeskr Laeger*. 2016;178(V08160612).

297. Schjerning A-M, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574-584.

298. Schmidt M, Olsen AMS, Fosbøl EL, et al. NSAID behandling hos patienter med hjertekarsygdom – et holdningspapir fra Dansk Cardiologisk Selskab. *Cardiologisk Forum*. 2016.

299. Jensen MP. NSAID. Available at http://pro.medicin.dk/laegemiddelgrupper/grupper/213010. Accessed on 1 November 2020. *Dan Pharmaceut Inform*. July 2019.

300. Ording AG, Horvath-Puho E, Prandoni P, et al. Usefulness of CHA2DS2-VASc Score to Predict Stroke Risk Independent of Atrial Fibrillation. *Am J Cardiol*. 2019;124(7):1059-1063.

301. Schmidt M, Szépligeti S, Horvath-Puho E, Pedersen L, Bøtker HE, Sørensen HT. Long-Term Survival Among Patients With Myocardial Infarction Before Age 50 Compared With the General Population: A Danish Nationwide Cohort Study. *Circ Cardiovasc Qual Outcomes*. 2016;9(5):523-531.

302. Schmidt M, Horvath-Puho E, Pedersen L, Sørensen HT, Bøtker HE. Time-dependent effect of preinfarction angina pectoris and intermittent claudication on mortality following myocardial infarction: A Danish nationwide cohort study. *Int J Cardiol*. 2015;187(C):462-469.

303. Schmidt M, Bøtker HE, Pedersen L, Sørensen HT. Young adulthood obesity and risk of acute coronary syndromes, stable angina pectoris, and congestive heart failure: a 36-year cohort study. *Ann Epidemiol*. 2014;24(5):356–361.e1.

304. Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sørensen HT. Acute infections and venous thromboembolism. *J Intern Med*. 2012;271(6):608-618.

305. Schmidt M, Pedersen L, Maeng M, et al. Nonsteroidal antiinflammatory drug use and cardiovascular risks after coronary stent implantation. *Pharmacotherapy*. 2011;31(5):458-468.

306. Schmidt M, Pedersen SB, Farkas DK, et al. Thirteen-year nationwide trends in use of implantable cardioverter-defibrillators and subsequent long-term survival. *Heart Rhythm*. April 2015.

307. Adelborg K, Grove EL, Sundbøll J, Laursen M, Schmidt M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart*. 2016;102(23):1883-1889.

308. Statens legemiddelverk. Voltarol (diklofenak) tabletter og kapsler blir reseptpliktig - iverksetting utsatt. Available at https://legemiddelverket.no/nyheter/diklofenak-tabletter-og-kapsler-blir-reseptpliktig. Accessed on 1 November 2020.

309. Swedish Medical Products Agency. Diclofenac tablets become prescription only drugs. Available at https://www.lakemedelsverket.se/sv/nyheter/tabletter-och-kapslar-med-diklofenak-blir-receptbelagda. Accessed on 1 November 2020. November 2019:k3426–1.

310. Chokesuwattanaskul R, Chiengthong K, Thongprayoon C, et al. Nonsteroidal anti-inflammatory drugs and incidence of atrial fibrillation: a meta-analysis. *QJM*. 2020;113(2):79-85.

311. Chuang S-Y, Hsu P-F, Lin F-J, et al. Association between nonsteroidal anti-inflammatory drugs and atrial fibrillation among a middle-aged population: a nationwide population-based cohort. *Br J Clin Pharmacol*. 2018;84(6):1290-1300.

312. Krijthe BP, Heeringa J, Hofman A, Franco OH, Stricker BH. Non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation: a population-based follow-up study. *BMJ Open*. 2014;4:e004059.

313. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of rofecoxib. *Eur Heart J*. 2012;33(15):1928-1933.

314. Schjerning Olsen A-M, Fosbøl EL, Pallisgaard J, et al. NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction: a nationwide study. *Eur Heart J Cardiovasc Pharmacother*. 2015;1(2):107-114.

315. Liu G, Yan Y-P, Zheng X-X, et al. Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of atrial fibrillation. *Am J Cardiol*. 2014;114(10):1523-1529.

316. Lee T, Lu N, Felson DT, et al. Use of non-steroidal anti-inflammatory drugs correlates with the risk of venous thromboembolism in knee osteoarthritis patients: a UK population-based case-control study. *Rheumatology*. 2016;55(6):1099-1105.

317. Ungprasert P, Srivali N, Wijarnpreecha K, Charoenpong P, Knight EL. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology*. 2015;54(4):736-742.

318. Bergendal A, Adami J, Bahmanyar S, et al. Non-steroidal anti-inflammatory drugs and venous thromboembolism in women. *Pharmacoepidemiol Drug Saf*. 2013;22(6):658-666.

319. Biere-Rafi S, Di Nisio M, Gerdes V, et al. Non-steroidal anti-inflammatory drugs and risk of pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2011;20(6):635-642.

320. Goy J, Paikin J, Crowther M. Rofecoxib does not appear to increase the risk of venous thromboembolism: a systematic review of the literature. *Thromb Res*. 2014;134(5):997-1003.

321. Nagai N, Hoylaerts MF, Gallacher DJ, Lu HR, Lijnen HR. Prothrombotic effect of Rofecoxib in a murine venous thrombosis model. *Thromb Res*. 2008;122(5):668-673.

322. Westgate EJ, FitzGerald GA. Pulmonary embolism in a woman taking oral contraceptives and valdecoxib. *PLoS Med*. 2005;2(7):e197.

323. Chan ALF. Celecoxib-induced deep-vein thrombosis. *Ann Pharmacother*. 2005;39(6):1138.

324. Crofford LJ, Crofford LJ, Oates JC, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors. A report of four cases. *Arthritis Rheum*. 2000;43(8):1891-1896.

325. Janssens ACJW, Gwinn M. Novel citation-based search method for scientific literature: application to meta-analyses. *BMC Med Res Methodol*. 2015;15(1):84.

10. Appendices

The supplementary material for each paper is available online at the journals' websites.

Paper I

BMJ

BMJ 2012;344:e356 doi: 10.1136/bmj.e356

RESEARCH

25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study

Morten Schmidt *junior research fellow*[1 2], Jacob Bonde Jacobsen *biostatistician*[1], Timothy L Lash *professor*[1], Hans Erik Bøtker *professor*[2], Henrik Toft Sørensen *professor*[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Skejby, Brendstrupgårdsvej 100, 8200 Aarhus N, Denmark

Abstract

Objectives To examine 25 year trends in first time hospitalisation for acute myocardial infarction in Denmark, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity.

Design Nationwide population based cohort study using medical registries.

Setting All hospitals in Denmark.

Subjects 234 331 patients with a first time hospitalisation for myocardial infarction from 1984 through 2008.

Main outcome measures Standardised incidence rate of myocardial infarction and 30 day and 31–365 day mortality by sex. Comorbidity categories were defined as normal, moderate, severe, and very severe according to the Charlson comorbidity index, and were compared by means of mortality rate ratios based on Cox regression.

Results The standardised incidence rate per 100 000 people decreased in the 25 year period by 37% for women (from 209 to 131) and by 48% for men (from 410 to 213). The 30 day, 31–365 day, and one year mortality declined from 31.4%, 15.6%, and 42.1% in 1984–8 to 14.8%, 11.1%, and 24.2% in 2004–8, respectively. After adjustment for age at time of myocardial infarction, men and women had the same one year risk of dying. The mortality reduction was independent of comorbidity category. Comparing patients with very severe versus normal comorbidity during 2004–8, the mortality rate ratio, adjusted for age and sex, was 1.96 (95% CI 1.83 to 2.11) within 30 days and 3.89 (3.58 to 4.24) within 31–365 days.

Conclusions The rate of first time hospitalisation for myocardial infarction and subsequent short term mortality both declined by nearly half between 1984 and 2008. The reduction in mortality occurred for all patients, independent of sex and comorbidity. However, comorbidity burden was a strong prognostic factor for short and long term mortality, while sex was not.

Introduction

Despite considerable improvements in prophylaxis and treatment,[1-3] myocardial infarction remains a common life threatening disease and an enormous burden on Western healthcare systems.[1] The incidence of and mortality from myocardial infarction are not continuously monitored by surveillance registries, despite the critical need for ongoing evaluation of its primary and tertiary prevention.

As people age, they are more likely to develop chronic medical conditions. About 45% of the adult population has at least one chronic disease.[4] This proportion increases to 90% in persons older than 65 years,[4] who represent more than half of patients with myocardial infarction.[5] Myocardial infarction shares risk factors with many chronic diseases (such as obesity, diabetes, chronic obstructive pulmonary disease, and cancer[6]), increasing the prevalence of comorbidity among patients with myocardial infarction.[7 8] Comorbidity potentially modifies effectiveness of therapies and the clinical course of a myocardial infarction.[8 9] However, clinical guidelines for treatment of myocardial infarction are based on the results of trials that often exclude patients of advanced age or with a large number of comorbid conditions.[10]

With the availability of new therapies that also benefit older patients,[11] it has become increasingly important to understand the impact of comorbidity on the prognosis of myocardial

Correspondence to: M Schmidt msc@dce.au.dk

Extra material supplied by the author (see http://www.bmj.com/content/344/bmj.e356?tab=related#webextra)

Supplementary figures A and B
Supplementary tables A–D

infarction and to determine whether trends in survival apply to all patients with myocardial infarction.[12] Previous studies on this topic have been limited by size (<4100 participants),[9 13] inclusion period (<6 years),[9 13] or selective inclusion of patients from specific hospitals[9 13] or age groups.[9] Also, the prognostic impact of sex remains unclear because of conflicting study findings.[14-17] We therefore conducted a nationwide, population based, cohort study to examine trends in first time hospitalisation for myocardial infarction over the 25 year period from 1984 to 2008, subsequent short term and long term mortality, and the prognostic impact of sex and comorbidity.

Methods

Setting

We conducted this cohort study in Denmark, which has 5.4 million inhabitants. The Danish National Health Service provides universal, tax supported, healthcare, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed drugs. Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark by means of the unique central personal registry number assigned to each Danish citizen at birth and to residents on immigration.[18]

Acute myocardial infarction

We used the Danish National Registry of Patients[19] to identify all first time hospitalisations for myocardial infarction from 1 January 1984 to 31 December 2008 among Danish born inhabitants aged 15 years or older. This registry contains data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995.[19] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses classified according to ICD-8 (international classification of diseases, 8th revision) until the end of 1993 and ICD-10 (10th revision) thereafter.[19] Patients with myocardial infarction are included in the Danish National Registry of Patients if they died in the ambulance on the way to the hospital or during the hospital admission, but not if they died at home. We used ICD-8 codes 410.09 and 410.99 and ICD-10 code I21 to identify myocardial infarction.

Mortality

We obtained information on all cause mortality until the end of 2009 from the Danish Civil Registration System.[18 20] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[18]

Comorbidity

We obtained information on comorbid conditions from inpatient and outpatient hospital diagnoses (all available primary or secondary diagnoses) recorded in the Danish National Registry of Patients in the five years before the myocardial infarction. To avoid inclusion of complications caused by the myocardial infarction, secondary diagnoses coded during the admission for myocardial infarction were excluded. We categorised the severity of comorbidity using the Charlson comorbidity index,[21] a scoring system that has been adapted for use with hospital discharge data[9] and validated for patients with acute and chronic ischaemic heart disease.[8 9 22 23] The index assigns between one and six points to a range of diseases, depending on the strength of their relation to mortality in the subsequent year (during the era when the Charlson comorbidity index was developed): one point for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes without end organ damage; two points for diabetes with end organ damage, hemiplegia, moderate to severe renal disease, non-metastatic solid tumour, leukaemia, and lymphoma; three points for moderate to severe liver disease; six points for metastatic cancer and AIDS. We computed the total Charlson score for each patient and defined four categories of comorbidity as used in the Predicting Risk of Death in Cardiac Disease Tool (PREDICT) study—that is, total scores of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).[22] Myocardial infarction was not included in the scoring. The Charlson comorbidity index and associated ICD codes are provided in web extra table A on bmj.com.

Statistical analysis

We computed and illustrated graphically the incidence rate of myocardial infarction (standardised to the age distribution of the Danish population in the year 2000) and subsequent 30 day and 31–365 day mortality (standardised to the age distribution of the population diagnosed with myocardial infarction in the year 2000) for men and women from 1984 through 2008.[23] We calculated confidence intervals using the approximate bootstrap method.[24 25] We repeated the analyses for subgroups of patients aged 35–49, 50–59, 60–69, 70–79, and ≥80 years.

We then characterised patients with myocardial infarction according to sex, age, and comorbidity category, overall and for five calendar periods of diagnosis (1984–8, 1989–93, 1994–8, 1999–2003, and 2004–8). We calculated the prevalence of individual Charlson comorbidities registered in the five years preceding the admission for myocardial infarction. We illustrated graphically the change in median age from 1984 through 2008 for both men and women.

We followed all patients until the date of death, emigration, or one year of follow-up, whichever came first. Using the Kaplan-Meier estimator,[25] we computed the 30 day and 31–365 day mortality risk associated with each calendar period of diagnosis and comorbidity category. We used Cox proportional hazards regression to estimate the mortality rate ratio (specifically, the hazard ratio) associated with calendar period of diagnosis and comorbidity category within 30 days and 31–365 days after myocardial infarction.

First, we compared mortality rates across calendar periods, using the earliest period as the reference and adjusting for sex, age groups, and comorbidity categories. To evaluate the potential for residual confounding by age and comorbidity, we repeated the analysis modelling age and comorbidity by three knot cubic splines.[25] The results were consistent with the categorical modelling strategy and are therefore not reported further. Second, we compared mortality rates across comorbidity categories, using normal comorbidity category as the reference and adjusting for sex and age groups. Within the 2004–8 calendar period of diagnosis, we also examined the 30 day and 31–365 day mortality rate ratios associated with the individual Charlson comorbidities, adjusting for the other comorbidities, age, and sex. The proportional hazards assumption was assessed graphically by plotting log(−log(survival function)) against time for all exposure variables and found to be valid.[25]

Results

Incidence

We identified 234 331 first time hospitalisations for myocardial infarction in Denmark from 1984 through 2008. The Danish population in this 25 year period consisted of 5 610 039 Danish born inhabitants aged 15 years or older. The annual standardised incidence rate of myocardial infarction (per 100 000 people) decreased during this period, by 37% for women (from 209 to 131) and by 48% for men (from 410 to 213) (fig 1⇓). A transient increase in incidence occurred between 2000 and 2004 (fig 1). It was driven by the incidence among people aged ≥70 years, particularly those aged ≥80 years (fig 2⇓). For patients younger than 70 years, the incidence steadily decreased throughout the 25 year period (fig 2).

Patient characteristics

Although the female proportion of patients with myocardial infarction increased slightly between the first five year calendar period (35.8%) and the last (38.8%), men still accounted for the majority (62.1%) of all hospitalisations for myocardial infarction (table 1⇓). The median age at time of diagnosis was 75 years for women and 68 for men. While the median age held fairly steady at about 68 years for men, it increased for women from 74 years in 1984 to 77 years in 2008 (web extra fig A on bmj.com). The prevalence of patients with normal comorbidity burden fell from 75.5% to 63.8% between the earliest and latest calendar period (table 1⇓). The percentage of patients with moderate comorbidity increased from 13.2% to 16.2%, the percentage with severe comorbidity increased from 7.4% to 10.5%, and the percentage with very severe comorbidity increased from 3.9% to 9.6% (the prevalence for Charlson scores 1 to 10 is provided in web extra table B). The most prevalent Charlson comorbidities were diabetes (7.0%), stroke (7.0%), congestive heart failure (5.8%), chronic pulmonary disease (5.8%), peripheral vascular disease (5.3%), cancer (5.4%), ulcer disease (2.5%), connective tissue disease (2.1%), and severe renal disease (1.6%).

Mortality

The standardised 30 day and 31–365 day mortality risks after first time myocardial infarction were similar for men and women, decreasing comparably between 1984 and 2008 (fig 3⇓). The 30 day mortality declined from 31.4% (95% confidence interval: 31.0% to 31.8%) during 1984–8 to 14.8% (14.5% to 15.2%) during 2004–8 (table 2⇓). The one year mortality declined overall from 42.1% (41.7% to 42.5%) during 1984–8 to 24.2% (23.8% to 24.7%) during 2004–8; and among 30 day survivors it fell from 15.6% (15.2% to 16.0%) during 1984–8 to 11.1% (10.7% to 11.4%) during 2004–8. When the latest five year period was compared with the earliest, the mortality rate ratio adjusted for age and comorbidity category was 0.37 (95% confidence interval 0.35 to 0.38) within 30 days and 0.48 (0.47 to 0.51) within 31–365 days. Age stratified analyses revealed no difference in mortality among men and women within age categories (web extra fig B on bmj.com).

Prognostic impact of comorbidity

The improvement in mortality after myocardial infarction between 1984 and 2008 was observed for all patients in all age groups, independent of their comorbidity category (fig 4⇓). The 30 day and 31–365 day mortality risks were strongly associated with the patient's category of comorbidity for all five year calendar periods (web extra table C on bmj.com). With normal comorbidity category as the reference, the mortality rate ratios adjusted for age and sex among patients with moderate comorbidity in 2004–8 were 1.35 (95% confidence interval 1.26 to 1.45) within 30 days and 1.83 (1.68 to 2.00) within 31–365 days (table 3⇓). Comparing patients with very severe and normal comorbidity in 2004–8, the adjusted mortality rate ratios were 1.96 (1.83 to 2.11) within 30 days and 3.89 (3.58 to 4.24) within 31–365 days (table 3⇓). The magnitude of the increased mortality rate ratios associated with increasing comorbidity categories was similar across calendar periods (web extra table C). Consistent with the principle that effect estimates are higher among those at lower baseline risk, we found that age modified the mortality rate ratio associated with each comorbidity category, with higher estimates in younger age groups (web extra table D).

Among the individual non-malignant comorbidities, liver disease and dementia were each associated with a roughly doubled mortality rate within 30 days after myocardial infarction compared with patients without comorbidity (table 4⇓). Within 31–365 days, twofold increased mortality rate ratios were also observed for patients with moderate to severe liver or renal diseases. Congestive heart failure, peripheral or cerebrovascular vascular disease, chronic pulmonary disease, and ulcer disease were associated with a 1.2 to 1.3-fold increased mortality rate ratio within 30 days, increasing to 1.5-fold within 31–365 days. Diabetes with end organ damage was associated with 1.3-fold increased short term and long term mortality rate ratios, whereas connective tissue disease was not.

Discussion

In this nationwide cohort study, we found an almost 50% reduction both in the first time hospitalisation for myocardial infarction between 1984 and 2008 and in subsequent short term mortality. During the same period, one year mortality among 30 day survivors declined by a third. The improved survival since 1984 applied to all myocardial infarction patients independently of sex and comorbidity. However, the comorbidity burden measured five years before admission was a strong predictor of mortality within 30 days after myocardial infarction and during the remainder of the first year, whereas sex was not.

Strengths and limitations of study

Several issues should be considered in interpreting our results. The population based design in a country with universal healthcare reduced selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. All patients were followed until death, emigration, or end of follow-up, and hence no one had incomplete registration.

The positive predictive values of diagnoses in the Danish National Registry of Patients have previously been validated and found to exceed 90% for both myocardial infarction (>90%)[26] and the Charlson comorbidities (98% overall).[27] A potential limitation was that patients with sudden cardiac death outside hospital or ambulance or who did not receive a resuscitation attempt at the emergency room were not registered in the Danish National Registry of Patients. To address this limitation, we compared over time the proportion of patients who had myocardial infarctions recorded as cause of death in the Danish Register of Causes of Death without having it or a previous myocardial infarction recorded in the Danish National Registry of Patients. This supplementary analysis revealed that such patients could not account for the observed incidence and mortality trends.

Other diseases such as diabetes and chronic pulmonary disease are likely to be under-represented in the Danish National Registry of Patients, because some patients are treated in primary care only. Although the 7% prevalence of diabetes among patients with myocardial infarction is substantially lower than in other Western countries,[2] it is only slightly lower than reported in the second Danish trial on Acute Myocardial Infarction (DANAMI-2) (11%).[28] Also, because the comparisons were made within a population of patients with myocardial infarction, underascertainment of comorbidities is unlikely to influence substantially the relative mortality estimates associated with comorbidity categories. The mortality data from the Danish Civil Registration System are virtually complete.[18]

As suggested for stable angina pectoris patients,[23] the Charlson comorbidity index could potentially be made even more appropriate for patients with myocardial infarction by assigning greater weight to some diseases (such as liver and renal disease) and omitting others lacking prognostic significance among patients with myocardial infarction (such as connective tissue disease) or with low prevalence (such as hemiplegia, leukaemia, and AIDS).[23 29] Also, peripheral and cerebrovascular disease may to some extent represent "disease staging" of underlying atherosclerosis that has progressed to multiple vascular systems, rather than representing separate disease entities.[29] However, despite these limitations regarding individual comorbidities, the Charlson comorbidity index in its original form has proved an adequate tool for measuring the prognostic impact of total comorbidity burden in patients with myocardial infarction.[9 30]

Comparison with other studies

Our study is the first to examine nationwide 25 year trends in myocardial infarction epidemiology. Its results are in line with previous US,[31-41] UK,[42 43] Australian,[44] and multinational[3 45] studies examining trends in the incidence and outcomes of myocardial infarction. Compared with our study, these studies were conducted over shorter time periods,[34-45] with data collection before the definition of myocardial infarction was amended in 2000,[32-34 38 42 45] or in modest sized cohorts such as the Atherosclerosis Risk in Communities Study,[35] Framingham Heart Study,[32 33] Minnesota Heart Survey,[34] Perth MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) cohort,[44] or Worcester Heart Attack Study.[31 39]

It is estimated that half of the decline in mortality since 1980 is attributable to primary prevention of myocardial infarction—that is, reduction in the prevalence of major cardiovascular risk factors such as smoking, sedentary lifestyle, and uncontrolled high blood pressure.[1 2] The other half is attributable to the introduction of thrombolysis, coronary artery bypass grafting, percutaneous coronary intervention, and improved tertiary medical prevention with antiplatelet regimens, β blockers, angiotensin converting enzyme inhibitors, and statins.[1 3] It is noteworthy that the incidence of myocardial infarction has continued to decline despite increased prevalence of obesity and diabetes.[1 2] The transient increase in incidence between 2000 and 2004 with local maximum in 2002 was presumably attributable to new diagnostic criteria that included troponin as the main diagnostic biomarker of myocardial infarction.[46] Although we did not discriminate between ST segment and non-ST segment elevation myocardial infarction, the changing biomarker use is likely to have increased the detection rate of smaller infarcts and thus predominantly the rates of non-ST segment elevation myocardial infarction.[35 36]

We observed a larger decrease in myocardial infarction incidence among men than women until 1997, after which the decreasing trend seemed independent of sex. One explanation for this difference is that cardiovascular disease previously was considered primarily a man's disease, and thus cardiovascular disease prevention primarily focused on risk modification among men. Also, within the last two to three decades, the lifestyles and risk behaviours of women and men became more similar with regard to smoking, sedentary work, and working outside the home. We observed that sex did not influence the prognosis of myocardial infarction as previously suggested.[14 15] Thus, age is the single most important prognostic factor to control for when comparing mortality from myocardial infarction between men and women.[16 17 47]

Our study is also the first to examine the short and long term mortality risks and rates associated with comorbidity burden in a nationwide population. We observed increased levels of comorbidity over time. This trend may, however, be explained partly by the increase in age at time of diagnosis, a more complete disease registration (owing to the addition of outpatient clinic diagnoses in the Danish National Registry of Patients) from 1995 onwards, and the introduction of the diagnosis related group system as a prospective payment system around 2000. Because short term mortality is likely to be closely related to the severity and progression of myocardial infarction, it is notable that comorbidity had a substantial influence on 30 day mortality. Also important, we found that improvements in survival among patients with myocardial infarction occurred independently of their comorbidity burden. In contrast, survival improvements for other major diseases, such as breast cancer, depend on patients' comorbidity categories, with poorer survival improvement among those with severe comorbidity.[12]

Our large study, including nearly 250 000 patients, extends the results of two smaller studies that also examined the prognostic impact of comorbidity burden as classified by the Charlson comorbidity index.[9 13] O'Connell et al based their analysis on the MONICA study of 4081 people aged 25–69 years who were admitted for myocardial infarction between 1988 and 1994 and who survived for at least 28 days.[9] Their reported association between comorbidity and mortality (adjusted hazard ratio 1.36 (95% confidence interval 1.07 to 1.72) for moderate to severe comorbidity and 2.74 (1.73 to 4.34) for very severe comorbidity) was consistent with our results. Núñez et al examined the association between comorbidity and mortality among 1035 patients admitted to hospital with myocardial infarction between 2000 and 2003.[13] The 30 day and one year mortality rate ratios that they reported were consistent with our results for the calendar period 1999–2003.

Comorbidity may influence the prognosis of myocardial infarction in several ways. Comorbid conditions may directly alter the effectiveness of treatments and affect the course of myocardial infarction. Although comorbidities are likely to increase non-cardiac mortality in particular,[48] the increased short term mortality also suggests an impact on cardiac mortality. Underuse of coronary reperfusion therapy among patients with comorbid diseases may account for some of the increased mortality associated with comorbidity within the first 30 days after hospitalisation for myocardial infarction.[7]

Generalisability, implications, and conclusions

The observed trend for incidence and mortality of myocardial infarction are likely generalisable to most industrial Western societies where changes in lifestyle, risk factor modification, and increasing use of aggressive medical and interventional treatment have followed international recommendations.[2]

Furthermore, the ratio of mortality rates associated with comorbidity categories should be unbiased because the comparisons over time were made between patients all with myocardial infarction.[25]

Our findings have implications for research and clinical care. Clinical trials should include patients with prevalent comorbid illness so that results may be extrapolated to the entire spectrum of patients with myocardial infarction.[5] Cardiovascular disease registries should measure comorbidities to permit fair inferences regarding mortality, process of care, and risk stratification after myocardial infarction.[8 22] Finally, comorbidity should be considered in individual patient counselling, with treatment optimised to improve the outcome both of the comorbid condition and the myocardial infarction. Our findings are particularly important for elderly people, given their high prevalence of comorbidity[4] and the increasing numbers of people of advanced age facing treatment decisions for coronary artery disease.[4 5]

In conclusion, we found that the rate of first time hospitalisation for myocardial infarction and subsequent short term mortality both declined by nearly half between 1984 and 2008. The reduction in mortality occurred for all patients, independent of sex and the severity of comorbidity. However, comorbidity burden was a strong prognostic factor for short and long term mortality, while sex was not.

Contributorship: MS, JBJ, and HTS conceived the study idea and designed the study. JBJ and HTS collected the data. MS, HEB, and HTS reviewed the literature. MS, JBJ, TLL, and HTS directed the analyses, which were carried out by JBJ. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

Funding: The study was supported by the Danish Medical Research Council (grant 271-05-0511), the Clinical Epidemiological Research Foundation, Denmark, and Aarhus University. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from any company for the submitted work. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study; (2) no authors have relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

Ethical approval: Not needed.

Data sharing: No additional data available.

1 Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in US deaths from coronary disease, 1980-2000. *N Eng J Med* 2007;356:2388-98.
2 Steinberg BA, Bhatt DL, Mehta S, Poole-Wilson PA, O'Hagan P, Montalescot G, et al. Nine-year trends in achievement of risk factor goals in the US and European outpatients with cardiovascular disease. *Am Heart J* 2008;156:719-27.
3 Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA* 2007;297:1892-900.
4 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269-76.
5 Beller GA. Are you ever too old to be risk stratified? *J Am Coll Cardiol* 1992;19:1399-401.
6 Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* 2004;109:3244-55.
7 Balzi D, Barchielli A, Buiatti E, Franceschini C, Lavecchia R, Monami M, et al. Effect of comorbidity on coronary reperfusion strategy and long-term mortality after acute myocardial infarction. *Am Heart J* 2006;151:1094-100.
8 Singh M. Scores for post-myocardial infarction risk stratification in the community. *Circulation* 2002;106:2309-14.
9 O'Connell RL, Lim LL. Utility of the Charlson comorbidity index computed from routinely collected hospital discharge diagnosis codes. *Methods Inf Med* 2000;39:7-11.
10 Krumholz HM, Gross CP, Peterson ED, Barron HV, Radford MJ, Parsons LS, et al. Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-1 study. *Am Heart J* 2003;146:839-47.
11 Newell MC, Henry JT, Henry TD, Duval S, Browning JA, Christiansen EC, et al. Impact of age on treatment and outcomes in ST-elevation myocardial infarction. *Am Heart J* 2011;161:664-72.
12 Cronin-Fenton D, Nørgaard M, Jacobsen JF, Garne J, Ewertz M, Lash TL, et al. Comorbidity and survival of Danish breast cancer patients from 1995 to 2005. *Br J Cancer* 2007;96:1462-8.
13 Núñez JE, Núñez E, Fácila L, Bertomeu V, Llàcer A, Bodí V, et al. [Prognostic value of Charlson comorbidity index at 30 days and 1 year after acute myocardial infarction.] *Rev Esp Cardiol* 2004;57:842-9.
14 Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van De Werf F, et al. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Eng J Med* 1999;341:226-32.
15 Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21-9.
16 MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol* 2001;38:729-35.
17 Nicolau JC, Auxiliadora Ferraz M, Nogueira PR, Coimbra Garzon SA, Serrano CV, Ramires JA. The role of gender in the long-term prognosis of patients with myocardial infarction submitted to fibrinolytic treatment. *Ann Epidemiol* 2004;14:17-23.
18 Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011;39:22-5.
19 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
20 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.
21 Charlson ME, Pompei P, Ales KI, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
22 Jacobs DR, Kroenke C, Crow R, Deshpande M, Gu DF, Gatewood L, et al. PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. *Circulation* 1999;100:599-607.
23 Sachdev M, Sun JL, Tsiatis AA, Nelson CL, Mark DB, Jollis JG. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. *J Am Coll Cardiol* 2004;43:576-82.
24 Swift M. A simulation study comparing methods for calculating confidence intervals for directly standardized rates. *Comput Stat Data An* 2010;54:1103-8.
25 Rothman KJ, Greenland S, Lash TL. *Modern epidemiology* . 3rd ed. Lippincott Williams & Wilkins, 2008.
26 Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* 2003;56:124-30.
27 Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.
28 Madsen MM, Busk M, Søndergaard HM, Bøttcher M, Mortensen LS, Andersen HR, et al. Does diabetes mellitus abolish the beneficial effect of primary coronary angioplasty on long-term risk of reinfarction after acute ST-segment elevation myocardial infarction compared with fibrinolysis? (A DANAMI-2 substudy). *Am J Cardiol* 2005;96:1469-75.
29 Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676-82.
30 Chirinos JA, Veerani A, Zambrano JP, Schob A, Perez G, Mendez AJ, et al. Evaluation of comorbidity scores to predict all-cause mortality in patients with established coronary artery disease. *Int J Cardiol* 2007;117:97-102.
31 Floyd KC, Yarzebski J, Spencer FA, Lessard D, Dalen JE, Alpert JS, et al. A 30-year perspective (1975-2005) into the changing landscape of patients hospitalized with initial acute myocardial infarction: Worcester Heart Attack Study. *Circ Cardiovasc Qual Outcomes* 2009;2:88-95.
32 Sytkowski PA, D'Agostino RB, Belanger A, Kannel WB. Sex and time trends in cardiovascular disease incidence and mortality: the Framingham Heart Study, 1950-1989. *Am J Epidemiol* 1996;143:338-50.
33 Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation* 2004;110:522-7.
34 McGovern PG, Jacobs DR, Shahar E, Arnett DK, Folsom AR, Blackburn H, et al. Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. *Circulation* 2001;104:19-24.
35 Myerson M, Coady S, Taylor H, Rosamond WD, Goff DC; ARIC Investigators. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2009;119:503-14.
36 Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Eng J Med* 2010;362:2155-65.
37 Masoudi FA, Foody JM, Havranek EP, Wang Y, Radford MJ, Allman RM, et al. Trends in acute myocardial infarction in 4 US states between 1992 and 2001: clinical characteristics, quality of care, and outcomes. *Circulation* 2006;114:2806-14.
38 Arciero TJ, Jacobsen SJ, Reeder GS, Frye RL, Weston SA, Killian JM, et al. Temporal trends in the incidence of coronary disease. *Am J Med* 2004;117:228-33.

What is already known on this topic

A marked decrease in incidence of acute myocardial infarction and associated mortality has occurred since 1980

As the population ages, an increasing proportion of patients with myocardial infarction will have comorbidities

What this study adds

This study of all 234 331 patients hospitalised in Denmark with first time myocardial infarction between 1984 and 2008 showed a near halving of incidence and short term mortality of myocardial infarction

The reduction in mortality occurred for all patients with myocardial infarction independent of sex and comorbidity

Comorbidity burden was a strong independent predictor of short term and long term mortality, while sex was not

39 McManus D, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg R. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med* 2010;124:40-7.
40 Movahed MR, John J, Hashemzadeh M, Jamal MM. Trends in the age adjusted mortality from acute ST segment elevation myocardial infarction in the United States (1988-2004) based on race, gender, infarct location and comorbidities. *Am J Cardiol* 2009;104:1030-4.
41 Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation* 2010;121:863-9.
42 Capewell S, Livingston BM, MacIntyre K, Chalmers JW, Boyd J, Finlayson A, et al. Trends in case-fatality in 117,718 patients admitted with acute myocardial infarction in Scotland. *Eur Heart J* 2000;21:1833-40.
43 Davies AR, Grundy E, Nitsch D, Smeeth L. Constituent country inequalities in myocardial infarction incidence and case fatality in men and women in the United Kingdom, 1996-2005. *J Public Health (Oxf)* 2011;33:131-8.
44 Briffa T, Hickling S, Knuiman M, Hobbs M, Hung J, Sanfilippo F, et al. Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984-2005. *BMJ* 2009;338:b36.
45 Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999;353:1547-57.
46 Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
47 D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol* 2011;107:651-4.
48 Kostis W, Deng Y, Pantazopoulos J, Moreyra A, Kostis J. Trends in mortality of acute myocardial infarction after discharge from the hospital. *Circ Cardiovasc Qual Outcomes* 2010;3:581-9.

Cite this as: *BMJ* 2012;344:e356

Tables

Table 1| Numbers (percentages) of people with a first time hospitalisation for myocardial infarction in Denmark in five year periods from 1984 through 2008 by sex, age, and comorbidity category

	Calendar periods of diagnosis					
	1984–8 (n=56 454)	1989–93 (n=50 249)	1994–8 (n=42 261)	1999–2003 (n=44 365)	2004–8 (n=41 002)	Total (n=234 331)
Sex:						
Female	20 201 (35.8)	18 691 (37.2)	16 238 (38.4)	17 652 (39.8)	15 926 (38.8)	88 708 (37.9)
Male	36 253 (64.2)	31 558 (62.8)	26 023 (61.6)	26 713 (60.2)	25 076 (61.2)	145 623 (62.1)
Age (years):						
15–34	206 (0.4)	196 (0.4)	223 (0.5)	228 (0.5)	224 (0.5)	1 077 (0.5)
35–49	3 845 (6.8)	3 521 (7.0)	2 974 (7.0)	3 172 (7.1)	3 185 (7.8)	16 697 (7.1)
50–59	8 334 (14.8)	7 241 (14.4)	6 176 (14.6)	6 859 (15.5)	6 296 (15.4)	34 906 (14.9)
60–69	15 610 (27.7)	12 978 (25.8)	10 020 (23.7)	9 604 (21.6)	9 227 (22.5)	57 439 (24.5)
70–79	18 465 (32.7)	16 080 (32.0)	13 309 (31.5)	12 617 (28.4)	10 526 (25.7)	70 997 (30.3)
≥80	9 994 (17.7)	10 233 (20.4)	9 559 (22.6)	11 885 (26.8)	11 544 (28.2)	53 215 (22.7)
Comorbidity category*:						
Normal	42 645 (75.5)	37 771 (75.2)	30 041 (71.1)	28 323 (63.8)	26 157 (63.8)	164 937 (70.4)
Moderate	7 455 (13.2)	6 845 (13.6)	6 409 (15.2)	7 599 (17.1)	6 633 (16.2)	34 941 (14.9)
Severe	4 168 (7.4)	3 701 (7.4)	3 571 (8.4)	4 592 (10.4)	4 295 (10.5)	20 327 (8.7)
Very severe	2 186 (3.9)	1 932 (3.8)	2 240 (5.3)	3 851 (8.7)	3 917 (9.6)	14 126 (6.0)

*Categories of comorbidity were based on Charlson comorbidity index scores of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

Table 2| 30 day and 31–365 day mortality risk and mortality rate ratio after first time hospitalisation for myocardial infarction in Denmark in five year periods of diagnosis from 1984 through 2008

Period of diagnosis	No of patients	Median age (years)	30 day mortality			31–365 day mortality		
			Mortality risk % (95% CI)	Mortality rate ratio (95% CI)		Mortality risk % (95% CI)	Mortality rate ratio (95% CI)	
				Unadjusted	Adjusted*		Unadjusted	Adjusted*
1984–8	56 454	70	31.4 (31.0 to 31.8)	1 (reference)	1 (reference)	15.6 (15.2 to 16.0)	1 (reference)	1 (reference)
1989–93	50 249	70	27.4 (27.1 to 27.8)	0.86 (0.84 to 0.88)	0.84 (0.82 to 0.86)	13.2 (12.9 to 13.6)	0.83 (0.80 to 0.87)	0.79 (0.76 to 0.82)
1994–8	42 261	71	23.8 (23.4 to 24.2)	0.73 (0.71 to 0.75)	0.68 (0.67 to 0.70)	11.7 (11.3 to 12.0)	0.73 (0.70 to 0.76)	0.63 (0.60 to 0.66)
1999–2003	44 365	72	18.1 (17.8 to 18.5)	0.54 (0.52 to 0.55)	0.46 (0.45 to 0.47)	12.2 (11.8 to 12.5)	0.76 (0.73 to 0.79)	0.56 (0.54 to 0.58)
2004–8	41 002	71	14.8 (14.5 to 15.2)	0.43 (0.42 to 0.44)	0.37 (0.35 to 0.38)	11.1 (10.7 to 11.4)	0.69 (0.66 to 0.72)	0.48 (0.47 to 0.51)

*Adjusted for age, sex, and comorbidity category.

Table 3| 30 day and 31–365 day mortality risk and mortality rate ratio after first time hospitalisation for myocardial infarction in Denmark between 2004 and 2008 associated with comorbidity category

Comorbidity category*	No of patients	30 day mortality			31–365 day mortality		
		Mortality risk % (95% CI)	Mortality rate ratio (95% CI)		Mortality risk % (95% CI)	Mortality rate ratio (95% CI)	
			Unadjusted	Adjusted†		Unadjusted	Adjusted†
Normal	26 157	10.8 (10.4 to 11.2)	1 (reference)	1 (reference)	6.2 (5.9 to 6.5)	1 (reference)	1 (reference)
Moderate	6633	19.2 (18.3 to 20.2)	1.85 (1.73 to 1.98)	1.35 (1.26 to 1.45)	15.5 (14.6 to 16.5)	2.64 (2.42 to 2.87)	1.83 (1.68 to 2.00)
Severe	4295	21.4 (20.2 to 22.7)	2.09 (1.94 to 2.25)	1.52 (1.41 to 1.64)	20.6 (19.3 to 22.1)	3.61 (3.30 to 3.96)	2.50 (2.29 to 2.74)
Very severe	3917	27.1 (25.7 to 28.5)	2.72 (2.53 to 2.91)	1.96 (1.83 to 2.11)	31.2 (29.5 to 32.9)	5.80 (5.34 to 6.31)	3.89 (3.58 to 4.24)

* Categories of comorbidity were based on Charlson comorbidity index scores of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

†Adjusted for sex and age.

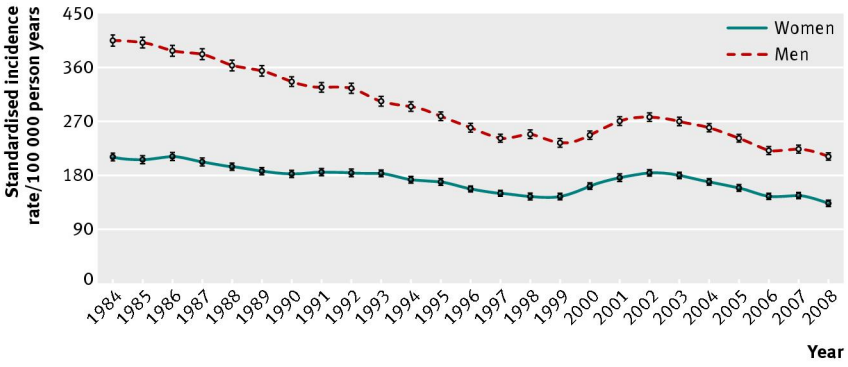
Table 4| 30 day and 31–365 day mortality rate ratios associated with individual comorbidities after first time hospitalisation for myocardial infarction in Denmark between 2004 and 2008

	Adjusted mortality rate ratio (95% CI)*	
	30 day	31-365 days
No comorbid diseases	1 (reference)	1 (reference)
Congestive heart failure	1.30 (1.20 to 1.41)	1.62 (1.48 to 1.78)
Peripheral vascular disease	1.23 (1.13 to 1.34)	1.47 (1.33 to 1.62)
Cerebrovascular disease	1.21 (1.12 to 1.30)	1.52 (1.39 to 1.65)
Dementia	1.81 (1.60 to 2.05)	1.52 (1.28 to 1.81)
Chronic pulmonary disease	1.21 (1.12 to 1.31)	1.54 (1.41 to 1.68)
Connective tissue disease	0.95 (0.82 to 1.09)	1.05 (0.89 to 1.23)
Ulcer disease	1.24 (1.10 to 1.39)	1.50 (1.31 to 1.72)
Mild liver disease	2.00 (1.48 to 2.71)	1.80 (1.22 to 2.67)
Diabetes without end organ damage	0.99 (0.89 to 1.09)	1.19 (1.05 to 1.34)
Diabetes with end organ damage	1.30 (1.16 to 1.46)	1.25 (1.09 to 1.44)
Hemiplegia	1.32 (0.79 to 2.19)	1.68 (0.97 to 2.89)
Moderate to severe renal disease	1.26 (1.11 to 1.42)	2.08 (1.83 to 2.36)
Non-metastatic solid tumour	1.22 (1.12 to 1.34)	1.69 (1.53 to 1.87)
Leukaemia	1.85 (1.32 to 2.59)	1.89 (1.21 to 2.95)
Lymphoma	1.40 (1.07 to 1.83)	1.60 (1.15 to 2.22)
Moderate to severe liver disease	2.21 (1.34 to 3.64)	1.97 (0.94 to 4.10)
Metastatic cancer	1.58 (1.25 to 2.01)	2.91 (2.33 to 3.63)

AIDS was omitted from the table because of its low prevalence (<0.1%).

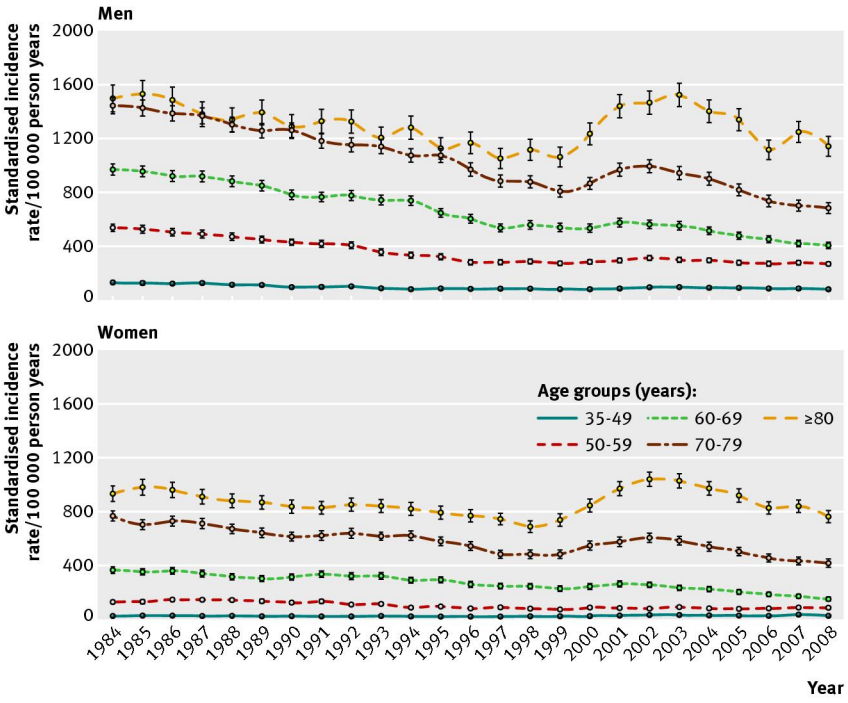
*Adjusted for the other comorbidities, age, and sex.

Figures



Transient increase in incidence starting around 2000 was presumably due to new diagnostic criteria for myocardial infarction[41 46]

Fig 1 Standardised incidence rates for first time hospitalisation for myocardial infarction in Denmark between 1984 and 2008 among men and women



Transient increase in incidence starting around 2000 for older age groups was presumably due to new diagnostic criteria for myocardial infarction[41 46]

Fig 2 Standardised incidence rates for first time hospitalisation for myocardial infarction between 1984 and 2008, for men and women within age groups

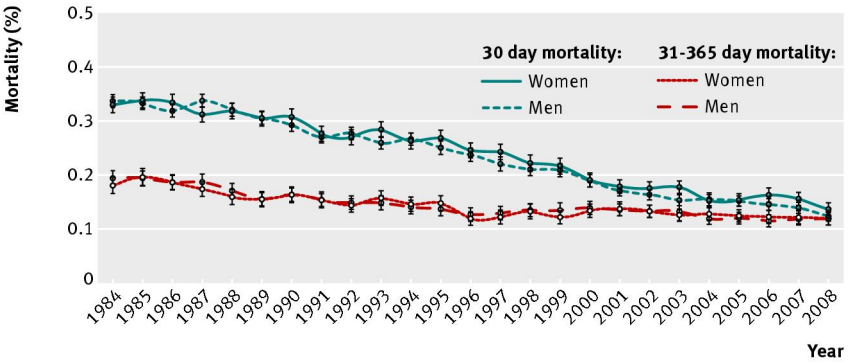


Fig 3 Standardised 30 day and 31–365 day mortality after first time hospitalisation for myocardial infarction among men and women between 1984 and 2008.

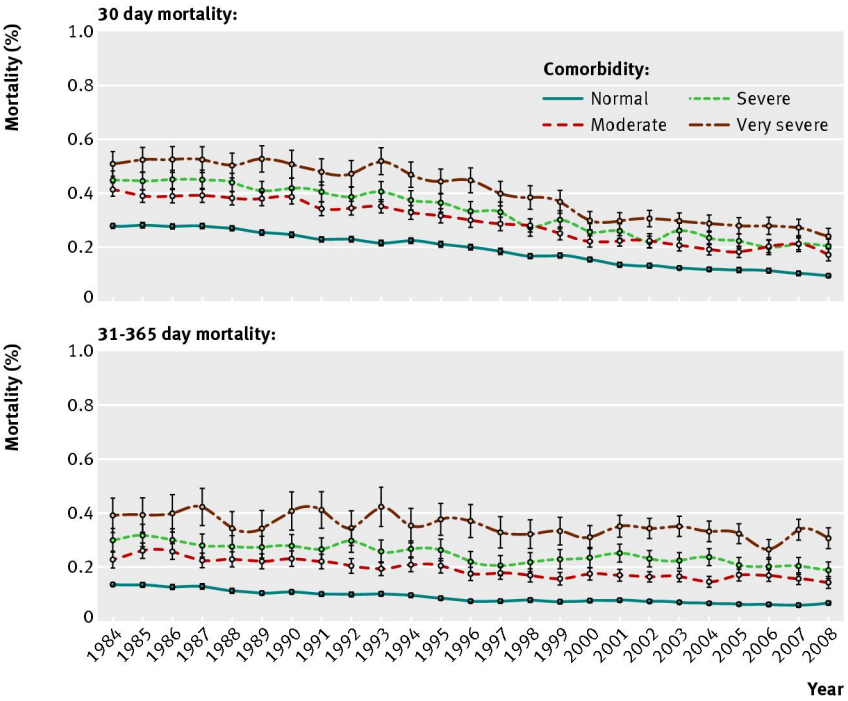


Fig 4 30 day and 31–365 day mortality after first time hospitalisation for myocardial infarction between 1984 and 2008, according to comorbidity category.

Paper II

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.486

Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study

Morten Schmidt[1]*, Sinna Pilgaard Ulrichsen[1], Lars Pedersen[1], Hans Erik Bøtker[2], and Henrik Toft Sørensen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark ; and [2]Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark

Received 21 September 2015; revised 23 November 2015; accepted 12 December 2015

Aims We examined 30-year nationwide trends in heart failure hospitalization and mortality rates, and the prognostic impact of co-morbidity.

Methods and results We conducted a population-based cohort study of 317 161 patients with first-time inpatient hospitalizations for heart failure during 1983–2012. We computed the standardized hospitalization rate and 5-year mortality risk. Co-morbidity levels and calendar periods of diagnosis were compared by means of mortality rate ratios (MRRs) based on Cox regression. The standardized hospitalization rate (per 100 000 persons) decreased between 1983 and 2012 by 25% for women (from 192 to 144) and by 14% for men (from 217 to 186). The decrease reflected an average annual 1% increase until 2000 and a 3.5% decline thereafter. Between 1983–1987 and 2008–2012, 1-year mortality declined from 45% to 33% and 1- to 5-year mortality from 59% to 43%. The decline occurred independently of patients' co-morbidity levels. Comparing 2008–2012 with 1983–1987, the 5-year age-, sex-, and co-morbidity-adjusted MRR was 0.57 [95% confidence interval (CI) 0.56–0.58]. Using low co-morbidity as reference, the adjusted 5-year MRR in 2003–2007 was increased by 43% for moderate, 66% for severe, and 2.2-fold for very severe co-morbidity. The magnitude of co-morbidity-associated mortality increased over time and was highest in the youngest patients.

Conclusions Hospitalization rates for heart failure have declined markedly since 2000 in Denmark. One- and five-year mortality declined >40% over the last three decades. The decline in mortality occurred for patients with all levels of co-morbidity, but co-morbidity burden was a strong prognostic factor.

Keywords Heart failure • Cohort study • Co-morbidity • Incidence • Mortality

Introduction

Heart failure is the most frequent cause of hospitalization among persons aged over 65 years.[1] Despite improvements in treatment, the 5-year mortality rate following heart failure remains similar to that of many cancers.[2] Increasing age at time of diagnosis and risk factors shared with many other chronic diseases make the co-morbidity burden high in heart failure patients.[3] It has therefore become increasingly important to understand how co-morbidities affect mortality in patients with heart failure. We conducted a nationwide population-based cohort study to examine 30-year trends in first-time hospitalization for heart failure, the subsequent long-term mortality rate, and the prognostic impact of co-morbidity.

*Corresponding author. Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43–45, 8200 Aarhus N, Denmark. Tel: +45 87168063, Fax: +45 87167215; E-mail: morten.schmidt@clin.au.dk

Methods

Setting

We conducted this cohort study in Denmark, whose cumulative population was 6 936 205 persons during 1983–2012. The Danish National Health Service provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications.[4] Accurate linkage of all registries at the individual level is possible in Denmark using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[5]

Heart failure

We used the Danish National Patient Registry to identify heart failure hospitalizations from 1 January 1983 to 31 December 2012 among Danish-born residents.[4] This registry contains data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995.[4] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and potentially several secondary diagnoses classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.[4] We identified heart failure using primary and secondary diagnoses from all inpatient admissions. To restrict our study population to patients with first-time hospitalizations, we excluded patients with inpatient or outpatient diagnoses of heart failure prior to our study period (i.e. from 1977 to 1982).

Mortality

We obtained information on all-cause mortality until the end of 2012 from the Danish Civil Registration System.[5] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[5]

Co-morbidity

We identified co-morbidities from inpatient and outpatient hospital diagnoses recorded in the Danish National Patient Registry in the 5 years preceding the heart failure diagnosis.[4] We categorized the severity of co-morbidity using the Charlson Comorbidity Index, a scoring system that has been adapted for use with hospital discharge data and validated for patients with acute and chronic ischaemic heart disease.[6] The Charlson Comorbidity Index assigns between one and six points to a range of diseases, depending on their association with mortality in the subsequent year. We computed the total Charlson score for each patient and defined the following categories of co-morbidity burden: Charlson score of 0 (low), 1 (moderate), 2 (severe), and ≥3 (very severe).[6] Myocardial infarction and heart failure were not included in the scoring. In addition to the Charlson co-morbidities, we also identified previous diagnoses of myocardial infarction, angina pectoris, peripheral arterial disease, AF, endocarditis, cardiomyopathy, valvular heart disease, hypertension, venous thrombo-embolism, obesity, diabetes, ischaemic stroke, and hyperthyroidism.

Statistical analysis

We characterized heart failure patients according to calendar period of diagnosis, age, sex, and co-morbidities. We computed the rate of first-time heart failure hospitalization (standardized to the age distribution of the Danish population in the year 2000) during 1983–2012, overall and according to sex, admission type (acute/non-acute), diagnosis type (primary/secondary), and high-risk patient groups (i.e. those with first-time myocardial infarction, AF, obesity, hypertension, diabetes, cardiomyopathy, or valvular heart disease). The high-risk groups were sampled as separate nationwide cohorts between 1983 and 2012, and the rate of hospitalization for heart failure was then estimated within each group. To examine the rate of heart failure independently of myocardial infarction, we excluded patients with myocardial infarction from all non-myocardial infarction groups. As a sensitivity analysis, we repeated the sampling of heart failure hospitalizations to include also first-time diagnoses from outpatient specialty clinics from 1995 onwards (i.e. when these began to be recorded). We estimated the annual rate of echocardiography and the standardized prevalence proportion of patients diagnosed with heart failure after 2000 (when data became available) who received an implantable cardioverter-defibrillator (ICD), ventricular assist device (HeartMate), or heart transplantation.[4]

We followed patients until date of death, emigration, or 5 years of follow-up, whichever came first. Using the Kaplan–Meier estimator, we computed 1-year, 1- to 5-year (i.e. 366–1826 days), and 5-year mortality risks (standardized to the age distribution of the population diagnosed with heart failure in the year 2000). The analyses were repeated according to age, sex, and co-morbidity, and for high-risk groups. We used Cox proportional hazards regression to estimate the mortality rate ratio (specifically, the hazard ratio) associated with calendar periods of diagnosis (adjusting for age, sex, and co-morbidity), co-morbidity level (adjusting for age and sex), and individual co-morbidities (adjusting for age, sex, and other co-morbidities). The proportional hazards assumption was assessed graphically by plotting log[−log(survival function)] vs. time for all exposure variables and found valid. The study was approved by the Danish Data Protection Agency (record number 1-16-02-1-08).

Research ethics and informed consent

As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

Results

Patient characteristics

Characteristics of the 317 161 patients with a first-time heart failure diagnosis between 1983 and 2012 are shown in *Table 1*. The proportion of males increased from 53% in 1983–1987 to 56% in 2008–2012. Median age at time of diagnosis was 75 years for men and 80 years for women. While the median age for men varied slightly around 75 years (range 73–76 years), it increased steadily for women from 78 years in 1983 to 81 years in 2012.

The proportion of patients with a low co-morbidity burden fell from 66% to 48% between the earliest and latest calendar period (*Table 1*). Concomitantly, the percentage of patients with moderate, severe, and very severe co-morbidity increased from 19, 10, and 5% during 1983–1987 to 21, 16, and 16% during 2008–2012, respectively. The most prevalent cardiovascular morbidities in the latest calendar period were hypertension (30%), angina pectoris

Table 1 Characteristics of patients with a first-time hospitalization for heart failure in Denmark in 5-year periods during 1983–2012

	Calendar periods of diagnosis						
	1983–1987	1988–1992	1993–1997	1998–2002	2003–2007	2008–2012	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	49 158 (100)	53 270 (100)	55 561 (100)	59 774 (100)	52 602 (100)	46 796 (100)	317 161 (100)
Male sex	25 950 (53)	27 635 (52)	28 339 (51)	30 472 (51)	27 710 (53)	26 322 (56)	166 428 (52)
Age, years							
<50	1333 (3)	1261 (2)	1151 (2)	1559 (3)	1916 (4)	1921 (4)	9141 (3)
50–59	3086 (6)	2986 (6)	2965 (5)	3985 (7)	3897 (7)	3581 (8)	20 500 (6)
60–69	9526 (19)	9373 (18)	9099 (16)	9196 (15)	8484 (16)	8334 (18)	54 012 (17)
70–79	18 426 (37)	19 328 (36)	19 584 (35)	19 393 (32)	15 333 (29)	13 098 (28)	105 162 (33)
≥80	16 787 (34)	20 322 (38)	22 762 (41)	25 641 (43)	22 972 (44)	19 862 (42)	128 346 (40)
Median age (IQR)	76 (69–82)	77 (70–83)	78 (71–84)	78 (70–85)	78 (69–85)	78 (68–85)	78 (69–84)
Co-morbidities							
Myocardial infarction	5532 (11)	5609 (11)	5936 (11)	5921 (10)	6063 (12)	5363 (11)	34 424 (11)
Angina pectoris	3043 (6)	3990 (7)	7667 (14)	11 376 (19)	11 805 (22)	10 834 (23)	48 715 (15)
Peripheral vascular disease	2631 (5)	2823 (5)	3364 (6)	4529 (8)	4502 (9)	4553 (10)	22 402 (7)
Atrial fibrillation	2435 (5)	3253 (6)	4911 (9)	7874 (13)	9353 (18)	10 673 (23)	38 499 (12)
Endocarditis	64 (0)	74 (0)	113 (0)	169 (0)	204 (0)	278 (1)	902 (0)
Cardiomyopathy	115 (0)	185 (0)	404 (1)	838 (1)	1223 (2)	1788 (4)	4553 (1)
Valvular heart disease	704 (1)	910 (2)	1650 (3)	2901 (5)	3740 (7)	4503 (10)	14 408 (5)
Hypertension	3231 (7)	3618 (7)	4102 (7)	6569 (11)	10 865 (21)	14 123 (30)	42 508 (13)
Venous thrombo-embolism	868 (2)	785 (1)	808 (1)	1236 (2)	1360 (3)	1479 (3)	6536 (2)
Obesity	1268 (3)	1086 (2)	850 (2)	1137 (2)	1579 (3)	1924 (4)	7844 (2)
Diabetes	4055 (8)	4619 (9)	4918 (9)	5871 (10)	6460 (12)	6910 (15)	32 833 (10)
Ischaemic stroke	801 (2)	838 (2)	1906 (3)	4120 (7)	4036 (8)	3457 (7)	15 158 (5)
Hyperthyroidism	418 (1)	418 (1)	643 (1)	1007 (2)	997 (2)	742 (2)	4225 (1)
Dementia	576 (1)	592 (1)	655 (1)	1117 (2)	1460 (3)	1309 (3)	5709 (2)
Chronic pulmonary disease	4823 (10)	5539 (10)	6665 (12)	8446 (14)	7787 (15)	7377 (16)	40 637 (13)
Connective tissue disease	1250 (3)	1372 (3)	1585 (3)	1914 (3)	1863 (4)	1744 (4)	9728 (3)
Ulcer disease	1462 (3)	1806 (3)	2468 (4)	2874 (5)	2462 (5)	1864 (4)	12 936 (4)
Mild liver disease	273 (1)	253 (0)	263 (0)	348 (1)	353 (1)	375 (1)	1865 (1)
Hemiplegia	188 (0)	159 (0)	117 (0)	114 (0)	99 (0)	121 (0)	798 (0)
Renal disease	822 (2)	740 (1)	951 (2)	1556 (3)	2139 (4)	2800 (6)	9008 (3)
Non-metastatic solid tumour	2098 (4)	2474 (5)	3194 (6)	4566 (8)	4015 (8)	4339 (9)	20 686 (7)
Leukaemia	141 (0)	150 (0)	202 (0)	249 (0)	247 (0)	278 (1)	1267 (0)
Lymphoma	191 (0)	210 (0)	287 (1)	464 (1)	471 (1)	484 (1)	2107 (1)
Moderate to severe liver disease	53 (0)	62 (0)	68 (0)	109 (0)	169 (0)	202 (0)	663 (0)
Metastatic cancer	320 (1)	297 (1)	327 (1)	410 (1)	509 (1)	479 (1)	2342 (1)
Comorbidity burden[a]							
Low	32 375 (66)	34 372 (65)	33 378 (60)	32 146 (54)	26 943 (51)	22 356 (48)	181 570 (57)
Moderate	9498 (19)	10 865 (20)	12 443 (22)	13 981 (23)	11 680 (22)	9831 (21)	68 298 (22)
Severe	4702 (10)	5343 (10)	6138 (11)	7979 (13)	7319 (14)	7267 (16)	38 748 (12)
Very severe	2583 (5)	2690 (5)	3602 (6)	5668 (9)	6660 (13)	7342 (16)	28 545 (9)

IQR, interquartile range.
[a]Four categories of co-morbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1 (moderate), 2 (severe), and ≥3 (very severe).

(23%), AF (23%), diabetes (15%), myocardial infarction (11%), peripheral vascular disease (10%), valvular heart disease (10%), and ischaemic stroke (7%). Chronic pulmonary disease (16%) and cancer (9%) were the most prevalent non-cardiovascular diseases.

Hospitalization rate

The hospitalization rate per 100 000 person-years decreased overall from 210 in 1983 to 164 in 2012 (*Figure 1*). The overall decrease reflected an initial average increase of 1.1% per year until 2000, followed by a subsequent decline of 3.5% per year (*Table 2*). The decline after 2000 occurred despite a marked increase in use of echocardiography in the same period (from 1045 to 2911 patients). The change in rate over time was driven by the hospitalization rate among persons 70 years or older, in particular among persons 80 years or older (*Figure 2*). The hospitalization rate for persons below 60 years of age remained low throughout the 30-year period.

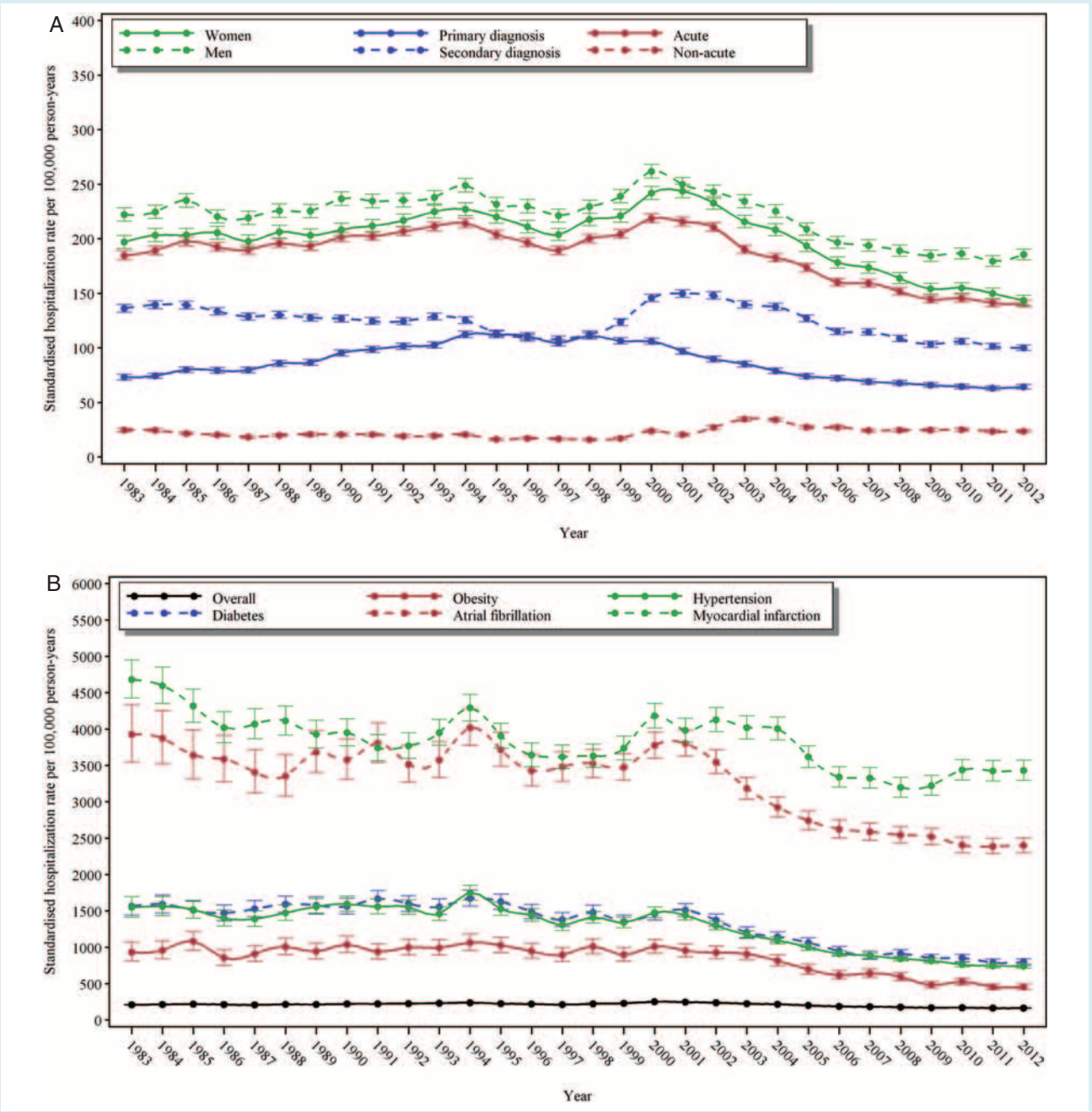


Figure 1 Standardized hospitalization rates for heart failure in Denmark during 1983–2012, according to patient sex, admission type, and diagnosis type (*A*), and patient subgroups (*B*).

Stratified hospitalization rates are provided in the Supplementary material online, *Table S1*. While the hospitalization rate per 100 000 person-years was consistently higher for men than for women, it decreased 25% for women (from 192 to 144) and 14% for men (from 217 to 186). Although the vast majority of patients were admitted acutely, the reduction in the hospitalization rate over time occurred among acute admissions (from 185 to 141 per 100 000 person-years) rather than among non-acute admissions (from 25 to 24). The hospitalization rate for heart failure listed as the primary diagnosis increased from 73 in 1983 to 112 in 1995 before decreasing to 64 in 2012. The hospitalization rate for heart failure listed as a secondary diagnosis decreased consistently from 136 in 1983 to 100 in 2012. The sensitivity analysis revealed that although heart failure was diagnosed primarily during inpatient admissions, an increasing rate of first-time diagnoses was observed in outpatient clinics between 1995 and 2012 (from 18 to 35 per 100 000 person-years).

Table 2 **Mean annual change in the standardized hospitalization rate for heart failure in Denmark during 1983–2012, overall and within high-risk patient groups**

Population	Number at risk	Standardized hospitalization rate (95% CI)[a]			Mean change in standardized hospitalization rate		
		1983	2000	2012	1983–2000	2001–2012	1983–2012
Overall	6 936 205	210 (205–214)	252 (247–256)	164 (161–168)	1.1%	−3.5%	−0.8%
Obesity[b]	237 637	934 (815–1067)	1010 (917–1110)	455 (418–495)	1.0%	−6.1%	−2.0%
Hypertension[b]	633 833	1550 (1415–1697)	1478 (1406–1552)	741 (713–769)	0.0%	−5.5%	−2.3%
Diabetes[b]	316 999	1566 (1443–1696)	1463 (1376–1554)	796 (750–844)	−0.2%	−4.8%	−2.1%
Valvular heart disease[b]	102 555	7393 (5922–10550)	4413 (4077–4770)	2362 (2211–2522)	−1.9%	−4.8%	−3.1%
Atrial fibrillation[b]	321 170	3928 (3551–4335)	3778 (3598–3964)	2403 (2304–2505)	0.0%	−3.6%	−1.5%
Myocardial infarction	313 551	4683 (4426–4952)	4184 (4016–4356)	3432 (3294–3574)	−0.5%	−1.5%	−0.9%
Cardiomyopathy[b]	27 633	6681 (4062–11656)	6219 (5388–7142)	6172 (5551–6853)	2.5%	0.2%	1.6%

CI, confidence interval.
[a]Rate per 100 000 person-years.
[b]Restricted to patients without concurrent history of myocardial infarction.

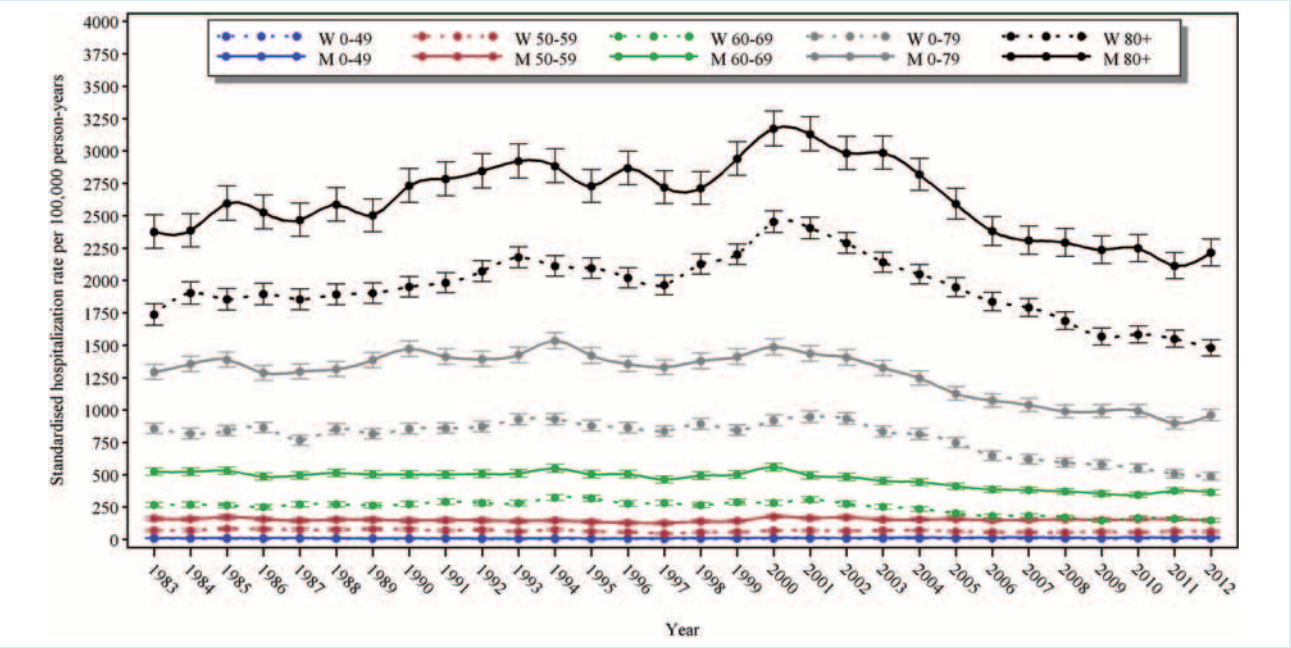


Figure 2 Standardized hospitalization rates for heart failure in Denmark during 1983–2012, by sex and age groups.

The temporal changes in the hospitalization rate for heart failure were similar for high-risk patients, with a decrease after 2000 (*Figure 1*). However, the absolute hospitalization rate varied substantially within the different high-risk patient groups (*Table 2*) and was highest for cardiomyopathy, myocardial infarction, and AF (rate in 2012: 6172, 3432, and 2403 per 100 000 patients, respectively). Among patients diagnosed between 2000 and 2010, 2.81% received ICD implantation (range: 1.27–5.19% within strata of diagnosis year), 0.08% received a ventricular assist device (range: 0.02–0.14%), and 0.18% underwent heart transplantation (range: 0.13–0.23%). The prevalence of heart failure increased consistently throughout the study period (Supplementary material online, *Table S2*).

Mortality

One-year and 1- to 5-year heart failure mortality decreased consistently between 1983 and 2012, overall (*Figure 3*) and within age (*Figure 4*), co-morbidity (Supplementary material online, *Figure S1*), and high-risk patient groups (Supplementary material online, *Figure S2*). While 1-year and 1- to 5-year mortality risks were higher for men than for women in 1983, the difference levelled

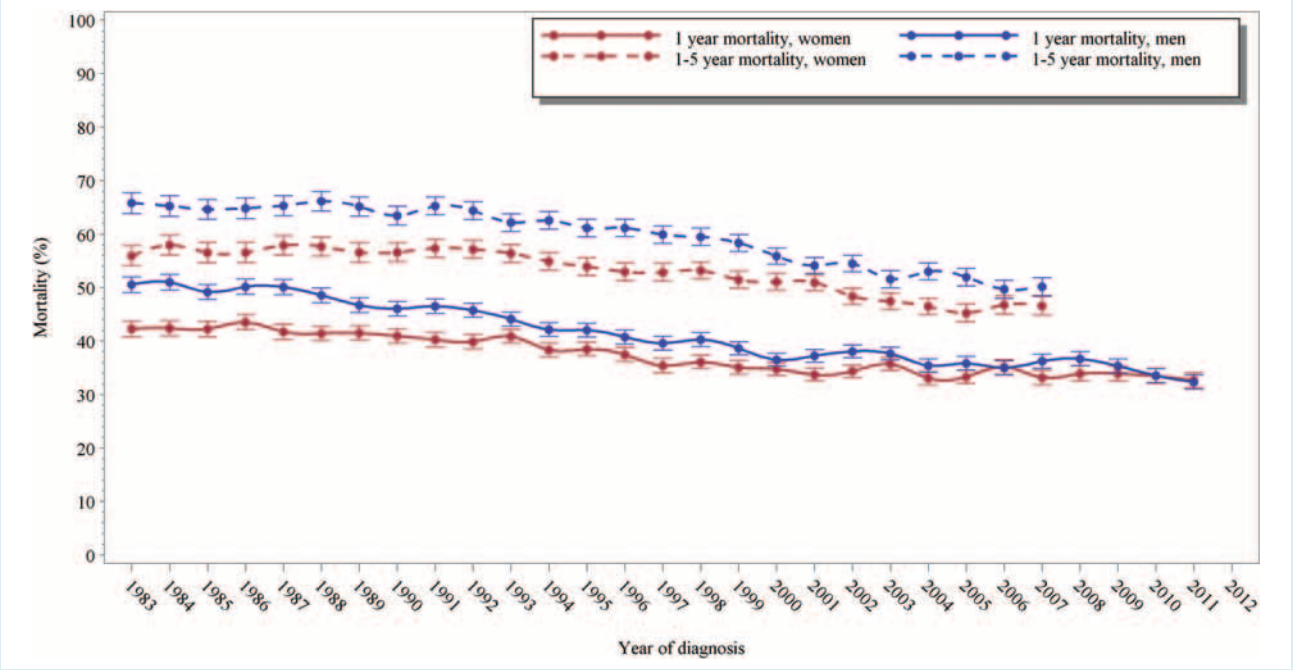


Figure 3 Standardized 1-year and 1- to 5-year mortality risk among men and women after first-time hospitalization for heart failure in Denmark during 1983–2012.

out over time, becoming almost identical by the end of the study period (*Figure 3*). One-year mortality declined from 45% during 1983–1987 to 33% during 2008–2012 (*Table 3*). During the same calendar periods, 1- to 5-year mortality declined from 59% to 43%. Comparing the latest with the first 5-year period, the 5-year age-, sex-, and co-morbidity-adjusted mortality rate ratio was 0.57 (95% confidence interval 0.56–0.58).

Prognostic impact of co-morbidity

Short- and long-term mortality risks were strongly associated with patients' co-morbidity levels (*Table 4*). Using low co-morbidity as reference, the adjusted 5-year mortality rate ratio in 2003–2007 was increased by 43% for moderate co-morbidity, 66% for severe co-morbidity, and 2.2-fold for patients with very severe co-morbidity. The magnitude of co-morbidity-associated mortality following heart failure was consistent within 1-year and 1- to 5-year intervals (*Table 4*), increased from the first to last calendar period (Supplementary material online, *Table S3*), and was highest in the youngest age groups (Supplementary material online, *Table S4*).

For individual non-malignant co-morbidities, the 5-year mortality rate ratio was increased by close to 20% among patients with valvular heart disease and ulcer disease; 30% among patients with diabetes, ischaemic stroke, hemiplegia, and intermittent claudication; 50% among patients with chronic pulmonary disease; 70–80% among patients with mild liver disease, renal disease, and dementia; and 2.2-fold among patients with severe liver disease (Supplementary material online, *Figure S3*).

Discussion

The rate of first-time hospitalization for heart failure increased slightly in Denmark between 1983 and 2000 and declined markedly thereafter. During the 30-year period, the 5-year mortality rate following heart failure declined by >40%. The reduction in mortality over time occurred for all age, sex, co-morbidity, and high-risk patient groups. Co-morbidity burden, measured 5 years before admission, was a strong prognostic factor for both short- and long-term mortality following first-time hospitalization for heart failure.

Comparison with the existing literature

Compared with our study, previous country-specific studies were conducted over shorter time periods.[7–15] Overall, hospitalization rates for heart failure in Western populations seem to have peaked in the 1990s and declined thereafter. This trend has been observed in The Netherlands (1980–1999),[16] Scotland (1986–2003),[14] Sweden (1987–2006),[7] New Zealand (1988–2008),[12] Australia (1990–2007),[13] Canada (1999–2007),[10] France (2000–2012),[15] and the USA (2001–2009).[8] The peak and subsequent decline in first-time hospitalizations occurred in the early 1990s in Western Australia,[13] in the mid 1990s in Sweden and Scotland,[7,14] and in the late 1990s in New Zealand.[12] However, not all populations experienced a decline in hospitalization rates. Most strikingly, Spain experienced markedly increasing hospitalization rates for heart failure up to 2005, with a subsequent apparent levelling off.[11] The reduction in mortality risk following heart failure was consistently

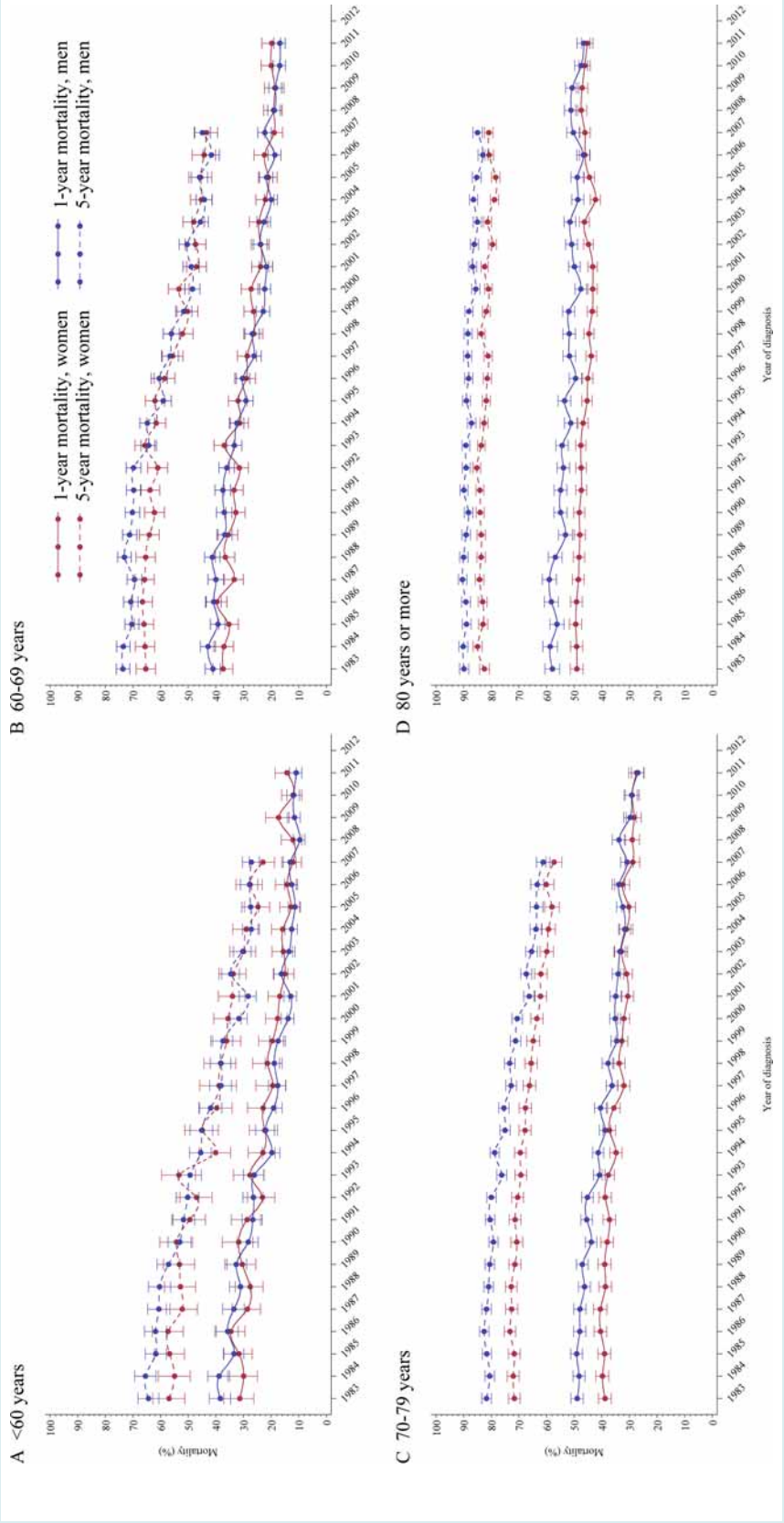


Figure 4 One-year and 5-year mortality risk among men and women after first-time hospitalization for heart failure in Denmark during 1983–2012, by age strata.

Table 3 Mortality risk and mortality rate ratio after first-time diagnosis of heart failure by 5-year calendar periods of diagnosis

		Mortality estimates (95% CIs)					
		1-year mortality		1- to 5-year mortality		Overall 5-year mortality	
Period of diagnosis	No.	Mortality risk, % (95% CI)	Mortality rate ratio (95% CI)[a]	Mortality risk, % (95% CI)	Mortality rate ratio (95% CI)[a]	Mortality risk, % (95% CI)	Mortality rate ratio (95% CI)[a]
1983–1987	49 158	45.4 (44.9–45.8)	1 (reference)	58.5 (57.9–59.1)	1 (reference)	77.3 (76.9–77.7)	1 (reference)
1988–1992	53 270	43.3 (42.9–43.8)	0.90 (0.89–0.92)	59.1 (58.5–59.6)	0.99 (0.96–1.01)	76.8 (76.4–77.2)	0.94 (0.92–0.95)
1993–1997	55 561	39.7 (39.3–40.2)	0.77 (0.76–0.79)	55.9 (55.4–56.4)	0.87 (0.85–0.89)	73.4 (73.1–73.8)	0.81 (0.80–0.83)
1998–2002	59 774	36.1 (35.7–36.5)	0.66 (0.65–0.67)	50.9 (50.4–51.4)	0.74 (0.73–0.76)	68.6 (68.2–69.0)	0.69 (0.68–0.70)
2003–2007	52 602	34.6 (34.2–35.0)	0.62 (0.60–0.63)	45.1 (44.5–45.6)	0.62 (0.61–0.63)	64.1 (63.7–64.5)	0.62 (0.61–0.63)
2008–2012	46 796	32.7 (32.3–33.2)	0.56 (0.55–0.58)	42.5 (39.8–45.3)	0.56 (0.54–0.58)	61.3 (59.5–63.2)	0.57 (0.56–0.58)

CI, confidence interval.
[a]Adjusted for age, sex, and co-morbidity level.

Table 4 Mortality after first-time diagnosis of heart failure in Denmark during 2003–2007, by co-morbidity level.

		Mortality estimates (95% confidence intervals)					
		1-year mortality		1- to 5-year mortality		Overall 5-year mortality	
Co-morbidity level[a]	No.	Mortality risk, %[b]	Mortality rate ratio[c]	Mortality risk, %[b]	Mortality rate ratio[c]	Mortality risk, %[b]	Mortality rate ratio[c]
Low	26 943	27.6 (27.1–28.2)	1 (reference)	37.0 (36.4–37.7)	1 (reference)	54.4 (53.8–55.0)	1 (reference)
Moderate	11 680	37.1 (36.2–38.0)	1.37 (1.32–1.42)	52.2 (51.1–53.4)	1.51 (1.45–1.57)	69.9 (69.1–70.8)	1.43 (1.39–1.47)
Severe	7319	42.5 (41.3–43.6)	1.65 (1.58–1.72)	54.6 (53.1–56.1)	1.66 (1.58–1.74)	73.9 (72.8–74.9)	1.66 (1.61–1.71)
Very severe	6660	49.9 (48.7–51.1)	2.12 (2.04–2.21)	64.3 (62.7–65.9)	2.26 (2.15–2.37)	82.1 (81.2–83.0)	2.18 (2.11–2.25)

[a]Four categories of co-morbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1 (moderate), 2 (severe), and ≥3 (very severe).
[b]Standardized on age and sex.
[c]Adjusted for age and sex.

observed in all the above countries. The trends we observed for the heart failure hospitalization rate and the mortality rate were similar to those in previous reports for patients with myocardial infarction[9] and AF.[17] Moreover, we add to the existing literature by providing data on hospitalization and mortality rates in additional high-risk patient groups.

Factors probably contributing to the decline in the hospitalization rate for heart failure after 2000 include (i) reductions in the prevalence of smoking, sedentary lifestyle, and uncontrolled high blood pressure; (ii) declining incidence of myocardial infarction; (iii) tertiary medical treatment after myocardial infarction with renin–angiotensin inhibitors, beta-blockers, aldosterone inhibitors, and statins; and (iv) the increasing number of heart failure patients diagnosed and treated in the primary care setting only. Of note, the decrease in hospitalization rates occurred despite an increasing prevalence of obesity, diabetes, and AF. The continued high hospitalization rate for heart failure following myocardial infarction underscores the continued need for new and better treatment strategies, including strategies to prevent reperfusion injury such as remote ischaemic pre-conditioning.[18] The decline in heart failure mortality is probably driven by improved guideline-recommended processes of care.[19] Still, 1- and 5-year mortality after diagnosed heart failure remains remarkably high.

Consistent with previous cohort studies including >200 patients, we showed that co-morbidity level was a strong prognostic factor for heart failure.[20,21] Among individual co-morbidities, COPD,[21–24] depression,[24] diabetes,[21,22,24] immobility,[22] stroke,[21–24] chronic kidney disease,[24] cancer,[21–24] dementia,[21–24] and liver disease[23] have previously been emphasized as poor prognostic factors for survival.

Co-morbidities may affect the course of heart failure by changing the physiological response to therapy, altering the effectiveness of patient preferences for treatment, and reducing patients' ability to adhere to recommendations.[25] Some co-morbidities, such as pulmonary, renal, and liver dysfunction, are often also associated with systemic inflammation and may affect LV function directly.[25]

Study strengths and limitations

The study's population-based design, within the setting of a tax-supported universal healthcare system and with virtually

complete follow-up of all patients, reduced selection biases.[5] All data were collected prospectively throughout the 30-year study period. Still, long-term trends in hospitalization rates should be interpreted with caution due to the introduction of new diagnostic technologies, changes in hospital admission practices (including the addition of outpatient contacts to the Danish National Patient Registry in 1995), and changes in disease classification systems over time (particularly the transition from ICD-8 to ICD-10).[4] The change from ICD-8 to ICD-10 may account for the transient increase in the hospitalization rate in around 1994. Increasing use of echocardiography starting in the late 1980s may have influenced the increasing hospitalization rate until 2000, but cannot explain the observed decline since 2000. The slight increase in first-time diagnoses received in outpatient clinics after 1995 also cannot explain the overall decrease in hospitalization rates after 2000. Mortality rates were calculated among inpatients and thus may not apply to patients diagnosed only in the outpatient setting.

A limitation shared with nearly all previous studies was that we studied hospitalization rates rather than true incidence rates. First-time hospitalization rates may reflect the incidence of the most severe and symptomatic cases of heart failure. While we lacked detailed clinical data such as the NYHA class or EF, we did have data on use of ICD, ventricular assist devices, and heart transplantation as measures of disease severity. Also, hospitalization rates among high-risk patients, who are more likely to undergo evaluation for cardiac dysfunction, are likely to be closer to the true incidence than hospitalization rates in the general population. Although the magnitude of hospitalization rates and true incidence rates may differ, the trend of declining hospitalization rates since 2000 still may reflect a decline in incidence. It falls to future studies to examine long-term trends in readmission rates.

The positive predictive values are adequate for heart failure (81–100%), myocardial infarction (82–100%), AF (92–99%), and co-morbidities included in the Charlson Comorbidity Index (97% overall).[4] The classification of admissions as acute and non-acute has an overall positive predictive value and sensitivity of 98%.[4] Co-morbidities such as diabetes and hypertension are likely to be under-reported in the Danish National Patient Registry, because some co-morbidities may be treated only in primary care.[4] Although the 10% prevalence of diabetes observed among patients with heart failure in Denmark may be lower than in other Western countries, it is only slightly lower than the prevalence reported in the second Danish trial on Acute Myocardial Infarction (DANAMI-2) (11%).[26] When estimating the prognostic effect of co-morbidities, it is important to emphasize that the comparisons were made within the heart failure cohort; under-reporting of co-morbidities is therefore unlikely to influence the relative mortality estimates substantially. Increasing levels of co-morbidity over time may also be explained in part by older age at time of diagnosis for women, the addition of outpatient clinic diagnoses to the Danish National Patient Registry starting in 1995, and the introduction of diagnosis-related groups as a prospective payment system around 2000. The increasing co-morbidity burden we observed in heart failure patients is also consistent with findings from other heart failure cohorts for whom a range of co-morbidities, in particular hypercholesterolaemia, diabetes, obesity, kidney disease, thyroid disease, and osteoporosis, have been reported to be increasingly prevalent among heart failure patients.[3] Mortality data were complete and accurate.[5]

Conclusions

The first-time hospitalization rate for heart failure in Denmark has declined markedly since 2000. Subsequent 5-year mortality declined by >40% over the last 30 years. The decline in mortality was independent of co-morbidity burden, but co-morbidity burden was a strong prognostic factor.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 1-year and 1-5-year mortality risk after first-time hospitalisation for heart failure in Denmark during 1983–2012, by comorbidity level.

Figure S2 One- and 5-year mortality after first-time hospitalisation for heart failure in Denmark during 1983–2012 within high-risk patient groups.

Figure S3 Five-year mortality rate ratio associated with individual comorbidities after first-time diagnosis of heart failure, 2003–2007.

Table S1 Standardized rate of first-time hospitalisation for heart failure in Denmark, 1983–2012.

Table S2 Prevalence of first-time hospitalisation for heart failure in Denmark, 1983–2012.

Table S3 Mortality risk and mortality rate ratio after first-time diagnosis of heart failure associated with comorbidity level, by 5-year calendar periods of diagnosis.

Table S4 Mortality after first-time hospitalisation for heart failure in Denmark during 2003–2007, according to comorbidity and age categories.

Funding

The study was supported by the Department of Clinical Epidemiology's Research Foundation, Aarhus University Research Foundation, Augustinus Foundation, Arvid Nilsson's Foundation, Bønnelykkefonden stiftet af Otto Bønnelykke og Zenia Grete Bønnelykke, the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation (H.T.S.), and the Danish Research Council (grants 11–108354 and 11–115818). None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Conflict of interest: none declared.

Authors' contributions: M.S. conceived the study idea and designed the study. H.T.S. and L.A.P. established and designed the cohort. M.S. reviewed the literature and directed the study-specific analyses, which were carried out by S.P.U. under the supervision of L.A.P. All authors participated in the discussion and interpretation

of the results. M.S. organized the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. H.T.S. is the guarantor.

References

1. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. *J Am Coll Cardiol* 2013;**61**:1259–1267.
2. Stewart S, Ekman I, Ekman T, Odén A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). *Circ Cardiovasc Qual Outcomes* 2010;**3**:573–580.
3. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med* 2011;**124**:136–143.
4. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen H. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.
5. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–549.
6. Jacobs DR, Kroenke C, Crow R, Deshpande M, Gu DF, Gatewood L, Blackburn H. PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. *Circulation* 1999;**100**:599–607.
7. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J* 2014;**35**:25–32.
8. Chen J, Dharmarajan K, Wang Y, Krumholz HM. National trends in heart failure hospital stay rates, 2001 to 2009. *J Am Coll Cardiol* 2013;**61**:1078–1088.
9. Chen J, Hsieh AF-C, Dharmarajan K, Masoudi FA, Krumholz HM. National trends in heart failure hospitalization after acute myocardial infarction for Medicare beneficiaries: 1998–2010. *Circulation* 2013;**128**:2577–2584.
10. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ* 2012;**184**:E765–E773.
11. Gomez-Soto FM, Andrey JL, Garcia-Egido AA, Escobar MA, Romero SP, Garcia-Arjona R, Gutierrez J, Gomez F. Incidence and mortality of heart failure: a community-based study. *Int J Cardiol* 2011;**151**:40–45.
12. Wasywich CA, Gamble GD, Whalley GA, Doughty RN. Understanding changing patterns of survival and hospitalization for heart failure over two decades in New Zealand: utility of 'days alive and out of hospital' from epidemiological data. *Eur J Heart Fail* 2010;**12**:462–468.
13. Teng T-HK, Finn J, Hobbs M, Hung J. Heart failure: incidence, case fatality, and hospitalization rates in Western Australia between 1990 and 2005. *Circ Heart Fail* 2010;**3**:236–243.
14. Jhund PS, MacIntyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JWT, Capewell S, McMurray JJV. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;**119**:515–523.
15. Gabet A, Juillière Y, Lamarche-Vadel A, Vernay M, Olié V. National trends in rate of patients hospitalized for heart failure and heart failure mortality in France, 2000–2012. *Eur J Heart Fail* 2015;**17**:583–590.
16. Mosterd A, Reitsma JB, Grobbee DE. Angiotensin converting enzyme inhibition and hospitalisation rates for heart failure in the Netherlands, 1980 to 1999: the end of an epidemic? *Heart* 2002;**87**:75–76.
17. McManus DD, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, Harrington J, Goldberg RJ. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). *Am J Cardiol* 2013;**111**:1460–1465.
18. Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, Pedersen L, Sørensen HT, Bøtker HE, CONDI Investigators. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J* 2014;**35**:168–175.
19. Nakano A, Johnsen SP, Frederiksen BL, Svendsen ML, Agger C, Schjødt I, Egstrup K. Trends in quality of care among patients with incident heart failure in Denmark 2003–2010: a nationwide cohort study. *BMC Health Serv Res* 2013;**13**:391.
20. Clarke B, Howlett J, Sapp J, Andreou P, Parkash R. The effect of comorbidity on the competing risk of sudden and nonsudden death in an ambulatory heart failure population. *Can J Cardiol* 2011;**27**:254–261.
21. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. *Arch Intern Med* 2002;**162**:1689–1694.
22. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Geriatric conditions and subsequent mortality in older patients with heart failure. *J Am Coll Cardiol* 2010;**55**:309–316.
23. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;**290**:2581–2587.
24. Ahluwalia SC, Gross CP, Chaudhry SI, Ning YM, Leo-Summers L, Van Ness PH, Fried TR. Impact of comorbidity on mortality among older persons with advanced heart failure. *J Gen Intern Med* 2012;**27**:513–519.
25. Triposkiadis FK, Skoularigis J. Prevalence and importance of comorbidities in patients with heart failure. *Curr Heart Fail Rep* 2012;**9**:354–362.
26. Madsen MM, Busk M, Søndergaard HM, Bøttcher M, Mortensen LS, Andersen HR, Nielsen TT, DANAMI-2 Investigators. Does diabetes mellitus abolish the beneficial effect of primary coronary angioplasty on long-term risk of reinfarction after acute ST-segment elevation myocardial infarction compared with fibrinolysis? (A DANAMI-2 substudy). *Am J Cardiol* 2005;**96**:1469–1475.

Paper III

Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity

Morten Schmidt, Jacob B. Jacobsen, Søren P. Johnsen, et al.

Neurology 2014;82;340-350 Published Online before print December 20, 2013
DOI 10.1212/WNL.0000000000000062

Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity

Morten Schmidt, MD
Jacob B. Jacobsen, MSc
Søren P. Johnsen, PhD
Hans E. Bøtker, PhD
Henrik T. Sørensen, PhD

Correspondence to Dr. Schmidt: morten.schmidt@dadlnet.dk

ABSTRACT

Objectives: To examine 18-year trends in short-term and long-term stroke mortality and the prognostic influence of comorbidity.

Methods: We conducted a nationwide population-based cohort study. Using the Danish National Registry of Patients, covering all Danish hospitals, we identified all 219,354 patients with a first-time hospitalization for stroke during 1994–2011. We computed standardized 30-day, 1-year, and 5-year mortality by sex. Comorbidity categories were defined by Charlson Comorbidity Index scores of 0 (none), 1 (moderate), 2 (severe), and 3 or more (very severe). Calendar periods of diagnosis (1994–1998, 1999–2003, 2004–2008, and 2009–2011) and comorbidity categories were compared by means of mortality rate ratios based on Cox regression.

Results: Over time, the 30-day mortality rate ratio adjusted for age, sex, and comorbidity decreased by approximately 45% for ischemic stroke (standardized risk decreased from 17.2% in 1994–1998 to 10.6% in 2009–2011) and by 35% for intracerebral hemorrhage (from 43.2% to 33.8%). The absolute mortality reduction occurred for all levels of comorbidity. Five-year mortality risk decreased from 56.4% in 1994–1998 to 46.1% in 2004–2008 for ischemic stroke and from 66.1% to 61.0% for intracerebral hemorrhage. Comparing very severe comorbidity with no comorbidity, 30-day and 5-year mortality rate ratios were both approximately 2.5-fold increased for ischemic stroke and 1.7-fold increased for intracerebral hemorrhage.

Conclusions: Short- and long-term mortality improved considerably between 1994 and 2011 for all types of stroke. Short-term mortality improved regardless of comorbidity burden. However, comorbidity burden was a strong prognostic factor for both short- and long-term mortality.
Neurology® 2014;82:340–350

GLOSSARY

CCI = Charlson Comorbidity Index; **CI** = confidence interval; **DNRP** = Danish National Registry of Patients; ***ICD*** = *International Classification of Diseases*; **MRR** = mortality rate ratio; **mRS** = modified Rankin Scale.

In coming decades, stroke is projected to remain a leading cause of death and disability worldwide, exceeded only by myocardial infarction.[1] Whereas myocardial infarction in Western populations has undergone a dramatic 50% decline in short-term mortality rates over the last 25 years,[2] short- and long-term mortality trends for stroke subtypes are less clear and remain to be examined in a nationwide setting.[3]

More than two-thirds of all strokes occur among persons aged 65 years or older.[4] This age group, in which 9 of 10 persons have at least one chronic disease, is projected to increase from 20% of the total population in 2000 to 35% in 2050.[1] Stroke shares risk factors with many chronic diseases (e.g., myocardial infarction, obesity, hypertension, kidney disease, diabetes, and cancer)—further increasing the prevalence of comorbidity among stroke patients.

With the aging of the population, it has become increasingly important to understand how comorbidity affects mortality from stroke. In previous research, patients' overall comorbidity burden has been found to increase inpatient mortality from stroke.[5] However, few studies have

Supplemental data at www.neurology.org

From the Departments of Clinical Epidemiology (M.S., J.B.J., S.P.J., H.T.S.) and Cardiology (M.S., H.E.B.), Aarhus University Hospital, Denmark.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

examined postdischarge outcomes in light of comorbidity levels.[6–9] Available studies were small (fewer than 1,000 participants) and selected patients from specific hospitals.[6–9]

We therefore conducted a population-based cohort study to examine nationwide trends in short- and long-term mortality after first-time hospitalization for ischemic stroke and intracerebral hemorrhage between 1994 and 2011, and the prognostic influence of comorbidity.

METHODS

Setting. We conducted the study in Denmark, which had 5,233,159 Danish-born inhabitants aged 15 years or older between 1994 and 2011. The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications. Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[10]

Stroke. There is a long tradition in Denmark for hospitalizing patients with acute stroke (an estimated 90% are admitted).[11] The Danish National Registry of Patients (DNRP)[12] contains data on dates of admission and discharge from all Danish nonpsychiatric hospitals since 1977 and from emergency room and outpatient specialist clinic visits since 1995.[12] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses classified according to *ICD-8* until the end of 1993 and *ICD-10* thereafter.[12] Patients with stroke are included in the DNRP if they died in the ambulance on the way to the hospital or during hospital admission, but not if they died at home without being hospitalized. To avoid problems stemming from the different registration criteria and different quality of the *ICD-8* and *ICD-10* systems, we restricted to all first-time inpatient hospitalizations for ischemic stroke and intracerebral hemorrhage among Danish-born inhabitants aged 15 years or older during the period January 1, 1994 to December 31, 2011 (all codes are provided in table e-1 on the *Neurology*® Web site at www.neurology.org). We classified *unspecified strokes* (40% of all stroke diagnoses) as ischemic strokes because more than two-thirds of all unspecified strokes are known to be ischemic strokes.[13,14] To restrict our study population to patients with incident events, we excluded patients who had diagnoses of cerebrovascular disease or hemiplegia before the stroke admission in our study period.

Mortality. We obtained information on all-cause mortality until the end of 2011 from the Danish Civil Registration System.[10] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[10]

Comorbidity. We obtained information on comorbid conditions using inpatient and outpatient hospital diagnoses recorded in the DNRP during the 15 years preceding the stroke (both primary and secondary diagnoses). To avoid considering stroke-related complications as comorbidities, other diagnoses coded during the hospital admission for stroke were excluded from the analyses.

We categorized severity of comorbidity using the Charlson Comorbidity Index (CCI), a scoring system that has been adapted for use with hospital discharge data.[8,15] The CCI assigns between 1 and 6 points to a range of diseases, depending on the strength of their relation with mortality.[8,15] We computed the total CCI score for each patient and defined 4 categories of comorbidity, i.e., total scores of 0 (none), 1 (moderate), 2 (severe), and 3 or higher (very severe).[16] Cerebrovascular disease and hemiplegia were not included in the scoring.

Statistical analysis. We characterized patients according to sex, age, and comorbidity, both overall and for 4 calendar periods of diagnosis (1994–1998, 1999–2003, 2004–2008, and 2009–2011). We illustrated graphically the age distribution at time of diagnosis and the change in median age from 1994 to 2011 for both men and women.

We followed all patients until date of death, emigration, 5 years of follow-up, or December 31, 2011, whichever came first. We illustrated graphically the 30-day, 1-year, and 5-year mortality (standardized to the age distribution of the population diagnosed with stroke in the year 2000). We computed confidence intervals (CIs) using the delta method. We repeated the analyses according to type of stroke (ischemic stroke and intracerebral hemorrhage) and in strata of age and sex. We used the Kaplan-Meier estimator to compute 30-day, 31- to 365-day, 1- to 5-year (specifically, 366- to 1,826-day), and overall 5-year mortality risks associated with the 4 calendar periods of diagnosis and comorbidity categories.

Within the same follow-up periods, we used Cox proportional-hazards regression to compute the hazard ratio as a measure of the mortality rate ratio (MRR) associated with the calendar period of diagnosis and comorbidity category. First, we compared mortality rates across calendar periods, using the earliest period as the reference and adjusting for sex, age, and comorbidity categories. Second, we compared mortality rates across comorbidity categories, using the "no comorbidity" category as the reference and adjusting for sex and age groups. For the 2004–2008 calendar period of diagnosis (to allow for up to 5 years of follow-up), we repeated the analyses for individual comorbidities included in the CCI plus atrial fibrillation or flutter, adjusting for age, sex, and the other individual comorbidities.

To reduce possible inaccurate coding in the DNRP, we conducted a subanalysis restricted to patients diagnosed after 2003 (when radiology data became available) and who had either a CT or MRI scan during their hospitalization. The proportional-hazards assumption was assessed graphically by log–log plots and found to be valid. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents. The study was approved by the Danish Data Protection Agency (record number 1-16-02-1-08). Because this study did not involve contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

RESULTS

Patient characteristics. We identified 219,354 first-time hospitalizations for stroke (table 1). Half of the patients were women. The median age was 77 years for women and 71 for men. While the median age decreased for ischemic stroke between 1994 and 2011 (from 73 to 71 years for men and from 78 to 77 years for women), it increased for intracerebral hemorrhage (from 66 to 71 years for men and from 71 to 75 years for women). Based on inpatient and outpatient hospital diagnoses within the 15 years

Table 1 Characteristics of patients with a first-time hospitalization for stroke in Denmark, 1994–2011

	Ischemic stroke					Intracerebral hemorrhage					
	Calendar periods of diagnosis					Calendar periods of diagnosis					
	1994–1998	1999–2003	2004–2008	2009–2011	Total	1994–1998	1999–2003	2004–2008	2009–2011	Total	Total
Total	52,495 (100)	59,439 (100)	53,545 (100)	29,115 (100)	194,594 (100)	6,175 (100)	7,194 (100)	7,237 (100)	4,154 (100)	24,760 (100)	219,354 (100)
Sex											
Female	25,813 (49.2)	29,776 (50.1)	26,251 (49.0)	14,028 (48.2)	95,868 (49.3)	2,948 (47.7)	3,543 (49.2)	3,579 (49.5)	1,978 (47.6)	12,048 (48.7)	107,916 (49.2)
Male	26,682 (50.8)	29,663 (49.9)	27,294 (51.0)	15,087 (51.8)	98,726 (50.7)	3,227 (52.3)	3,651 (50.8)	3,658 (50.5)	2,176 (52.4)	12,712 (51.3)	111,438 (50.8)
Age, y											
15–49	2,639 (5.0)	3,216 (5.4)	3,537 (6.6)	2,113 (7.3)	11,505 (5.9)	753 (12.2)	858 (11.9)	767 (10.6)	418 (10.1)	2,796 (11.3)	14,301 (6.5)
50–59	5,011 (9.5)	6,808 (11.5)	6,265 (11.7)	3,356 (11.5)	21,440 (11.0)	897 (14.5)	1,122 (15.6)	1,014 (14.0)	559 (13.5)	3,592 (14.5)	25,032 (11.4)
60–69	9,854 (18.8)	11,018 (18.5)	11,193 (20.9)	6,408 (22.0)	38,473 (19.8)	1,387 (22.5)	1,391 (19.3)	1,483 (20.5)	914 (22.0)	5,175 (20.9)	43,648 (19.9)
70–79	17,599 (33.5)	18,496 (31.1)	14,839 (27.7)	7,838 (26.9)	58,772 (30.2)	1,865 (30.2)	2,017 (28.0)	1,934 (26.7)	1,050 (25.3)	6,866 (27.7)	65,638 (29.9)
≥80	17,392 (33.1)	19,901 (33.5)	17,711 (33.1)	9,400 (32.3)	64,404 (33.1)	1,273 (20.6)	1,806 (25.1)	2,039 (28.2)	1,213 (29.2)	6,331 (25.6)	70,735 (32.2)
Comorbidity burden[a]											
None	31,242 (59.5)	33,918 (57.1)	29,413 (54.9)	15,430 (53.0)	110,003 (56.5)	4,196 (68.0)	4,648 (64.6)	4,348 (60.1)	2,297 (55.3)	15,489 (62.6)	125,492 (57.2)
Moderate	10,189 (19.4)	11,201 (18.8)	10,065 (18.8)	5,263 (18.1)	36,718 (18.9)	945 (15.3)	1,142 (15.9)	1,174 (16.2)	685 (16.5)	3,946 (15.9)	40,664 (18.5)
Severe	6,606 (12.6)	8,033 (13.5)	7,254 (13.5)	4,126 (14.2)	26,019 (13.4)	645 (10.4)	824 (11.5)	936 (12.9)	585 (14.1)	2,990 (12.1)	29,009 (13.2)
Very severe	4,458 (8.5)	6,287 (10.6)	6,813 (12.7)	4,296 (14.8)	21,854 (11.2)	389 (6.3)	580 (8.1)	779 (10.8)	587 (14.1)	2,335 (9.4)	24,189 (11.0)
Comorbidities											
Myocardial infarction	4,362 (8.3)	4,841 (8.1)	4,278 (8.0)	2,252 (7.7)	15,733 (8.1)	263 (4.3)	302 (4.2)	381 (5.3)	228 (5.5)	1,174 (4.7)	16,907 (7.7)
Congestive heart failure	4,223 (8.0)	5,111 (8.6)	4,606 (8.6)	2,457 (8.4)	16,397 (8.4)	262 (4.2)	343 (4.8)	420 (5.8)	256 (6.2)	1,281 (5.2)	17,678 (8.1)
Atrial fibrillation or flutter	4,553 (8.7)	6,373 (10.7)	6,693 (12.5)	4,234 (14.5)	21,853 (11.2)	359 (5.8)	550 (7.6)	840 (11.6)	576 (13.9)	2,325 (9.4)	24,178 (11.0)
Peripheral vascular disease	3,779 (7.2)	4,779 (8.0)	4,394 (8.2)	2,596 (8.9)	15,548 (8.0)	269 (4.4)	360 (5.0)	425 (5.9)	254 (6.1)	1,308 (5.3)	16,856 (7.7)
Dementia	909 (1.7)	1,342 (2.3)	1,586 (3.0)	948 (3.3)	4,785 (2.5)	80 (1.3)	153 (2.1)	241 (3.3)	169 (4.1)	643 (2.6)	5,428 (2.5)
Chronic pulmonary disease	3,369 (6.4)	4,552 (7.7)	5,050 (9.4)	3,129 (10.7)	16,100 (8.3)	354 (5.7)	426 (5.9)	557 (7.7)	418 (10.1)	1,755 (7.1)	17,855 (8.1)
Connective tissue disease	1,499 (2.9)	1,964 (3.3)	2,065 (3.9)	1,213 (4.2)	6,741 (3.5)	175 (2.8)	201 (2.8)	229 (3.2)	161 (3.9)	766 (3.1)	7,507 (3.4)
Ulcer disease	3,022 (5.8)	3,562 (6.0)	3,216 (6.0)	1,652 (5.7)	11,452 (5.9)	305 (4.9)	399 (5.5)	414 (5.7)	210 (5.1)	1,328 (5.4)	12,780 (5.8)
Mild liver disease	378 (0.7)	493 (0.8)	583 (1.1)	337 (1.2)	1,791 (0.9)	86 (1.4)	141 (2.0)	133 (1.8)	80 (1.9)	440 (1.8)	2,231 (1.0)
Diabetes without end-organ damage	3,026 (5.8)	2,898 (4.9)	2,447 (4.6)	1,476 (5.1)	9,847 (5.1)	185 (3.0)	190 (2.6)	211 (2.9)	152 (3.7)	738 (3.0)	10,585 (4.8)
Diabetes with end-organ damage	1,697 (3.2)	2,498 (4.2)	2,657 (5.0)	1,580 (5.4)	8,432 (4.3)	113 (1.8)	187 (2.6)	231 (3.2)	176 (4.2)	707 (2.9)	9,139 (4.2)
Moderate to severe renal disease	811 (1.5)	1,200 (2.0)	1,502 (2.8)	992 (3.4)	4,505 (2.3)	143 (2.3)	169 (2.3)	179 (2.5)	150 (3.6)	641 (2.6)	5,146 (2.3)
Nonmetastatic solid tumor	3,974 (7.6)	5,307 (8.9)	5,194 (9.7)	3,328 (11.4)	17,803 (9.1)	411 (6.7)	598 (8.3)	712 (9.8)	485 (11.7)	2,206 (8.9)	20,009 (9.1)

Continued

Table 1 Continued

	Ischemic stroke					Intracerebral hemorrhage				
	Calendar periods of diagnosis					Calendar periods of diagnosis				
	1994–1998	1999–2003	2004–2008	2009–2011	Total	1994–1998	1999–2003	2004–2008	2009–2011	Total
Leukemia	111 (0.2)	146 (0.2)	171 (0.3)	116 (0.4)	544 (0.3)	39 (0.6)	39 (0.5)	50 (0.7)	33 (0.8)	161 (0.7)	705 (0.3)
Lymphoma	191 (0.4)	288 (0.5)	358 (0.7)	172 (0.6)	1,009 (0.5)	24 (0.4)	43 (0.6)	46 (0.6)	27 (0.6)	140 (0.6)	1,149 (0.5)
Moderate to severe liver disease	96 (0.2)	157 (0.3)	205 (0.4)	149 (0.5)	607 (0.3)	23 (0.4)	46 (0.6)	65 (0.9)	55 (1.3)	189 (0.8)	796 (0.4)
Metastatic cancer	305 (0.6)	443 (0.7)	560 (1.0)	373 (1.3)	1,681 (0.9)	41 (0.7)	62 (0.9)	104 (1.4)	73 (1.8)	280 (1.1)	1,961 (0.9)

Data are presented as n (%). AIDS was omitted from the table because of its low prevalence (<0.0%).
[a] Four categories of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (none), 1 (moderate), 2 (severe), and 3 or more (very severe) comorbidities.

before the stroke diagnosis, 57.2% had no comorbidity, 18.5% had moderate comorbidity, 13.2% had severe comorbidity, and 11.0% had very severe comorbidity. From the first to the last calendar period, the proportion of patients without any comorbidity decreased 6.5 percentage points for ischemic stroke (from 59.5% to 53.0%) and 12.7 percentage points for intracerebral hemorrhage (from 68.0% to 55.3%), while the proportion of patients with very severe comorbidity increased 6.3 percentage points (from 8.5% to 14.8%) for ischemic stroke and 7.8 percentage points (from 6.3% to 14.1%) for intracerebral hemorrhage. The most prevalent comorbidities at the time of stroke diagnosis were atrial fibrillation or flutter (11.0%), cancer (10.9%), diabetes (9.0%), congestive heart failure (8.1%), chronic pulmonary disease (8.1%), peripheral vascular disease (7.7%), myocardial infarction (7.7%), ulcer disease (5.8%), connective tissue disease (3.4%), dementia (2.5%), and severe renal disease (2.3%).

Mortality. Age-standardized 30-day and 1-year mortality risks were comparable for men and women and decreased similarly between 1994 and 2011 (figure 1). This finding held within age groups (figure e-1). The 5-year mortality risk also decreased similarly for men and women. However, the risk was higher for men than women (figure 1) in the age groups above 70 years (figure e-1).

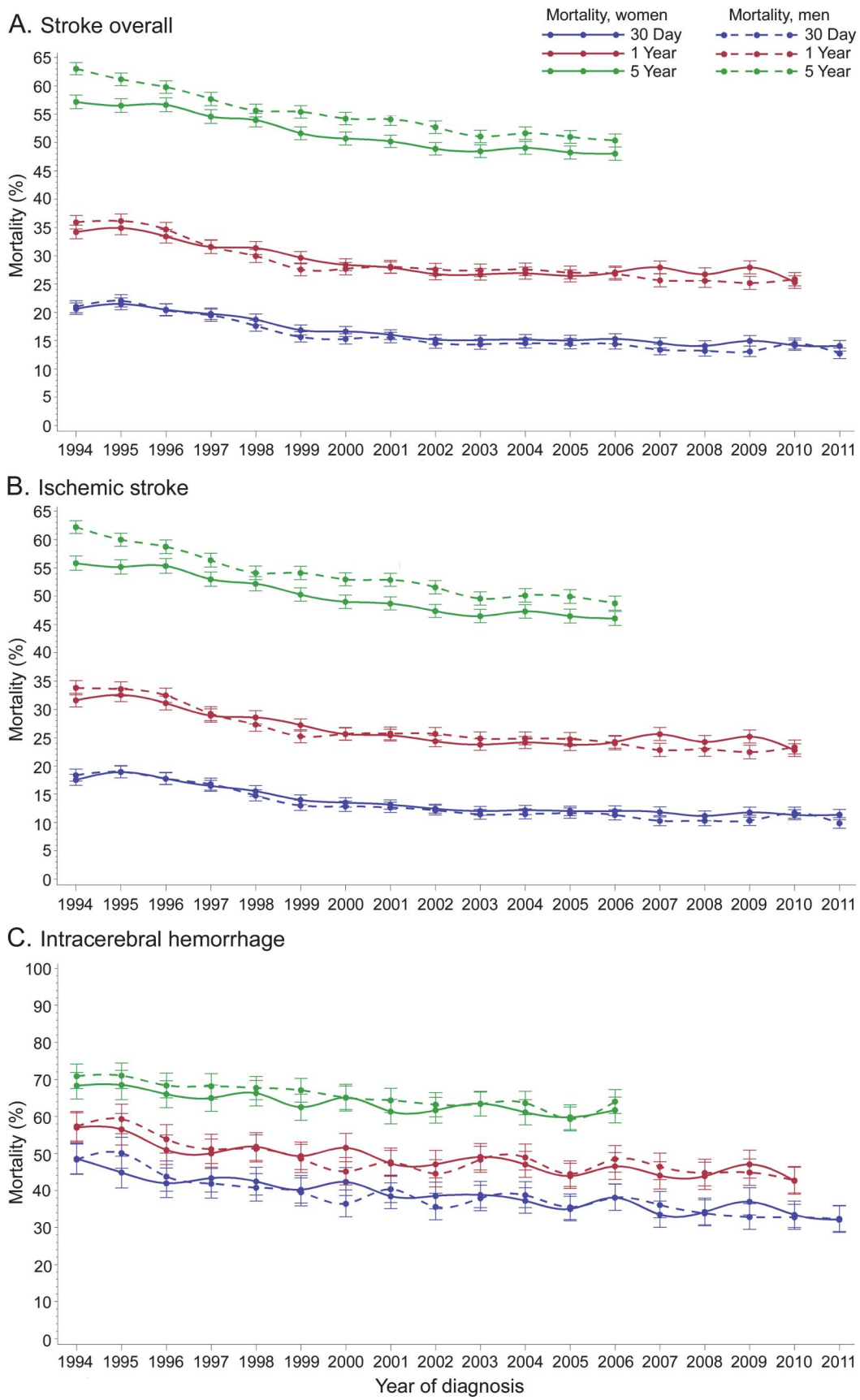
Thirty-day mortality risk declined overall from 20.0% in 1994–1998 to 13.5% in 2009–2011 (table 2), corresponding approximately to a 40% reduction in MRR after adjusting for age, sex, and comorbidity (MRR = 0.62, 95% CI: 0.60–0.64). Mortality risks decreased from 17.2% in 1994–1998 to 10.6% in 2009–2011 for ischemic stroke and from 43.2% in 1994–1998 to 33.8% in 2009–2011 for intracerebral hemorrhage. This overall reduction in 30-day mortality reflected a decrease of approximately 45% for ischemic stroke (MRR = 0.56, 95% CI: 0.54–0.58) and of 35% for intracerebral hemorrhage (MRR = 0.67, 95% CI: 0.63–0.72).

The 1-year mortality risk among 30-day survivors also decreased substantially from 1994–1998 to 2009–2011. The adjusted MRR was 0.73 (95% CI: 0.70–0.76) for ischemic stroke and 0.79 (95% CI: 0.69–0.91) for intracerebral hemorrhage.

When we compared calendar periods with up to 5 years of follow-up, we observed that overall 5-year mortality declined from 56.4% in 1994–1998 to 46.1% in 2004–2008 for ischemic stroke (MRR = 0.70, 95% CI: 0.69–0.72) and from 66.1% in 1994–1998 to 61.0% in 2004–2008 for intracerebral hemorrhage (MRR = 0.78, 95% CI: 0.75–0.82).

Prognostic influence of comorbidity. Throughout the 18-year study period, higher levels of comorbidity

Figure 1 Standardized mortality risk estimates after first-time hospitalization for stroke among men and women between 1994 and 2011



(A) Stroke overall. (B) Ischemic stroke. (C) Intracerebral hemorrhage.

Table 2 Mortality after first-time hospitalization for stroke by 5-year calendar periods of diagnosis

Period of diagnosis	No.	Median age, y	30 d		31–365 d		1–5 y		Overall 5 y	
			Mortality risk, %	Mortality rate ratio[a]	Mortality risk, %	Mortality rate ratio[a]	Mortality risk, %	Mortality rate ratio[a]	Mortality risk, %	Mortality rate ratio[a]
Stroke overall										
1994–1998	58,670	74	20.0 (19.7–20.3)	1 (reference)	16.4 (16.1–16.7)	1 (reference)	36.3 (35.8–36.8)	1 (reference)	57.4 (57.0–57.8)	1 (reference)
1999–2003	66,633	74	15.4 (15.1–15.7)	0.73 (0.71–0.75)	14.4 (14.1–14.7)	0.82 (0.80–0.85)	32.5 (32.1–33.0)	0.84 (0.82–0.86)	51.1 (50.7–51.5)	0.80 (0.79–0.81)
2004–2008	60,782	74	14.1 (13.8–14.4)	0.66 (0.64–0.68)	13.9 (13.6–14.2)	0.78 (0.76–0.81)	29.5 (29.0–29.9)	0.74 (0.72–0.76)	47.8 (47.4–48.3)	0.72 (0.71–0.74)
2009–2011	33,269	73	13.5 (13.1–13.9)	0.62 (0.60–0.64)	13.3 (12.8–13.7)	0.74 (0.71–0.77)	—	—	—	—
Ischemic stroke										
1994–1998	52,495	75	17.2 (16.9–17.6)	1 (reference)	16.5 (16.1–16.8)	1 (reference)	36.9 (36.4–37.4)	1 (reference)	56.4 (55.9–56.8)	1 (reference)
1999–2003	59,439	75	12.6 (12.4–12.9)	0.69 (0.67–0.72)	14.3 (14.0–14.6)	0.82 (0.79–0.85)	32.8 (32.4–33.3)	0.83 (0.81–0.85)	49.7 (49.3–50.1)	0.79 (0.78–0.80)
2004–2008	53,545	74	11.1 (10.9–11.4)	0.60 (0.58–0.62)	13.8 (13.5–14.1)	0.77 (0.75–0.80)	29.6 (29.1–30.1)	0.73 (0.72–0.75)	46.1 (45.6–46.5)	0.70 (0.69–0.72)
2009–2011	29,115	73	10.6 (10.3–11.0)	0.56 (0.54–0.58)	13.1 (12.6–13.5)	0.73 (0.70–0.76)	—	—	—	—
Intracerebral hemorrhage										
1994–1998	6,175	70	43.2 (42.0–44.5)	1 (reference)	15.4 (14.3–16.7)	1 (reference)	29.4 (27.7–31.0)	1 (reference)	66.1 (64.9–67.3)	1 (reference)
1999–2003	7,194	71	38.2 (37.1–39.3)	0.83 (0.78–0.87)	14.6 (13.6–15.7)	0.86 (0.77–0.97)	29.1 (27.7–30.6)	0.90 (0.82–0.98)	62.6 (61.5–63.7)	0.85 (0.82–0.89)
2004–2008	7,237	72	36.2 (35.1–37.3)	0.75 (0.71–0.79)	15.4 (14.4–16.5)	0.86 (0.77–0.97)	27.8 (26.3–29.3)	0.81 (0.74–0.89)	61.0 (59.9–62.2)	0.78 (0.75–0.82)
2009–2011	4,154	72	33.8 (32.4–35.2)	0.67 (0.63–0.72)	15.2 (13.8–16.7)	0.79 (0.69–0.91)	—	—	—	—

[a] Adjusted for age, sex, and comorbidity category.

were associated with higher short- and long-term mortality risks (figure e-2). From 1994–1998 to 2009–2011, the overall 30-day mortality risk decreased from 16.8% to 9.7% for patients without comorbidity and from 30.1% to 23.2% for patients with very severe comorbidity (table e-2). This decrease in mortality across levels of comorbidity was also seen for stroke subtypes (table e-2).

In 2004–2008, stroke patients without comorbidity had an overall 10.5% 30-day mortality risk, increasing to 36.6% within 5 years (table 3). The corresponding mortality risks associated with very severe comorbidity were 23.9% and 74.5%. Compared with patients without comorbidity, the 30-day MRR was 1.36 (95% CI: 1.28–1.44) for moderate comorbidity, 1.57 (95% CI: 1.47–1.66) for severe comorbidity, and 2.14 (95% CI: 2.02–2.27) for very severe comorbidity. Similar overall 5-year MRRs were observed (table 3). The increased MRR associated with comorbidity burden was consistent for both ischemic stroke and intracerebral hemorrhage (table 3), although slightly higher for ischemic stroke. It was also consistent across calendar periods of diagnosis (table e-2). In age-stratified analyses, comorbidity burden had the strongest effect on the MRR in the younger age groups (table e-3).

The effect of individual comorbidities on mortality risk within 5 years is shown in table 4. Among individual noncancer comorbidities, the 30-day MRR was increased approximately 15% for ulcer disease and diabetes with end-organ damage, 20% for peripheral vascular disease, 25% for chronic pulmonary disease, 35% for congestive heart failure and atrial fibrillation or flutter, 45% for moderate to severe renal disease, 60% for dementia, and 1.8- to 2.4-fold for mild to severe liver disease. Myocardial infarction, connective tissue disease, and diabetes without end-organ damage were not associated with any substantial differences in short-term mortality. The magnitude of all 5-year MRRs was similar to the 30-day MRRs (estimates for stroke subtypes are provided in table e-4). The subanalysis including only patients with CT or MRI supported the overall results.

DISCUSSION Short-term and long-term mortality risk improved considerably between 1994 and 2011 for both ischemic stroke and intracerebral hemorrhage. Although patients with intracerebral hemorrhage had a 2 to 3 times higher 30-day mortality risk than patients with ischemic stroke, the absolute mortality reduction over time was fairly similar for both stroke subtypes and occurred for all levels of comorbidity. However, comorbidity burden was a strong prognostic factor for both short-term and long-term mortality.

Table 3 Mortality risk and mortality rate ratio after first-time hospitalization for stroke in Denmark by comorbidity category, 2004–2008

		5-y mortality estimates (95% confidence intervals)							
		30 d		31–365 d		1–5 y		Overall 5 y	
Comorbidity category[a]	No.	Mortality risk, %	Mortality rate ratio[b]	Mortality risk, %	Mortality rate ratio[b]	Mortality risk, %	Mortality rate ratio[b]	Mortality risk, %	Mortality rate ratio[b]
Stroke overall									
None	33,761	10.5 (10.1–10.8)	1 (reference)	9.2 (8.9–9.6)	1 (reference)	22.0 (21.5–22.5)	1 (reference)	36.6 (36.1–37.1)	1 (reference)
Moderate	11,239	15.5 (14.8–16.2)	1.36 (1.28–1.44)	15.8 (15.0–16.5)	1.51 (1.42–1.61)	35.4 (34.3–36.5)	1.52 (1.45–1.59)	54.0 (53.0–55.0)	1.46 (1.42–1.51)
Severe	8,190	18.2 (17.4–19.1)	1.57 (1.47–1.66)	20.2 (19.2–21.2)	1.86 (1.75–1.99)	40.4 (39.0–41.9)	1.68 (1.60–1.77)	61.1 (60.0–62.2)	1.69 (1.63–1.75)
Very severe	7,592	23.9 (22.9–24.9)	2.14 (2.02–2.27)	28.0 (26.9–29.2)	2.79 (2.62–2.96)	53.4 (51.8–55.0)	2.57 (2.44–2.70)	74.5 (73.4–75.5)	2.47 (2.39–2.55)
Ischemic stroke									
None	29,413	7.5 (7.2–7.8)	1 (reference)	9.0 (8.6–9.3)	1 (reference)	22.0 (21.5–22.6)	1 (reference)	34.3 (33.8–34.9)	1 (reference)
Moderate	10,065	12.5 (11.9–13.2)	1.50 (1.40–1.61)	15.6 (14.9–16.4)	1.56 (1.46–1.66)	35.5 (34.4–36.7)	1.54 (1.47–1.62)	52.4 (51.4–53.4)	1.54 (1.48–1.59)
Severe	7,254	15.1 (14.3–15.9)	1.77 (1.64–1.90)	19.8 (18.8–20.8)	1.88 (1.76–2.02)	40.2 (38.8–41.7)	1.69 (1.60–1.78)	59.3 (58.1–60.5)	1.76 (1.70–1.82)
Very severe	6,813	20.7 (19.8–21.7)	2.55 (2.38–2.73)	28.0 (26.8–29.2)	2.89 (2.71–3.08)	53.4 (51.7–55.1)	2.61 (2.47–2.75)	73.4 (72.3–74.5)	2.66 (2.57–2.75)
Intracerebral hemorrhage									
None	4,348	30.8 (29.5–32.2)	1 (reference)	11.6 (10.5–12.8)	1 (reference)	21.6 (20.0–23.3)	1 (reference)	52.0 (50.5–53.6)	1 (reference)
Moderate	1,174	41.1 (38.3–43.9)	1.27 (1.14–1.41)	17.3 (14.7–20.4)	1.19 (0.96–1.46)	34.0 (30.0–38.3)	1.30 (1.09–1.54)	67.8 (65.1–70.6)	1.27 (1.17–1.38)
Severe	936	42.3 (39.2–45.5)	1.30 (1.16–1.45)	24.8 (21.4–28.7)	1.78 (1.46–2.18)	43.0 (38.0–48.4)	1.70 (1.42–2.03)	75.3 (72.3–78.1)	1.46 (1.34–1.60)
Very severe	779	51.7 (48.3–55.3)	1.69 (1.51–1.89)	29.0 (24.7–33.9)	2.11 (1.70–2.62)	53.7 (47.1–60.5)	2.27 (1.87–2.76)	84.1 (81.2–86.8)	1.87 (1.71–2.05)

[a] Four categories of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (none), 1 (moderate), 2 (severe), and 3 or more (very severe).
[b] Adjusted for sex and age.

Table 4 Mortality rate ratio associated with individual comorbidities after first-time hospitalization for stroke in Denmark, 2004–2008

	Adjusted mortality rate ratio[a] (95% confidence interval)			
	30 d	31–365 d	1–5 y	Overall 5 y
No comorbid diseases	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Myocardial infarction	1.00 (0.93–1.08)	1.05 (0.97–1.14)	1.07 (1.01–1.14)	1.05 (1.00–1.09)
Congestive heart failure	1.35 (1.26–1.44)	1.44 (1.34–1.55)	1.37 (1.29–1.46)	1.37 (1.32–1.42)
Atrial fibrillation or flutter	1.37 (1.30–1.45)	1.23 (1.15–1.31)	1.25 (1.18–1.31)	1.28 (1.23–1.32)
Peripheral vascular disease	1.18 (1.10–1.27)	1.32 (1.23–1.42)	1.33 (1.25–1.41)	1.27 (1.22–1.32)
Dementia	1.62 (1.48–1.77)	1.84 (1.67–2.03)	2.21 (2.03–2.41)	1.84 (1.75–1.94)
Chronic pulmonary disease	1.26 (1.18–1.34)	1.23 (1.15–1.32)	1.46 (1.38–1.55)	1.33 (1.28–1.38)
Connective tissue disease	0.95 (0.86–1.05)	1.08 (0.97–1.20)	1.18 (1.08–1.28)	1.08 (1.02–1.14)
Ulcer disease	1.13 (1.05–1.22)	1.19 (1.10–1.30)	1.22 (1.14–1.30)	1.18 (1.13–1.24)
Mild liver disease	1.78 (1.51–2.10)	1.43 (1.15–1.77)	2.01 (1.73–2.34)	1.80 (1.63–1.99)
Diabetes without end-organ damage	1.07 (0.97–1.17)	1.15 (1.03–1.27)	1.14 (1.05–1.24)	1.12 (1.06–1.18)
Diabetes with end-organ damage	1.16 (1.06–1.27)	1.28 (1.17–1.41)	1.50 (1.39–1.62)	1.33 (1.26–1.39)
Moderate to severe renal disease	1.46 (1.32–1.61)	1.70 (1.53–1.90)	1.68 (1.53–1.86)	1.58 (1.49–1.68)
Nonmetastatic solid tumor	1.28 (1.20–1.36)	1.54 (1.44–1.64)	1.35 (1.28–1.43)	1.37 (1.33–1.42)
Leukemia	2.24 (1.79–2.82)	1.96 (1.47–2.61)	1.90 (1.44–2.51)	2.04 (1.76–2.37)
Lymphoma	1.50 (1.23–1.83)	1.38 (1.09–1.74)	1.26 (1.02–1.56)	1.38 (1.22–1.56)
Moderate to severe liver disease	2.41 (1.88–3.07)	3.14 (2.41–4.09)	2.89 (2.29–3.64)	2.87 (2.49–3.31)
Metastatic cancer	2.38 (2.07–2.74)	4.34 (3.78–4.98)	2.26 (1.90–2.68)	2.87 (2.63–3.12)

[a] Adjusted for the other comorbidities, age, and sex.

Most previous studies have shown improved survival rates after stroke over time,[17–24] but not all.[25–27] The decreasing 30-day mortality during our study period was in line with a recent systematic review of 56 population-based studies including 37,016 incident strokes from 47 centers in 28 different countries.[3] As a consequence, we note that studies of outcome in stroke patients need to take temporal variations in stroke mortality into account when using historical controls. In comparison with studies reporting worse[25,28,29] or improved[30] prognosis for women than for men, we found that sex did not affect short-term mortality substantially. We did observe a higher 5-year mortality risk in men than women, but only in elderly persons older than age 70. The relative mortality reduction over time was higher for ischemic stroke than for intracerebral hemorrhage. However, these results should not be compared directly because the absolute mortality risk was much higher for intracerebral hemorrhage.

Our study extends previous research by associating comorbidity burden with short- and long-term outcome of both ischemic stroke and intracerebral hemorrhage. A previous cohort study of 266 ischemic stroke patients concluded that the CCI score was not associated with an unfavorable functional outcome (defined as modified Rankin Scale [mRS][31] score >2).[6] In contrast, another cohort study of 133 women hospitalized with ischemic stroke found that higher CCI scores were the sole factor independently associated with poorer 90-day mRS scores.[7] The CCI score has also been found to predict 12-month functional outcome after intracerebral hemorrhage (the odds ratio for 1-point worsening of mRS scores was 2.3 for CCI score = 2 and 3.5 for score ≥ 3).[9] Finally, a study including 960 patients admitted with ischemic stroke to Veterans Affairs Hospitals in the United States between 1995 and 1997 reported a 37% increased risk of poor functional outcome (mRS ≥ 2) at discharge, 60% increased 30-day mortality, and 72% increased 1-year mortality associated with a CCI score ≥ 2 compared with ≤ 1.[8] Although we used different reference groups, our effect estimates were even larger.[8]

Among individual comorbidities, diabetes has been associated with increased 30-day and 1-year mortality, most often in the range of 20% to 50%.[6,32–36] One study, however, found no association.[37] In our study, we observed different prognostic effects of diabetes with vs without end-organ failure. Peripheral vascular disease and myocardial infarction have been observed to have an association with poorer long-term, but not always short-term mortality from stroke.[6,32,34] We did not find previous myocardial infarction to be a predictor of either short- or long-term stroke mortality.

Consistent with previous reports, we found that a history of atrial fibrillation predicted a poor outcome.[6,32–35,38] It should be noted that although we estimated the prognostic effect of individual comorbid conditions, comorbidities often coexist and therefore may interact and worsen the prognosis beyond that expected from the independent effects of each comorbid condition alone.

Improved mortality likely stems from several factors, including the clinical history of stroke with a shift toward less severe strokes and improved stroke care over the past decades.[22] Less severe attacks is likely attributable to better management of risk factors for stroke (in particular hypertension, smoking, atrial fibrillation, and dyslipidemia) and increased diagnostic sensitivity.[39] Comorbidity may influence the clinical outcome of stroke through several clinical pathways including the disease, the diagnostic process, treatment effects, complication rates, and rehabilitation. Although comorbidities increase mortality from causes other than stroke, the increased short-term mortality also suggests a direct effect on stroke outcome.

Several issues should be considered when interpreting our results. The study's nationwide population-based design, within the setting of a tax-supported universal health care system and with complete follow-up for all patients, eliminated selection bias.

The positive predictive value of recorded diagnoses in the DNRP has previously been examined and was found to be high for cerebrovascular disease (94%)[40]—highest for ischemic stroke (97%)[13] and lowest for intracerebral hemorrhage (72%),[13] and also high for the diseases included in the CCI (98% overall).[40] Mortality data in the Danish Civil Registration System are complete.[10]

The 17-year minimum washout period (1977 to at least 1993) increased the likelihood of distinguishing first-time from recurrent strokes. Because we classified the *unspecified strokes* as ischemic strokes, we inevitably misclassified some intracerebral hemorrhages (approximately 6%) as ischemic strokes.[14] Still, intracerebral hemorrhage accounted for the expected proportion (11%) of all strokes, and the proportion of misclassified cases likely decreased over time. Importantly, such misclassification cannot account for the time trends or the prognostic influence of comorbidity, as these results were consistent for the separate stroke types as well as stroke overall.

Some comorbidity is likely to be underrecorded, because some patients are treated only in the primary care setting. Thus, the 9% prevalence of diabetes in our cohort is lower than that observed in the Danish Stroke Registry (13%) and in other Western countries.[4] However, because comparisons were made within a population of stroke patients, underascertainment of certain diseases is unlikely to affect substantially the relative mortality estimates associated with categories of comorbidity. Increased levels of comorbidity observed over time may reflect patients' progression to poor health, but also may be explained in part by more complete disease registration in the DNRP because of the introduction of diagnosis-related groups as a payment system in Denmark in 2000. The CCI potentially could be made even more appropriate for patients with stroke by assigning greater weight to some diseases (e.g., dementia, liver disease, and renal disease) and omitting others lacking prognostic significance for stroke patients (e.g., connective tissue disease) or with low prevalence (e.g., leukemia and AIDS). Despite current limitations regarding individual comorbidities, however, the CCI has proven to be a valid tool for predicting mortality from comorbidity in patients with stroke.[8,15]

We found that short- and long-term mortality improved considerably between 1994 and 2011 for all types of stroke. Short-term mortality improved regardless of comorbidity burden. However, comorbidity burden was a strong prognostic factor for both short- and long-term mortality.

AUTHOR CONTRIBUTIONS

M.S. and H.T.S. conceived the study idea and developed it in collaboration with the other coauthors. All authors contributed to the design of the study. J.B.J. and H.T.S. collected the data. M.S., S.P.J., and H.T.S. reviewed the literature. M.S., S.P.J., J.B.J., and H.T.S. directed the analyses, which were performed by J.B.J. All authors participated in the discussion and interpretation of the results. M.S. organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version before submission. H.T.S. had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENT

Grethe Andersen, MD, DMSc, from the Danish Stroke Center, Department of Neurology, Aarhus University Hospital, Denmark, is acknowledged as contributor for reviewing the final manuscript before submission.

STUDY FUNDING

The study was supported by the Department of Clinical Epidemiology's Research Foundation, the Danish Brain Injury Association, Augustinus Foundation, Arvid Nilsson's Foundation, Direktør Jacob Madsens & Hustru Olga Madsens Fond, TrygFonden, and Danish Research Council (grants 11-108354 and 11-115818). None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 10, 2013. Accepted in final form October 8, 2013.

REFERENCES

1. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol 2006;13:581–598.
2. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation

for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ 2012;344:e356.
3. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355–369.
4. Palnum KD, Petersen P, Sørensen HT, et al. Older patients with acute stroke in Denmark: quality of care and short-term mortality: a nationwide follow-up study. Age Ageing 2008;37:90–95.
5. Ovbiagele B. Nationwide trends in in-hospital mortality among patients with stroke. Stroke 2010;41:1748–1754.
6. Fischer U, Arnold M, Nedeltchev K, et al. Impact of comorbidity on ischemic stroke outcome. Acta Neurol Scand 2006;113:108–113.
7. Bushnell CD, Lee J, Duncan PW, Newby LK, Goldstein LB. Impact of comorbidities on ischemic stroke outcomes in women. Stroke 2008;39:2138–2140.
8. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. Stroke 2004;35:1941–1945.
9. Bar B, Hemphill JC. Charlson Comorbidity Index adjustment in intracerebral hemorrhage. Stroke 2011;42:2944–2946.
10. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39(7 suppl):22–25.
11. Thorvaldsen P, Davidsen M, Brønnum-Hansen H, Schroll M. Stable stroke occurrence despite incidence reduction in an aging population: stroke trends in the Danish Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) population. Stroke 1999;30:2529–2534.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 suppl):30–33.
13. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology 2007;28:150–154.
14. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in the Danish National Registry of Patients. J Clin Epidemiol 2002;55:602–607.
15. Tessier A, Finch L, Daskalopoulou SS, Mayo NE. Validation of the Charlson Comorbidity Index for predicting functional outcome of stroke. Arch Phys Med Rehabil 2008;89:1276–1283.
16. Jacobs DR, Kroenke C, Crow R, et al. PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina—the Minnesota Heart Survey. Circulation 1999;100:599–607.
17. Sturgeon JD, Folsom AR. Trends in hospitalization rate, hospital case fatality, and mortality rate of stroke by subtype in Minneapolis–St. Paul, 1980–2002. Neuroepidemiology 2007;28:39–45.
18. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999–2008: time-trend analysis from the General Practice Research Database. BMJ Open 2011;1:e000269.
19. Redon J, Olsen MH, Cooper RS, et al. Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure. Eur Heart J 2011;32:1424–1431.
20. Hallström B, Jönsson AC, Nerbrand C, Norrving B, Lindgren A. Stroke incidence and survival in the beginning of the 21st century in southern Sweden: comparisons with the late 20th century and projections into the future. Stroke 2008;39:10–15.
21. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925–1933.
22. Carter KN, Anderson CS, Hackett ML, Barber PA, Bonita R; Auckland Regional Community Stroke Study Group. Improved survival after stroke: is admission to hospital the major explanation? Trend analyses of the Auckland Regional Community Stroke Studies. Cerebrovasc Dis 2007;23:162–168.
23. Modig K, Andersson T, Drefahl S, Ahlbom A. Age-specific trends in morbidity, mortality and case-fatality from cardiovascular disease, myocardial infarction and stroke in advanced age: evaluation in the Swedish population. PLoS One 2013;8:e64928.
24. Davídkovová H, Kysely J, Kríz B, Vojtísek P, Bobák M. Trends in cardiovascular mortality and hospitalisations, and potential contribution of inhospital case-fatality rates to changes in national mortality in the Czech Republic 1994–2009. Heart 2013;99:409–416.
25. Marsden DL, Spratt NJ, Walker R, et al. Trends in stroke attack rates and case fatality in the Hunter region, Australia 1996–2008. Cerebrovasc Dis 2010;30:500–507.
26. Harmsen P, Wilhelmsen L, Jacobsson A. Stroke incidence and mortality rates 1987 to 2006 related to secular trends of cardiovascular risk factors in Gothenburg, Sweden. Stroke 2009;40:2691–2697.
27. Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. Stroke 2008;39:776–782.
28. Wu SH, Ho SC, Chau PH, Goggins W, Sham A, Woo J. Sex differences in stroke incidence and survival in Hong Kong, 2000–2007. Neuroepidemiology 2012;38:69–75.
29. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. Stroke 2009;40:1082–1090.
30. Palnum KD, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Sex-related differences in quality of care and short-term mortality among patients with acute stroke in Denmark: a nationwide follow-up study. Stroke 2009;40:1134–1139.
31. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
32. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. Stroke 2011;42:2806–2812.
33. Kaarisalo MM, Räihä I, Sivenius J, et al. Diabetes worsens the outcome of acute ischemic stroke. Diabetes Res Clin Pract 2005;69:293–298.
34. Wong KS. Risk factors for early death in acute ischemic stroke and intracerebral hemorrhage: a prospective hospital-based study in Asia. Asian Acute Stroke Advisory Panel. Stroke 1999;30:2326–2330.
35. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German Stroke Registers Study Group. Arch Intern Med 2004;164:1761–1768.

36. Megherbi SE, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke 2003;34:688–694.
37. Szczudlik A, Słowik A, Turaj W, et al. Early predictors of 30-day mortality in supratentorial ischemic stroke patients: first episode. Med Sci Monit 2000;6:75–80.
38. Thygesen SK, Frost L, Eagle KA, Johnsen SP. Atrial fibrillation in patients with ischemic stroke: a population-based study. Clin Epidemiol 2009;1:55–65.
39. von Weitzel-Mudersbach P, Andersen G, Hundborg HH, Johnsen SP. Transient ischemic attack and minor stroke are the most common manifestations of acute cerebrovascular disease: a prospective, population-based study—the Aarhus TIA study. Neuroepidemiology 2013;40:50–55.
40. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson Comorbidity Index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.

Paper IV

International Journal of Cardiology 308 (2020) 1–8

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: A nationwide cohort study

Morten Schmidt [a,b,*], Erzsébet Horváth-Puhó [a], Anne Gulbech Ording [a], Hans Erik Bøtker [c], Timothy L. Lash [a,d], Henrik Toft Sørensen [a]

[a] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark
[c] Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[d] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 23 August 2019
Received in revised form 9 January 2020
Accepted 24 January 2020
Available online 29 January 2020

Keywords:
Comorbidity
Myocardial infarction
Interaction
Mortality
Prognosis

ABSTRACT

Background: Whether the prognostic impact of comorbidity on myocardial infarction (MI) mortality is due to comorbidity alone or/and its interaction effect is unknown.
Methods: We used Danish medical registries to conduct a nationwide cohort study of all first-time MIs during 1995–2016 (n = 179,515) and a comparison cohort matched on age, sex, and individual comorbidities (n = 880,347). We calculated age-standardized 5-year all-cause mortality rates. Interaction was examined on an additive scale by calculating interaction contrasts (difference in rate differences).
Results: Among individuals without comorbidity, the 30-day mortality rate per 1000 person-years was 1851 (95% CI: 1818–1884) for MI patients and 22 (21–24) for comparison cohort members (rate difference = 1829). For individuals with low comorbidity, corresponding baseline mortality rates were 2498 (2436–2560) in the MI and 54 (50–57) in the comparison cohort (rate difference = 2444). The interaction contrast (616) indicated that the interaction accounted for 25% (616/2498) of the total 30-day mortality rate in MI patients with low comorbidity. This percentage increased further for moderate (35%) and severe (45%) comorbidity levels. Absolute and relative interaction effects were largest within the first 30 days and younger individuals. Dose-response patterns were also observed during 31–365 days and 1–5 years of follow-up (*p*-values for trends<0.002). The interaction differed substantially between individual types of cardiac and non-cardiac comorbidities.
Conclusion: Cardiac and non-cardiac comorbidities interact with MI to increase short- and long-term mortality beyond that explained by their additive effects. The interaction had a dose-response relation with comorbidity burden and a magnitude of clinical importance.

1. Introduction

Despite considerable reduction in incidence and mortality in past decades, myocardial infarction (MI) remains a common life-threatening disease[1,2]. Aging of the population increases the prevalence of multiple chronic diseases in the general population as well as among MI patients[3]. The median age of MI patients is approximately 68 years for men and 75 years for women[2]. Shared risk factors with other chronic diseases further increases the burden of comorbidity among MI patients and almost two-thirds of MI patients have at least one comorbid chronic disease at time of their coronary event[3].

The prevalence of multi-morbidity is a concern because individual comorbidities, such as diabetes[4,5] and chronic obstructive pulmonary disease[6], aggravate MI prognosis. However, a systematic overview of the interaction effect of both cardiac and non-cardiac comorbidities is lacking. Moreover, it remains unclear how the clustering of multiple cardiac and non-cardiac comorbidities influences clinical outcome[7].

While comorbidity burden has been established as an important prognostic factor for MI prognosis[2], it remains unanswered whether its prognostic effect is explained by the effect of comorbidity itself, or whether comorbidity and MI interact with one another to reduce survival beyond their independent effects acting alone. We undertook the current study to answer this question.

2. Methods

2.1. Setting and data sources

The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general

* Corresponding author at: Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark.
E-mail address: morten.schmidt@dadlnet.dk (M. Schmidt).

https://doi.org/10.1016/j.ijcard.2020.01.059
0167-5273/

practitioners and hospitals, and partial reimbursement for prescribed medications[8]. Accurate linkage of all registries at the individual level is possible in Denmark using the unique Central Personal Register number assigned to each Danish citizen at birth and to residents upon immigration[9].

We used the Danish National Patient Registry to identify the study population and their comorbidities[10]. The registry contains data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995[10]. Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and potentially several secondary diagnoses classified according to the *International Classification of Diseases*, *Eighth Revision* until the end of 1993 and *Tenth Revision* thereafter[10]. We obtained information on all-cause mortality and migration status from the Danish Civil Registration System[9], which has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates[9].

2.2. Comorbidity

We extracted all available inpatient and outpatient clinic discharge diagnoses of comorbidities from the Danish National Patient Registry for the 10-year period preceding the index date[10]. We categorized severity of comorbidity burden using the Charlson Comorbidity Index (CCI)[11], a scoring system that has been adapted for use with hospital discharge data[12] and validated for patients with acute ischemic heart disease[13,14]. The CCI assigns between one and six points to a range of diseases, depending on the strength of their relation to mortality in the subsequent year (during the era when the CCI was developed). One point is assigned for MI, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes without end-organ damage; two points are assigned for diabetes with end-organ damage, hemiplegia, moderate to severe renal disease, non-metastatic solid tumor, leukemia, and lymphoma; three points are assigned for moderate to severe liver disease; and six points are assigned for metastatic cancer and AIDS. We computed the total CCI score for each patient (omitting MI) and defined four categories of comorbidity: 0 (none), 1 (low), 2–3 (moderate), and ≥4 (severe). Finally, we defined individual non-cardiac comorbidities from CCI comorbidities (excluding MI and congestive heart failure) and assessed major cardiac comorbidities previously validated[15].

2.3. Design and study population

We conducted a nationwide study of all adult patients (aged >18 years) with an inpatient diagnosis of MI between 1995 and 2016 and a comparison cohort of persons without MI. In the primary analysis, the comparison cohort were drawn from the general population and matched 5:1 (if possible) to MI patients on year of birth (5-year intervals), sex, and individual Charlson comorbidities. In the secondary analysis of cardiac comorbidity, we resampled the comparison cohort as previously, but replaced the Charlson comorbidities with the individual cardiac comorbidities. Matching was done without replacement in chronological order. The date of MI diagnosis defined the matching date (index date).

Among 184,916 MI patients, 5401 (2.9%) persons could not be matched with a member of the general population comparison cohort and were excluded. The combination of older age and specific pattern of multi-morbidity precluded matching. Thus, unmatched patients were older (59% were ≥80 years vs. 24% of matched patients) and had a higher comorbidity burden (78.0% had a CCI score of ≥3 vs. 8.4% of matched patients).

2.4. Statistical analysis

We followed cohort members from their index dates until death from any cause (the study outcome), emigration, five years of follow-up, or 31 December 2016, whichever came first. We stratified the follow-up period by the first 30 days, 31–365 days, and > 1–5 years after the index date. Members of the two cohorts were categorized by age (0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, calendar period, baseline CCI score, and individual CCI comorbidities. Calendar period reflected the first, second, and third universal re-definitions of MI in 2000, 2007, and 2012 (1995–1999, 2000–2006, 2007–2011, and 2012–2016).

Standardized mortality rates and 95% confidence intervals were computed using age weights based on the index dates of the MI cohort. We then performed stratified Cox proportional-hazard regression to compute hazard ratios as an estimate of the mortality rate ratio comparing MI patients with members of the matched cohort.

Analyses were also restricted to individual comorbidities diseases and stratified by sex and age groups. Using the stratified Cox regression, we implicitly controlled for matching factors by study design. As the matching was done on 5-year age-groups, we decided to dissolve the matching in the stratified analyses by different age categories and Cox proportional-hazards regressions were applied with adjustment for matching factors. Age was included as continuous variable in these regression models. The shape of the log-log plots indicated that the proportional-hazards assumption was not violated in the analyzed time intervals.

The interaction effect of MI and comorbidity on the mortality rate was examined by calculating interaction contrasts[16]. The interaction contrast is a measure of the excess or deficit mortality rate above or below what can be explained given the baseline mortality rate among persons without MI and comorbidity, the effect of MI on the mortality rate, and the effect of comorbidity on the mortality rate. An example of the calculation of the interaction contrast is presented in Fig. 1. Within each follow-up period, we tested for a dose-response effect between comorbidity burden and the size of the interaction contrast using the Cochran-Armitage test for trends [17].

2.5. Sensitivity analyses

We conducted four sensitivity analyses: (1) As recently diagnosed comorbidities may be more prevalent among MI patients than matched comparison cohort members and also influence MI prognosis more than chronic comorbidities, we resampled comorbidity burden by 1- and 5-year look-back windows to explore impact of potential differential baseline risk; (2) As MI mortality rate depends on ST-segment deviations, we stratified by MI type (STEMI, NSTEMI, unknown); (3) As the definitions and patient management of MI have changed over time, we stratified by index year period to explore temporal variations in interaction contrasts; (4) As non-compliance of standard post-MI medical therapy may influence the interaction effect, we repeated the 1–5 year mortality analysis among 1-year MI survivors. To ensure that the CCI score reflected comorbidity and not MI complications, we kept the matching at baseline, but acknowledge an inherent risk of healthy selection bias. We examined 1-year post-MI compliance of antithrombotic (antiplatelet or anticoagulant) drugs, statins, and beta blockers from post-MI prescription redemptions within 6–12 months. Independent of other indications for anticoagulant therapy (e.g., atrial fibrillation), standard post-MI antithrombotic therapy included dual therapy within 6–12 months and monotherapy thereafter. We therefore subcategorized antithrombotic therapy as none, single, or dual. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

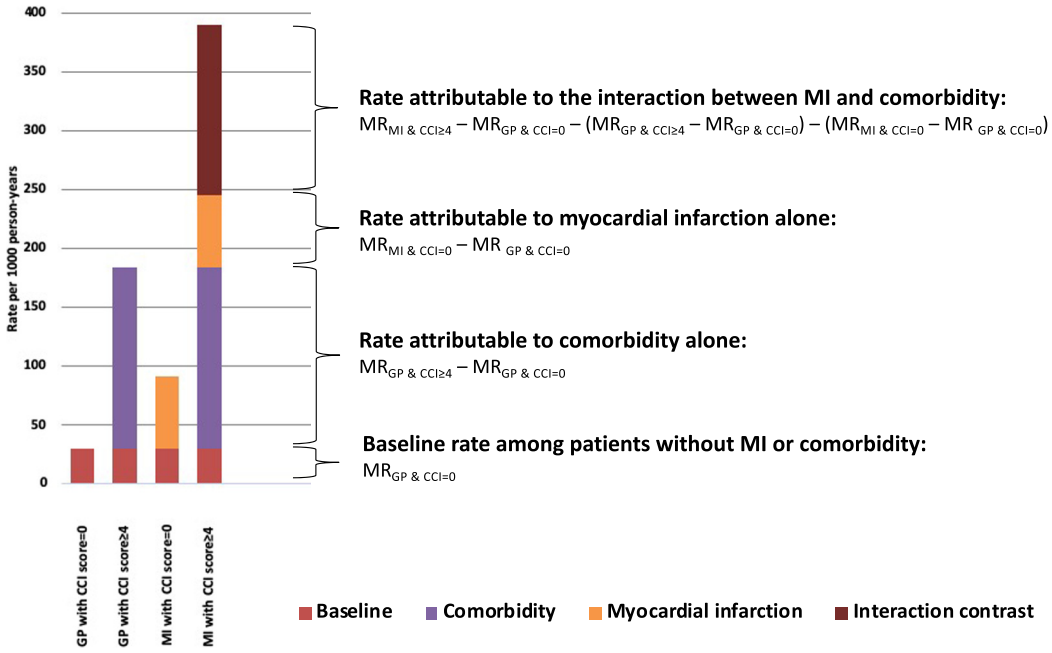


Fig. 1. Proportion of the total 31–365 day mortality rate attributable to myocardial infarction, comorbidity, and their interaction. Abbreviations: CCI, Charlson Comorbidity Index; GP, general population; MI, myocardial infarction; MR, mortality rate.

3. Results

3.1. Characteristics

Patient characteristics are provided in Table 1 and eTable1. We identified 179,515 MI patients and 880,347 Charlson comorbidity-matched comparison cohort members, of which 62% were male and the median age in both cohorts was 70 years (interquartile range: 60 to 80 years). Cumulative mortality risks are shown as eFig. 1. The median follow-up time was 4.3 (interquartile range: 0.8–5.0) years for the MI cohort and 5 (interquartile range: 3.0–5.0) years for the Charlson-comorbidity matched comparison cohort.

3.2. Comorbidity burden

Among individuals without comorbidity, the mortality rate per 1000 person-years during 30 days of follow-up was 1851 (95% confidence interval (CI): 1818–1884) for MI patients and 22 (95% CI: 21–24) for comparison cohort members, yielding a rate difference of 1829. For individuals with low comorbidity, corresponding baseline mortality rates per 1000 person-years were 2498 (95% CI: 2436–2560) in the MI cohort and 54 (95% CI: 50–57) in the comparison cohort (rate difference = 2444).

An interaction contrast of 616 (95% CI: 545–686) indicates that the interaction accounted for 25% (616/2498) of the total mortality rate in MI patients with low comorbidity. The percentage of the 30-day mortality rate explained by interaction increased further to 35% for moderate comorbidity levels [interaction contrast: 1049 (95% CI: 967–1131)] and to 45% for severe comorbidity levels [1662 (95% CI: 1461–1862)] (P for trend <0.0001).

The interaction effect was largest within the first 30 days of follow-up, but similar dose-response patterns were also observed during 31–365 days of follow-up (percentage of rate explained by interaction was 23% for low, 34% for moderate, and 37% for severe comorbidity burden, P for trend = 0.0015), as well as during 1–5 years of follow-up (percentage of rate explained by interaction was 8% for low, 10% for moderate, and 25% for severe comorbidity burden, p for trend<0.0001) (Table 2).

The results were independent of sex but influenced by age (eTable 2). Thus, the percentage of the rate explained by the interaction was highest in the younger age groups and decreased (although remaining substantial) with increasing age. As an example, during 30-day follow-up, the percentage of the rate explained by the interaction in patients with severe comorbidity was 79% in MI patients younger than 50 years of age, 68% in MI patients 50–59 years of age, 68% in MI patients 60–69 years of age, 44% in MI patients 70–79 years of age, and 24% in MI patients 80 years of age or older. A similar pattern was observed for 31–365 days and for 1–5 years of follow-up.

3.3. Individual comorbidities

The proportions of the total mortality rate attributable to MI, individual comorbidities, and their interactions are shown in Fig. 2. During the first 30 days of follow-up, the rate attributable to MI was high. The interaction effect for non-cardiac comorbidity was most pronounced for dementia, liver disease, diabetes (especially with end-organ damage), hemiplegia, renal disease, and metastatic solid tumor. In contrast, short-term MI mortality rate was not substantially influenced by interactions with connective tissue disease or lymphoma. Among cardiac comorbidities, the interaction effect was substantial for congestive heart failure and pulmonary hypertension, but also pronounced for valvular heart disease, pericarditis, and aortic aneurysm/dilatation. Endocarditis could not be assessed due to small numbers.

Within 31–365 days of follow-up, the attributable rate of comorbidity increased substantially, and for many patient groups exceeded that attributable to MI. The non-cardiac comorbidities with the strongest interaction effect on the mortality rate did not differ substantially from the first 30 days. Exceptions included far less interaction effect from liver disease and a higher attributable rate due to interaction with malignancies (leukemia, lymphoma, and metastatic solid tumor). Among cardiac comorbidities, the interaction effect was strongest for endocarditis, congestive heart failure, cardiomyopathy, and valvular heart disease, but smaller effects were also observed for pulmonary

Table 1
Characteristics of the myocardial infarction and Charlson comorbidity-matched comparison cohorts, Denmark, 1995–2016.

	Myocardial infarction cohort, n (%)	Comparison cohort, n (%)
Total	179,515 (100)	880,347 (100)
Female	68,975 (38)	338,040 (38)
Age[a]		
<50 years	16,486 (9.2)	84,100 (9.6)
50–59 years	29,307 (16)	145,870 (17)
60–69 years	42,056 (23)	207,770 (24)
70–79 years	48,365 (27)	237,165 (27)
80+ years	43,301 (24)	205,442 (23)
Calendar period[b]		
1995–1999	41,384 (23)	205,074 (23)
2000–2006	63,080 (35)	309,297 (35)
2007–2011	38,886 (22)	189,409 (22)
2012–2016	36,165 (20)	176,567 (20)
Comorbidity burden[c]		
None	111,464 (62)	557,204 (63)
Low	33,076 (18)	164,608 (19)
Moderate	28,831 (16)	137,956 (16)
Severe	6144 (3.4)	20,579 (2.3)
Non-cardiac comorbidities		
Peripheral vascular disease	12,566 (7.0)	55,828 (6.3)
Cerebrovascular disease	16,917 (9.4)	78,724 (8.9)
Dementia	2127 (1.2)	9511 (1.1)
Chronic pulmonary disease	14,723 (8.2)	68,588 (7.8)
Connective tissue disease	5272 (2.9)	23,871 (2.7)
Ulcer disease	6068 (3.4)	27,282 (3.1)
Mild liver disease	990 (0.6)	4358 (0.5)
Diabetes I and II	14,108 (7.9)	63,413 (7.2)
Hemiplegia	253 (0.1)	954 (0.1)
Moderate to severe renal disease	4140 (2.3)	16,586 (1.9)
Diabetes with end-organ damage	7831 (4.4)	33,237 (3.8)
Any tumor without MI	9585 (5.3)	44,962 (5.1)
Leukemia	408 (0.2)	1653 (0.2)
Lymphoma	752 (0.4)	3249 (0.4)
Moderate to severe liver disease	199 (0.1)	768 (0.1)
Metastatic solid tumor	1001 (0.6)	4401 (0.5)

[a] Median age and interquartile range were 70 (60, 80) years for both cohorts.
[b] Calendar period reflected the first, second, and third universal definitions of myocardial infarction in 2000, 2007, and 2012, respectively.
[c] Categories of comorbidity were based on Charlson Comorbidity Index scores of 0 (none), 1 (low), 2–3 (moderate), and ≥ 4 (severe).

hypertension, atrial fibrillation/flutter, aortic aneurysm/dilatation, and arterial claudication.

Five-year mortality rates among 1-year survivors were influenced substantially by comorbidity burden per se. Still, strong interaction between non-cardiac comorbidity and MI was seen for patients with hemiplegia, moderate to severe renal or liver disease, and metastatic solid tumor. Endocarditis, pulmonary hypertension, and pericarditis were the cardiac comorbidities with strongest interaction effect, although all cardiac comorbidities showed interaction effect at some extent.

3.4. Sensitivity analyses

Sensitivity analyses showed no substantial interaction effect modification by (1) comorbidity look-back window (eTable 3); (2) MI type (eTable 4); (3) calendar period of diagnosis (eTable 5); or compliance in use of antithrombotic drugs, statins, and beta blockers among 1-year survivors (eTable 6). Of note, the proportion of mortality due to the interaction of severe comorbidity burden seemed larger among patients on dual (75%) compared with single (26%) and no (34%) antithrombotic therapy, but wide confidence intervals prevented firm conclusions.

4. Discussion

We showed an additive interaction effect of comorbidity on short- and long-term MI mortality. As expected, comorbidity diminished 5-year MI survival. However, the poorer prognosis was not explained solely by the prognostic impact of comorbidity per se, but to a large extent by the interaction between comorbidity burden and MI. The dose-response relation between comorbidity burden and size of the interaction effect supported these findings. The interaction effect was most pronounced for short-term mortality, but persisted for 31–365-day survival, as well as 5-year mortality among 1-year survivors. It was consistent for both men and women, strongest in young MI patients, and varied in magnitude according to individual cardiac and non-cardiac comorbidities.

4.1. Previous literature

Previous studies have shown how comorbidity burden has increased over time among MI patients[2]. Temporal improvements in MI survival during the last three decades have occurred independently of MI patients' comorbidity burden, but comorbidity has remained a strong prognostic factor in these patients. Few studies have quantified the prognostic influence of comorbidity burden as defined by the CCI[7].

An Australian cohort study (1988–1994) of 4081 28-day survivors of a 'definite' or 'possible' MI showed a 1.4-fold increased mortality rate associated with CCI scores of 1–2 and a 2.7-fold increased mortality rate for scores of 3 or more[12]. The restriction to 28-day survivors was justified by the authors because 'short-term mortality was likely to be closely related to the severity of the AMI and its progression[12].

An Italian cohort study (1991–2009) of MI patients with renal dysfunction also demonstrated that the CCI score (excluding chronic kidney disease) was associated with in-hospital death (relative risk (RR) per point: 1.10, 95% CI: 1.07–1.13)[18]. A Spanish cohort study (2000−2003) of 1035 MI patients, approximately half with ST-elevation MI, showed that comorbidity independently predicted mortality and recurrent MI within both 30 days (1.6–1.8-fold increased RR for CCI scores of 2–4) and 1 year (RR increasing from 1.6 for a CCI score of 2 to 2.2 for a score of 4)[19].

Two Swiss cohort studies examined patients with acute coronary syndrome overall, as well as 8330 patients with ST-segment elevation MI undergoing percutaneous coronary intervention during 2005–2012 [20]. The latter showed that CCI scores ≥2 increased 1-year risk of major adverse cardiovascular and cerebrovascular events by 40% (RR: 1.42; 95% CI, 1.05–1.92)[20]. The prognostic importance of comorbidity in patients with non–ST-segment elevation MI has also been confirmed in a US cohort study (2002–2008) (RR per CCI point: 1.3; 95% CI, 1.2–1.4)[21]. In a Danish cohort study of 234,331 MI patients (1984–2008), we previously found a 2-fold increased mortality rate ratio within 30 days, increasing to 4-fold increased within the remaining one year, when comparing patients with CCI scores ≥3 vs. 0 during 2004–2008[2].

Recently, a UK cohort study (2003−2013) identified three phenotype clusters of comorbidity burden among 693,388 MI patients: concomitant heart failure, peripheral vascular disease, and hypertension (severe); peripheral vascular disease and hypertension (moderate); and few comorbidities (low)[3]. Compared with low comorbidity, moderate and severe comorbidity were associated with 1.5-fold and 2.4-fold increased hazards of death and a loss in life expectancy of 1.52 and 2.89 years, respectively, over the 8.4-year follow-up period. Heart failure, renal failure, and cerebrovascular disease were the strongest prognostic factors. However, only seven comorbidities were examined, not including cancer and liver disease[3].

A recent meta-analysis summarized most available data and estimated that each increase in the CCI score increased mortality by 30% for patients with acute coronary syndrome (RR: 1.33; 95% CI, 1.15–1.54) and by 20% for patients undergoing percutaneous coronary

Table 2
Comorbidity-stratified mortality rates, interaction contrasts, and mortality rate ratios in the myocardial infarction cohort and matched population comparison cohort during 30 days, 31–-365 days, and > 1–5 year follow-up.

Comorbidity burden[a]	Cohort	No. of persons	No. of deaths	PY	Standardized MR per 1000 PY (95% CI)	Interaction contrast (95% CI)[b]	Adjusted MRR (95% CI)	% Rate due to interaction[c]	*P* value for trend
30 days of follow-up									
Overall	MI	179,515	27,153	12,951	2236 (2209–2263)	N/A	47.09 (45.28–48.97)		
	Comparison	880,347	3549	72,055	50 (49–52)				
None	MI	111,464	12,564	8304	1851 (1818–1884)	Reference	93.37 (86.40–100.90)	Reference	
	Comparison	557,204	845	45,660	22 (21–24)				
Low	MI	33,076	6434	2296	2498 (2436–2560)	616 (545–686)	47.62 (43.98–51.57)	25%	
	Comparison	164,608	892	13,469	54 (50–57)				
Moderate	MI	28,831	6540	1947	2984 (2909–3059)	1049 (967–1131)	28.08 (26.34–29.95)	35%	
	Comparison	137,956	1403	11,256	107 (101−113)				
Severe	MI	6144	1615	405	3723 (3527–3920)	1662 (1461–1862)	15.46 (13.70–17.45)	45%	<0.0001
	Comparison	20,579	409	1670	233 (208–258)				
31–365 days of follow-up									
Overall	MI	151,813	14,848	127,802	138 (135–140)	N/A	2.84 (2.78–2.90)		
	Comparison	873,951	37,949	76,8041	52 (51–52)				
None	MI	98,545	5466	85,345	91 (89–94)	Reference	3.25 (3.14–3.36)	Reference	
	Comparison	554,493	12,001	493,073	30 (29–31)				
Low	MI	26,559	3618	21,820	158 (153–163)	37 (31–43)	2.82 (2.70–2.94)	23%	
	Comparison	163,283	10,109	142,418	60 (58–61)				
Moderate	MI	22,205	4444	17,377	237 (230–244)	80 (72–87)	2.58 (2.49–2.68)	34%	
	Comparison	136,093	12,793	116,223	96 (95–98)				
Severe	MI	4504	1320	3258	390 (368–413)	146 (122–169)	2.26 (2.09–2.43)	37%	0.0015
	Comparison	20,082	3046	16,328	184 (177–191)				
>1–5 years of follow-up									
Overall	MI	131,150	25,547	420,595	85 (84–86)	N/A	1.49 (1.47–1.51)		
	Comparison	804,382	139,895	2,657,013	63 (62–63)				
None	MI	89,333	11,723	300,498	64 (63–66)	Reference	1.53 (1.50–1.57)	Reference	
	Comparison	522,436	58,655	1,798,078	45 (45–46)				
Low	MI	21,993	6298	66,325	105 (102–107)	8.8 (5.6–12)	1.47 (1.43–1.52)	8%	
	Comparison	1477,80	37,589	465,286	77 (76–78)				
Moderate	MI	16,873	6077	46,962	136 (132–139)	14 (9.8–18)	1.42 (1.38–1.46)	10%	
	Comparison	118,208	37,611	351,239	103 (101–104)				
Severe	MI	2951	1449	6811	221 (208–233)	55 (42–69)	1.55 (1.44–1.67)	25%	<0.0001
	Comparison	15,958	6040	42,410	146 (142–151)				

Abbreviations: CI, confidence interval; MR, mortality rate; MRR, mortality rate ratio; PY, person-years.
[a] Categories of comorbidity were based on Charlson Comorbidity Index scores of 0 (none), 1 (low), 2–3 (moderate), and ≥ 4 (severe).
[b] The interaction contrast is calculated as the difference in rate differences and measures the combined mortality effect of comorbidity and myocardial infarction that cannot be explained by summing estimates of their individual effects.
[c] The proportion of the rate explained by interaction is calculated as the interaction contrast divided by baseline myocardial infarction mortality rate.

intervention (RR: 1.21; 95% CI, 1.12–1.31). A CCI score above 2 increased the mortality rate 2.5-fold (2.52; 95% CI, 1.58–4.04) for patients with acute coronary syndrome and more than 3-fold for patients undergoing percutaneous coronary intervention (RR: 3.36; 95% CI, 2.14–5.29)[7].

Although comorbidities are likely to increase non-cardiac mortality in particular (as assumed by some studies[12]), the consistent increased short-term cardiac mortality observed by others, as discussed above, also suggests a direct impact on cardiac mortality, and hence an actual interaction[2]. However, none of the previous studies were able to address this issue. Moreover, we added detailed information on the interaction effect of individual cardiac and non-cardiac comorbidities.

4.2. Mechanisms

Comorbidity may influence MI prognosis in several ways. Although comorbidities are likely to increase long-term non-cardiac mortality in particular[22], we found that the interaction effect was most pronounced for short-term mortality. The higher baseline mortality rate among older individuals without MI or comorbidity likely explains why the interaction effect was less pronounced in this group (confounding by baseline rate). Comorbidity may affect the course of MI, reduce the likelihood of receiving guideline-recommended care, and alter the effectiveness of treatments. Patients with severe comorbidity more often have NSTEMI and are less likely to receive standard therapy in both the acute (aggressive antithrombotic therapy) and post-MI phase (e.g., aspirin, beta-blockers, and statins)[3]. Even after adjustment for patient demographics and the likelihood of receiving guideline-recommended treatment, previous studies have, however, found that severe comorbidity remains strongly associated with mortality[3]. These findings were also supported by our sensitivity analyses on MI type or drug compliance. The more infrequent practice of coronary reperfusion therapy among patients with severe comorbidity may contribute to increased short-term mortality[23].

4.3. Strengths and limitations

Several issues should be considered when interpreting our results. The study's population-based design in a country with universal healthcare reduced selection biases stemming from selective inclusion of specific hospitals and health insurance systems. All patients were followed until death, emigration, or end of follow-up, and hence no one was lost to censoring. We matched patients on the exact diseases in the CCI, rather than on the index value itself. The positive predictive values of diagnoses in the Danish National Patient Registry have been validated previously and found high for both MI (>90%)[10,15], cardiac morbidities[10,15], and CCI comorbidities (98% overall)[24]. Mortality data from the Danish Civil Registration System are considered accurate and complete[9].

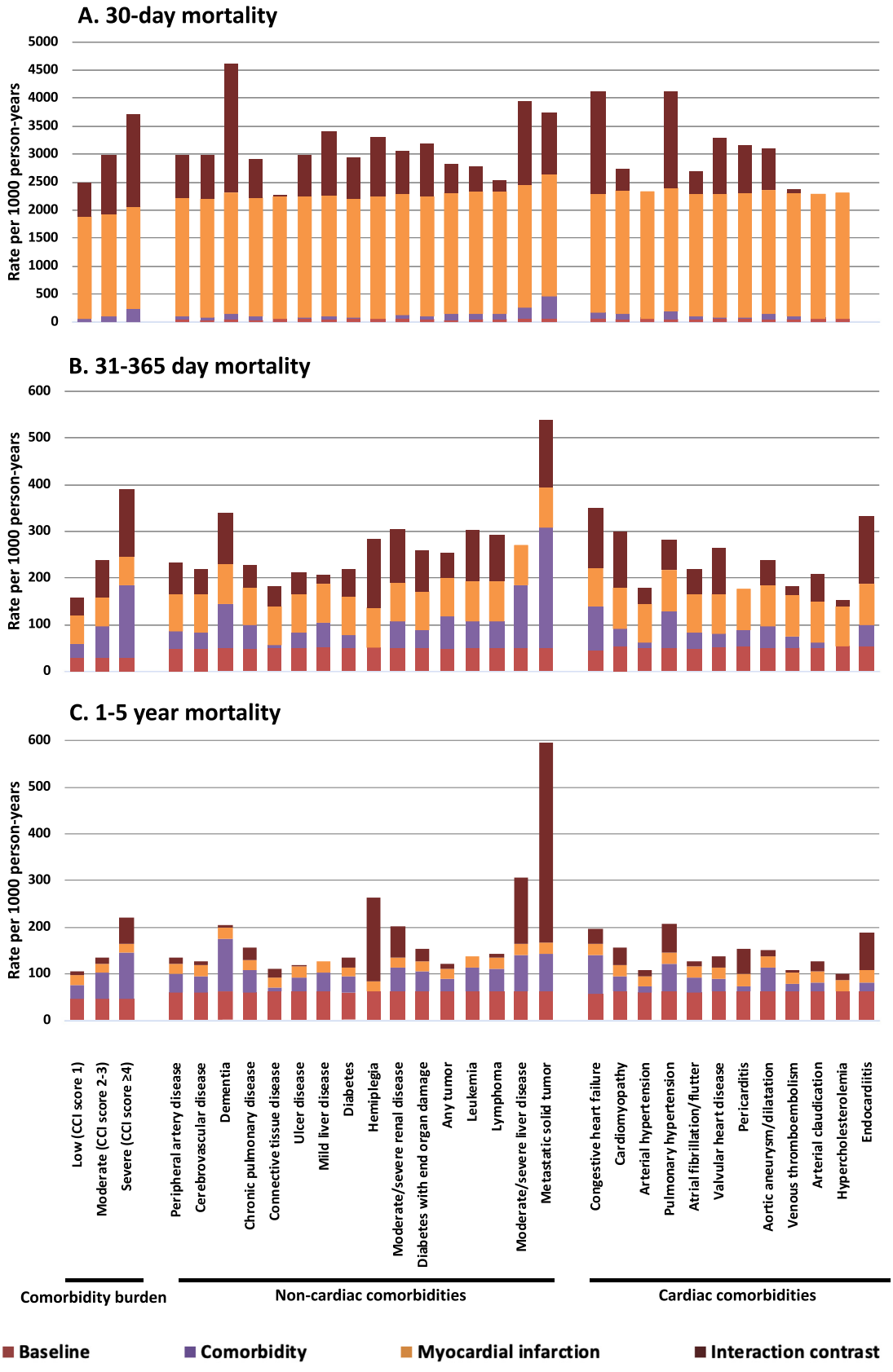


Fig. 2. Proportion of the total mortality rate attributable to myocardial infarction, individual comorbidities, and their interaction during (A) 30 days, (B) 31–365 days, and (C) >1–5 years of follow-up.

Of note, the Danish National Patient Registry only registers diseases that require inpatient or outpatient hospital treatment, hence not including those treated solely in general practice. To some extent, we therefore may have underestimated total comorbidity burden for diseases treated only in the general practice setting. However, it is important to recall that the CCI was developed as a prognostic index for prevalent comorbid conditions measured in hospitalized patients, analogous in this regard to the present study's setting. As suggested for stable angina pectoris patients[25], the CCI potentially could be made even more appropriate for patients with MI by assigning greater weight to some diseases (such as liver and renal disease) and omitting others lacking prognostic significance among patients with MI (such as connective tissue disease) or with low prevalence (such as hemiplegia, leukemia, and AIDS)[25,26]. Also, peripheral and cerebrovascular disease may indicate to some extent "disease staging" of underlying atherosclerosis that has progressed to multiple vascular systems, rather than representing separate disease entities[26]. Despite these limitations regarding individual comorbidities, however, the CCI in its original form has proved to be an adequate tool for measuring the prognostic impact of total comorbidity burden in patients with MI[25,27].

5. Conclusions and implications

Comorbidity influence MI mortality to a substantial degree through an interaction effect. Thus, comorbidities interact with MI to increase the mortality rate beyond that explained by the additive effect of MI and comorbidities acting alone, particularly in younger patients and in the first month after MI. Furthermore, the interaction showed a dose-response relation with comorbidity burden and a magnitude of clinical importance. As a consequence, guideline-recommended care of comorbidities is warranted to reduce MI-related premature death. Treating physicians, such as cardiologists and general practitioners, should acknowledge this responsibility. Additional to improving provision of evidence-based care, novel interventions are warranted, including design of new pharmacotherapies and/or greater use of community-based interventions such as home care, telemedicine, and follow-up visits. Finally, future randomized trials are obliged not only to focus on single disease pathways in patients without comorbidity, but to a larger extent test interventions in patients with multiple diseases who reflect the typical MI patients treated in every-day clinical practice.

Data permission

The study was approved by the Danish Data Protection Agency (Record number 2015-57-0002).

Contributorship statement

All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MS is the guarantor.

Source of funding

The study was supported by Department of Clinical Epidemiology's Research Foundation and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation and the Danish Research Council (grants 11-108354 and 11-115818). The funding sources had no role in the design, conduct, analysis, or reporting of the study.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval

No ethics committee approval was needed, according to Danish law.

Dissemination declaration

Results will be disseminated to relevant patient organisations.

Data sharing

Not allowed.

Patient involvement statement

No patient involvement.

CRediT authorship contribution statement

Morten Schmidt: Conceptualization, Writing - original draft, Validation.**Erzsébet Horváth-Puhó:**Formal analysis, Validation.**Anne Gulbech Ording:**Conceptualization, Validation.**Hans Erik Bøtker:**Validation. **Timothy L. Lash:**Conceptualization, Validation.**Henrik Toft Sørensen:** Conceptualization, Validation.

Declaration of competing interest

The authors report no conflicts of interest in this work. None of the authors has received any fees, honoraria, grants or consultancies that would constitute a conflict of interest with the current study. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of those studies has any relation to the present study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.01.059.

References

[1] E.S. Ford, U.A. Ajani, J.B. Croft, et al., Explaining the decrease in U.S. deaths from coronary disease, 1980–2000, 356 (23) (2007) 2388–2398.
[2] M. Schmidt, J.B. Jacobsen, T.L. Lash, H.E. Bøtker, H.T. Sørensen, 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study, BMJ 344 (2012) e356.
[3] M. Hall, T.B. Dondo, A.T. Yan, et al., Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: latent class analysis of a nationwide population-based cohort, PLoS Med. 15 (3) (2018), e1002501.
[4] A. Norhammar, J. Lindback, L. Rydén, L. Wallentin, U. Stenestrand, On behalf of the Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish register of information and knowledge about Swedish heart intensive care admission, Heart 93 (12) (2006) 1577–1583.
[5] O.A. Alabas, M. Hall, T.B. Dondo, et al., Long-term excess mortality associated with diabetes following acute myocardial infarction: a population-based cohort study, J. Epidemiol. Community Health 71 (1) (2017) 25–32.
[6] N.M. Hawkins, Z. Huang, K.S. Pieper, et al., Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), Eur. J. Heart Fail. 11 (3) (2009) 292–298.
[7] M. Rashid, C.S. Kwok, C.P. Gale, et al., Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis, Eur Heart J Qual Care Clin Outcomes 3 (1) (2017) 20–36.
[8] M. Schmidt, S.A.J. Schmidt, K. Adelborg, et al., The Danish health care system and epidemiological research: from health care contacts to database records, Clin Epidemiol 11 (2019) 563–591.

[9] M. Schmidt, L. Pedersen, H.T. Sørensen, The Danish Civil Registration System as a tool in epidemiology, Eur. J. Epidemiol. 29 (8) (2014) 541–549.
[10] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, Clin Epidemiol 7 (2015) 449–490.
[11] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (5) (1987) 373–383.
[12] R.L. O'Connell, L.L. Lim, Utility of the Charlson comorbidity index computed from routinely collected hospital discharge diagnosis codes, Methods Inf. Med. 39 (1) (2000) 7–11.
[13] M. Singh, Scores for post-myocardial infarction risk stratification in the community, Circulation 106 (18) (2002) 2309–2314.
[14] D.R. Jacobs, C. Kroenke, R. Crow, et al., PREDICT: a simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey, Circulation 100 (6) (1999) 599–607.
[15] J. Sundbøll, K. Adelborg, T. Munch, et al., Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study, BMJ Open 6 (11) (2016), e012832.
[16] T.J. VanderWeele, On the distinction between interaction and effect modification, Epidemiology 20 (6) (2009) 863–871.
[17] A. Agresti, Categorical Data Analysis. Chapter 5, Logistic Regression, Hoboken, New Jersey, John Wiley & Sons, Inc, 2002.
[18] F. Fabbian, M. Pala, A. De Giorgi, et al., In-hospital mortality in patients with renal dysfunction admitted for myocardial infarction: the Emilia-Romagna region of Italy database of hospital admissions, Int. Urol. Nephrol. 45 (3) (2012) 769–775.
[19] J.E. Núñez, E. Núñez, L. Fácila, et al., Prognostic value of Charlson comorbidity index at 30 days and 1 year after acute myocardial infarction, 57 (9) (2004) 842–849.
[20] R. Jeger, M. Jaguszewski, B.N. Nallamothu, et al., Acute multivessel revascularization improves 1-year outcome in ST-elevation myocardial infarction: a nationwide study cohort from the AMIS Plus registry, Int. J. Cardiol. 172 (1) (2014) 76–81.
[21] J. Sanchis, J. Núñez, V. Bodí, et al., Influence of comorbid conditions on one-year outcomes in non–ST-segment elevation acute coronary syndrome, Mayo Clin. Proc. 86 (4) (2011) 291–296.
[22] W.J. Kostis, Y. Deng, J.S. Pantazopoulos, A.E. Moreyra, J.B. Kostis, Trends in mortality of acute myocardial infarction after discharge from the hospital, Circ Cardiovasc Qual Outcomes 3 (6) (2010) 581–589.
[23] D. Balzi, E. Buiatti, C. Franceschini, et al., Effect of comorbidity on coronary reperfusion strategy and long-term mortality after acute myocardial infarction, Am. Heart J. 151 (5) (2006) 1094–1100.
[24] S.K. Thygesen, C.F. Christiansen, S. Christensen, T.L. Lash, H.T. Sørensen, The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients, BMC Med. Res. Methodol. 11 (2011) 83.
[25] M. Sachdev, J.L. Sun, A.A. Tsiatis, C.L. Nelson, D.B. Mark, J.G. Jollis, The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease, J. Am. Coll. Cardiol. 43 (4) (2004) 576–582.
[26] H. Quan, B. Li, C.M. Couris, et al., Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries, Am. J. Epidemiol. 173 (6) (2011) 676–682.
[27] J.A. Chirinos, A. Veerani, J.P. Zambrano, et al., Evaluation of comorbidity scores to predict all-cause mortality in patients with established coronary artery disease, Int. J. Cardiol. 117 (1) (2007) 97–102.

Paper V

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI): Development, Validation and Comparison with Existing Comorbidity Indices

This article was published in the following Dove Press journal:
Clinical Epidemiology

Lisbeth Wellejus Albertsen[1]
Uffe Heide-Jørgensen[1]
Sigrun
Alba Johannesdottir Schmidt[1]
Corina Grey[2]
Rod Jackson[2]
Henrik Toft Sørensen[1]
Morten Schmidt[1,3,4]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Section of Epidemiology and Biostatistics, School of Population Health, University of Auckland, Auckland, New Zealand; [3]Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark; [4]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Objective: To develop and validate the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) for adjustment of comorbidity burden in studies of myocardial infarction prognosis.

Methods: Using medical registries, we identified patients with first-time myocardial infarction in Denmark during 2000–2013 (n=36,685). We developed comorbidity indices predicting 1-year all-cause mortality from all comorbidities (DANCAMI) and restricted to non-cardiovascular comorbidities (rDANCAMI). For variable selection, we eliminated comorbidities stepwise using hazard ratios from multivariable Cox models. We compared DANCAMI/rDANCAMI with Charlson and Elixhauser comorbidity indices using standard performance measures (Nagelkerke's R^2, Harrell's C-statistic, the Integrated Discrimination Improvement, and the continuous Net Reclassification Index). We assessed the significance of the novel DANCAMI variables not included in the Charlson Comorbidity Index. External validation was performed in patients with myocardial infarction in New Zealand during 2007–2016 (n=75,069).

Results: The DANCAMI included 24 comorbidities. The rDANCAMI included 17 non-cardiovascular comorbidities. In the Danish cohort, the DANCAMI indices outperformed both the Charlson and the Elixhauser comorbidity indices on all performance measures. The DANCAMI indices included multiple variables that were significant predictors of 1-year mortality even after controlling for all variables in the Charlson Comorbidity Index. These novel variables included valvular heart disease (hazard ratio for 1-year mortality=1.25, 95% CI: 1.14–1.35), coagulopathy (1.13, 95% CI: 1.05–1.22), alcohol and drug abuse (1.35, 95% CI: 1.15–1.58), schizophrenia (1.60, 95% CI: 1.46–1.76), affective disorder (1.29, 95% CI: 1.22–1.36), epilepsy (1.26, 95% CI: 1.05–1.50), neurodegenerative disorder (1.30, 95% CI: 1.10–1.54) and chronic pancreatitis (1.71, 95% CI: 1.14–2.56). The results were supported by the external validation in New Zealand.

Conclusion: DANCAMI assessed comorbidity burden of patients with first-time myocardial infarction, outperformed existing comorbidity indices, and was generalizable to patients outside Denmark. DANCAMI is recommended as a standard approach for comorbidity adjustment in studies of myocardial infarction prognosis.

Keywords: comorbidity, myocardial infarction, prognosis, risk score

Introduction

Comorbidity burden is a strong predictor of myocardial infarction (MI) mortality.[1] Although declining, 30-day MI mortality risk remains around 15% overall and

Correspondence: Morten Schmidt
Email Morten.schmidt@clin.au.dk

increases to almost 30% among patients with a Charlson Comorbidity Index (CCI) score of ≥3.[1] Underlining its clinical and public health importance, the prevalence of a high comorbidity burden in patients with MI is increasing with the aging population.[1] The need to better understand the effect of a comorbidity burden on MI prognosis is therefore compelling.

Comorbidity prediction models (indices) are widely used for this purpose. Comorbidity indices have been developed specifically for cardiac patients[2–6] and for mixed populations with subsequent testing in cardiac patients.[7–10] The CCI is one of the most commonly used comorbidity indices in research.[7] It was developed in 1984 from 559 medical inpatients to predict 1-year mortality.[7] It did not include psychiatric diagnoses although the need for exploring the coexistence of physical and mental illness has recently been highlighted.[11] A more contemporary comorbidity index is the van Walraven-weighted version of the Elixhauser Comorbidity Index (ECI),[8] developed from a mixed patient group to predict in-hospital mortality. Neither index seems ideal for assessing the predictive ability of comorbidity burden in contemporary MI patients. We therefore developed and validated the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) for adjustment of comorbidity burden in research on MI patients.

Methods

Setting and Data Sources

The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals in Denmark.[12] All Danish residents are assigned a unique central personal registry (CPR) number at birth or upon immigration.[13] Using the CPR number, we linked the Danish Civil Registration System (mortality and migration data),[13] The Danish National Patient Registry (DNPR) (hospital discharge data),[14] the Aarhus University Prescription Database (dispensed prescriptions),[15] and the Clinical Laboratory Information System Research Database (laboratory data).[16]

Study Cohort and Outcome

We used the DNPR to identify all patients aged ≥15 years hospitalized with a first-time inpatient MI diagnosis in the Northern and Central Denmark Regions between 1 January 2000 and 31 December 2013. We excluded patients with any previous in- or outpatient MI diagnosis recorded in the DNPR. Follow-up continued through 2014. We defined the outcome as time to all-cause mortality within 1 year from MI admission.[13]

Potential Predictors

We assembled a list of comorbidities from previously constructed indices and clinical knowledge. For each MI patient, we identified comorbidities from all in- and outpatient diagnoses in the DNPR within the 5 years before MI hospitalization. This included diagnoses recorded during the index admission, except for potential complications of MI, antithrombotic treatment, or associated immobilization (angina pectoris, heart failure, venous thromboembolism, atrial fibrillation/flutter, heart block, ventricular tachycardia, valvular heart disease, and stroke).

Based on Danish 5-year mortality estimates, we categorized cancer as high-risk (survival <30%) or low-risk (survival ≥30%) cancer. High-risk cancers included cancers of the hypopharynx, esophagus, stomach, liver, gallbladder, pancreas, trachea and lung, as well as mesothelioma, acute myeloid leukemia, unspecified leukemia, and secondary cancer. All remaining types of cancer were considered low-risk cancers.

Diabetes, chronic pulmonary disease, and hypertension might be treated solely in general practice, and not be registered in the DNPR.[14] We therefore also identified diabetes as a HbA1c level >48 mmol/L[16] or from antidiabetic prescriptions.[15] We supplemented diagnosis codes for chronic pulmonary disease with any prescription record for a drug used to treat obstructive airway disease.[15] We defined hypertension as a hospital diagnosis, redemption of antihypertensive combination tablets, or redemption of at least two antihypertensive drugs within 90 days before MI admission. Finally, we supplemented diagnosis codes for schizophrenia and affective disorders with relevant prescriptions within 90 days.[15]

The final list of potential predictors included 41 individual comorbidities (eTable 1). In addition to developing a comorbidity index accounting for both cardiovascular and non-cardiovascular comorbidities (DANCAMI), we also developed an index restricted to non-cardiovascular comorbidities (rDANCAMI) to enable researchers to adjust for individual non-cardiovascular comorbidities. The potential predictors for rDANCAMI included the 24 non-cardiovascular comorbidities from the final list of 41 comorbidities.

Existing Comorbidity Indices

Table 1 provides an overview of the variables included in the DANCAMI, CCI and ECI. For each MI patient, we calculated the CCI[7] and the ECI[8] scores. We based the CCI score on 18 comorbidities (MI excluded) and categorized it in four groups (0, 1, 2, and ≥3).[7] The ECI score was based on 30 comorbidities and categorized in four groups (≤0, 1–5, 6–13, and ≥14).[8]

External Validation Cohort

We validated the performance of DANCAMI/rDANCAMI in patients with first-time MI in New Zealand between 1 January 2007 and 31 December 2016. We used the unique New Zealand National Health Index (NHI) number, assigned to patients at entry into the public health system (>98% of the population),[17] to link the New Zealand National Minimum Dataset (hospital inpatient data),[17] the National Mortality Collection (vital status),[18] and the National Pharmaceutical Collection (dispensed prescriptions).[19] The National Minimum Dataset includes nationwide information on all patients discharged from publicly funded hospitals, including admission dates, primary diagnoses, and secondary diagnoses.[17] Except for HbA1c data (unavailable), the eligibility criteria, covariables, and outcome of the validation cohort were identical to those used for the Danish development cohort.

Statistical Analysis

Model Development

We used Cox regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for the minimally (sex and age) adjusted association between each comorbidity and 1-year mortality. To select variables for the DANCAMI, we included in the Cox models all 41 comorbidities, sex and age, regardless of the results from the minimally adjusted analyses.[20] Fractional polynomials supported a linear association between age and 1-year mortality. We then eliminated comorbidities with a HR <1.10 or a CI that overlapped 1. We fitted revised models with the remaining comorbidities, sex, and age. We repeated this approach until the models included only comorbidities with a HR ≥1.10. We tested the proportionality assumption using the global test based on scaled Schoenfeld residuals[21] and with log-log plots for variables that appeared non-proportional. We assigned weights to each comorbidity in the final index by multiplying the beta coefficient from the multivariable models by ten and rounding to the nearest integer to yield the score components (Table 2). The final DANCAMI score was formed by adding the weights of each of the individual patient's comorbidities.[22,23] We repeated the above steps with the 24 non-cardiovascular comorbidities to develop rDANCAMI. In addition to continuous comorbidity scores, we categorized them into no (score=0), low (score=1–3), moderate (score=4–5) and severe comorbidity burden (score ≥6). The categorization cut-off values were based on the survival curves of the individual DANCAMI/rDANCAMI scores.

Model Performance

The focus of performance measurements was discriminatory ability because the DANCAMI was intended for research rather than clinical use. We evaluated the performance of the continuous and categorical comorbidity index scores using standard performance measures, including: (1) a modified version of Nagelkerke's R^2 to measure overall performance with explained variation; (2) Harrell's C-statistic, which is equivalent to the area under the Receiver Operating Characteristic curve and indicates the proportion of all pairs of patients in which the patient who died first has higher predicted mortality;[20] (3) the integrated discrimination improvement (IDI); and (4) the continuous Net Reclassification Index (NRI) performance measures. The IDI and NRI indicate how much a predictor adds to a model's discriminatory power and are joint measures of a model's comparative improvement in sensitivity and specificity.[20] The NRI represents the net proportion of patients with a change in predicted risk in the correct direction when the comorbidity score is added to a baseline model containing age and sex.[20] The IDI integrates the NRI over all possible cut-offs for the probability of an outcome and is the difference between predicted probabilities in those who do and those who do not experience the outcome. It corresponds to the difference in discrimination slopes of two models.[20] A positive NRI or IDI indicates better prediction in the new model compared with the baseline model. We used resampling methods to calculate CIs for the performance measures.

Comparison with Existing Comorbidity Indices

We calculated Nagelkerke's R^2 and Harrell's C-statistic for the (1) baseline model (age and sex) and the baseline model plus the (2) DANCAMI, (3) rDANCAMI, (4)

Table 1 Comorbidities included in the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI), Charlson Comorbidity Index (CCI), and Elixhauser Comorbidity Index (ECI)

Disease Categories	DANCAMI	CCI	ECI
Cardiovascular disease	Heart failure Intermittent arterial claudication Stroke Hypertension Aortic disease Valvular heart disease	Congestive heart failure Peripheral vascular disease Cerebrovascular disease Myocardial infarction†	Congestive heart failure Peripheral vascular disorder Hypertension Valvular disease Cardiac arrhythmias Pulmonary circulation disorders
Kidney disease	Chronic kidney disease	Moderate to severe renal disease	Renal failure
Endocrine disease	Diabetes uncomplicated Diabetes with end-organ damage	Diabetes Diabetes with end-organ damage	Diabetes uncomplicated Diabetes complicated Obesity Hypothyroidism Fluid and electrolyte disorders Weight loss
Cancer	High-risk cancer* Low-risk cancer*	Any tumor Metastatic solid tumor Lymphoma Leukemia	Solid tumor without metastasis Metastatic cancer Lymphoma
Hematologic disease	Coagulopathy*	AIDS	Coagulopathy AIDS/HIV Blood-loss anemia Deficiency anemia
Psychiatric disease	Schizophrenia* Affective disorder* Alcohol and drug abuse*		Psychosis Depression Alcohol abuse Drug abuse
Neurologic disease	Hemiplegia* Dementia* Neurodegenerative disorder* Epilepsy*	Hemiplegia Dementia	Paralysis Neurodegenerative disorders
Pulmonary disease	Chronic pulmonary disease*	Chronic pulmonary disease	Chronic pulmonary disease
Gastrointestinal disease	Ulcer disease* Mild liver disease* Moderate to severe liver disease* Chronic pancreatitis*	Ulcer disease Mild liver disease Moderate or severe liver disease	Peptic ulcer disease, no bleeding Liver disease
Rheumatic disease		Connective tissue disease	Rheumatoid arthritis/collagen vascular disease

Notes: *Included in the restricted (r)DANCAMI together with obesity and connective tissue diseas. † Myocardial infarction was not included in the Charlson Comorbidity Index score in the analyses.

CCI, and (5) ECI. The relative difference between performance of the baseline model and the four different comorbidity indices was assessed. IDI and NRI were assessed to compare the baseline model with each of the four comorbidity indices. Of note, these standard model performance measures have largely been developed for assessing the performance of dichotomous diagnostic tests. The application of these metrics to risk prediction scores are questionable because they are insensitive to the addition of important predictors.[20]

Table 2 The Model Development of the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI)

Covariables	β coefficient	Standard error	Hazard ratio (95% CI)	Weight
DANCAMI*				
Heart failure	0.320	0.037	1.38 (1.28–1.48)	3
Intermittent arterial claudication	0.229	0.055	1.26 (1.13–1.40)	2
Aortic disease	0.209	0.082	1.23 (1.05–1.45)	2
Valvular heart disease	0.233	0.042	1.26 (1.16–1.37)	2
Stroke	0.254	0.042	1.29 (1.19–1.40)	3
Hypertension	0.121	0.025	1.13 (1.08–1.18)	1
High-risk cancer	1.043	0.053	2.84 (2.56–3.15)	10
Low-risk cancer	0.190	0.036	1.21 (1.13–1.30)	2
Coagulopathy	0.127	0.037	1.14 (1.06–1.22)	1
Diabetes uncomplicated	0.183	0.034	1.20 (1.12–1.28)	2
Diabetes with end-organ damage	0.315	0.040	1.37 (1.27–1.48)	3
Dementia	0.327	0.063	1.39 (1.23–1.57)	3
Alcohol and drug abuse	0.302	0.080	1.35 (1.16–1.58)	3
Schizophrenia	0.464	0.048	1.59 (1.45–1.75)	5
Affective disorder	0.255	0.027	1.29 (1.22–1.36)	3
Epilepsy	0.287	0.090	1.33 (1.12–1.59)	3
Neurodegenerative disorder	0.286	0.085	1.33 (1.13–1.57)	3
Hemiplegia	0.577	0.183	1.78 (1.24–2.55)	6
Chronic kidney disease	0.373	0.047	1.45 (1.32–1.59)	4
Chronic pulmonary disease	0.226	0.024	1.25 (1.20–1.31)	2
Ulcer disease	0.176	0.048	1.19 (1.08–1.31)	2
Mild liver disease	0.286	0.129	1.33 (1.03–1.71)	3
Moderate to severe liver disease	0.664	0.190	1.94 (1.34–2.82)	7
Chronic pancreatitis	0.500	0.207	1.65 (1.10–2.47)	5
rDANCAMI†				
High-risk cancer	1.041	0.053	2.83 (2.55–3.14)	10
Low-risk cancer	0.193	0.036	1.21 (1.13–1.30)	2
Coagulopathy	0.260	0.037	1.30 (1.21–1.39)	3
Obesity	0.248	0.085	1.28 (1.09–1.51)	2
Dementia	0.362	0.063	1.44 (1.27–1.62)	4
Alcohol and drug abuse	0.336	0.080	1.40 (1.20–1.64)	3
Schizophrenia	0.470	0.048	1.60 (1.46–1.76)	5
Affective disorder	0.299	0.027	1.35 (1.28–1.42)	3
Epilepsy	0.392	0.090	1.48 (1.24–1.76)	4
Neurodegenerative disorder	0.295	0.085	1.34 (1.14–1.59)	3
Hemiplegia	0.637	0.183	1.89 (1.32–2.71)	6
Chronic pulmonary disease	0.265	0.024	1.30 (1.24–1.36)	3
Ulcer disease	0.247	0.048	1.28 (1.16–1.41)	2
Mild liver disease	0.359	0.130	1.43 (1.11–1.85)	4
Moderate to severe liver disease	0.554	0.191	1.74 (1.20–2.53)	6
Chronic pancreatitis	0.643	0.207	1.90 (1.27–2.85)	6
Connective tissue disease	0.105	0.533	1.11 (1.00–1.23)	1

Notes: *Includes both cardiovascular and non-cardiovascular comorbidities. †Restricted to non-cardiovascular comorbidities.
Abbreviation: CI, confidence interval.

Improved performance is therefore better assessed by the HRs of the additional predictors in our index that were not included in the existing indices. As a key analysis, we therefore tested the significance of the novel DANCAMI variables not included in the CCI by including them in a model containing the CCI variables. In this model, significant HRs of the novel DANCAMI variables would support an improved ability of DANCAMI over the CCI in predicting 1-year all-cause mortality.

External Validation

For external validation, we estimated the ability to predict 1-year mortality in the New Zealand MI cohort by using the DANCAMI/rDANCAMI. We applied the same methods described above to assess performance and for comparison with existing comorbidity indices.

Sensitivity Analyses

We performed eight sensitivity analyses. To evaluate how the decisions made during model development affected the final indices, we (1) changed the HR cut-off from 1.10 to 1.20; (2) used the exact rather than rounded beta coefficients for score components; (3) used the HRs instead of beta coefficients for score components; (4) performed split-sample internal validation according to diagnosis year (temporal validation rather than randomly)[20] by repeating the model development in the derivation cohort (2000–09) and assessed performance in the validation cohort (2010–13); (5) restricted to MI hospital survivors; and stratified by (6–7) age and sex and (8) ethnicity groups in New Zealand (European, Maori, Pacific, Indian, and Chinese/other Asian). All statistical analyses were conducted using Stata Version 14.2 (Stata Corp, College Station, Texas, USA).

Results

Model Development

The Danish cohort included 36,685 MI patients (61% men) with a median age of 72 years (interquartile range: 61–81 years). eTable 1 presents the prevalence of each comorbidity assessed and their associations with 1-year mortality (adjusted for age and sex). The most prevalent comorbidity in the population was hypertension (53%), followed by chronic pulmonary disease (22%), and stable angina pectoris (19%). We observed significant associations with 1–year mortality for most predictors, except deep vein thrombosis in a lower limb, pulmonary embolism, heart block, immune system disorders, human immunodeficiency virus infection, endocrine disorders (excluding diabetes), anxiety and behavioural disorders, and inflammatory bowel disease. Nonsignificant associations were due to a combination of small effect sizes and low prevalence. The model development resulted in the inclusion of 24 comorbidities in the DANCAMI and 17 in the rDANCAMI. Weights indicating the severity of each included variable are presented in Table 2.

The characteristics of the Danish and New Zealand cohorts are shown in Table 3. The 1-year mortality in the Danish MI cohort was 24%. Most of these deaths occurred during hospital admission with in-hospital mortality at 14%. The DANCAMI score categories showed that 29% had no, 41% had low, 11% had moderate, and 19% had severe comorbidity burden. The corresponding proportions for rDANCAMI were 57%, 26%, 5.2%, and 12%, respectively. Survival decreased with increasing comorbidity burden (Figure 1).

Model Performance

The explained variance (R^2) was significantly higher in the prediction model including age, sex and DANCAMI (R^2=0.33, 95% CI: 0.32–0.34) than in the baseline model containing only age and sex (R^2=0.28, 95% CI: 0.27–0.29) (Table 4). Similarly, the discrimination of DANCAMI was better than the baseline model (C-statistic: 0.75 vs. 0.73). Adding the DANCAMI score to the baseline model improved discrimination (IDI=0.054) compared with the baseline model alone. Similarly, improved discrimination was observed by a total NRI of 0.52 where 77% of non-events and 49% of events had a better predicted probability of 1-year mortality (eTable 2). DANCAMI score categories performed almost as well in R^2 and C-statistics as the continuous score (Table 4), but the IDI was lower (0.044 vs. 0.054) and the NRI higher (0.55 vs. 0.52).

Comparison with Existing Comorbidity Indices

Compared with the CCI and the ECI, both the continuous and the categorical DANCAMI scores performed better in the four standard performance measures (Table 4). Although the differences in performance measures were minor, the superiority of DANCAMI over the CCI was strongly supported by the result that each of the eight DANCAMI variables, not included in the CCI, predicted 1-year mortality despite adjustment for the CCI (Table 5). These novel variables included valvular heart disease (HR for 1-year mortality=1.25, 95% CI: 1.14–1.35), coagulopathy (HR=1.13, 95% CI: 1.05–1.22), alcohol and drug abuse (HR=1.35, 95% CI: 1.15–1.58), schizophrenia (HR=1.60, 95% CI: 1.46–1.76), affective disorder (HR=1.29, 95% CI: 1.22–1.36), epilepsy (HR=1.26, 95% CI: 1.05–1.50), neurodegenerative disorder (HR=1.30, 95% CI: 1.10–1.54) and chronic pancreatitis (HR=1.71, 95% CI: 1.14–2.56).

External Validation

In the New Zealand MI cohort (n=75,069), the 1-year mortality was 20% (half of which occurred in-hospital), the male

Table 3 Characteristics of the Danish and New Zealand Myocardial Infarction Cohorts

	Myocardial Infarction Cohorts	
	Denmark	**New Zealand**
Number of patients, n (%)	36,685 (100)	75,069 (100)
Follow-up time, person years	29,293	63,263
1-year mortality, n (%)	8974 (24)	14,951 (20)
In-hospital mortality, n (%)	5014 (14)	7095 (9.5)
Sex, n (%)		
Female	14,255 (39)	30,514 (41)
Male	22,430 (61)	44,555 (59)
Age, median year (IQR)	72 (61–81)	71 (59–81)
>75 years, n (%)	14,978 (41)	31,027 (41)
Comorbidities (%)		
Most prevalent	Hypertension (53)	Hypertension (38)
Second most prevalent	Chronic pulmonary disease (22)	Chronic pulmonary disease (17)
Third most prevalent	Stable angina pectoris (19)	Diabetes with end-organ failure (16)
DANCAMI score, n (%)		
0	10,725 (29)	25,047 (33)
1–3	14,953 (41)	21,393 (29)
4–5	4184 (11)	8136 (11)
≥6	6823 (19)	20,493 (27)
rDANCAMI score, n (%)		
0	20,775 (57)	39,558 (53)
1–3	9691 (26)	16,921 (23)
4–5	1913 (5.2)	5195 (6.9)
≥6	4306 (12)	13,395 (18)
CCI score, n (%)		
0	21,893 (60)	37,008 (49)
1	6515 (18)	8633 (12)
2	4232 (12)	11,841 (16)
≥3	4045 (11)	17,587 (23)
ECI score, n (%)		
≤0	22,705 (62)	39,427 (53)
1–5	9285 (25)	14,559 (19)
6–13	3923 (11)	12,363 (16)
≥14	772 (2.1)	8720 (12)
Ethnicity, n (%)		
European	NA	58,315 (78)
Maori	NA	7544 (10)
Pacific	NA	3915 (5.2)
Indian	NA	2412 (3.2)
Chinese/Other Asian	NA	1693 (2.3)
Other	NA	1190 (1.6)

Abbreviations: CCI, Charlson Comorbidity Index; DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhauser Comorbidity Index; IQR, interquartile range; NA, not available; rDANCAMI, DANCAMI restricted to non-cardiovascular comorbidities.

proportion was 59%, and the median age was 71 years (Table 3). The proportion of MI patients with at least one comorbidity (DANCAMI score >0) was slightly lower than in Denmark (67% vs. 71%), but higher in patients with at least one non-cardiovascular comorbidity (rDANCAMI >0) (47% vs. 43%). As in the Danish cohort, the two most

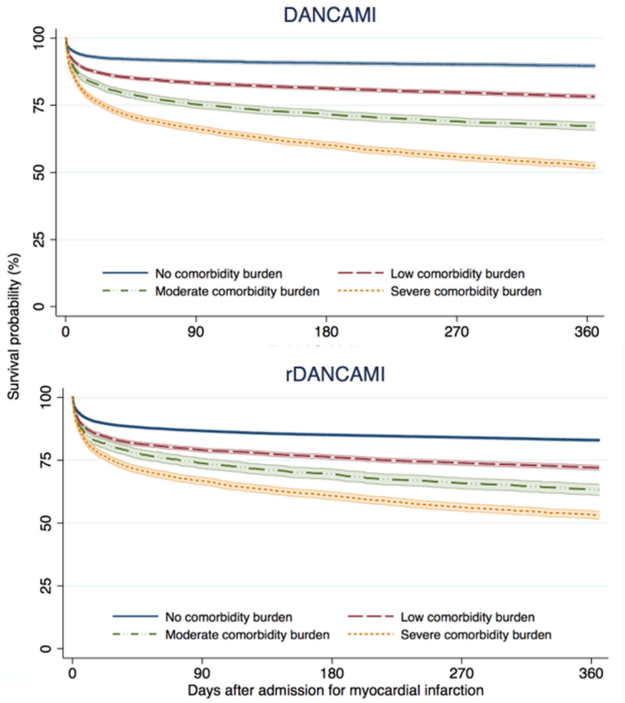


Figure 1 Survival according to the DANish Comorbidity index for Acute Myocardial Infarction (DANCAMI) score categories of comorbidity burden with 95% confidence intervals.
Abbreviations: rDANCAMI, DANCAMI restricted to non-cardiovascular comorbiditis

prevalent comorbidities were hypertension (38%) and chronic pulmonary disease (17%), but here diabetes with end-organ failure came third (16%) (Table 3).

DANCAMI scores also added to the predictive performance compared with the baseline model. Discrimination was better than that of the baseline model (C-statistic 0.77 vs. 0.73) and R^2 was higher (0.37 vs. 0.28). IDI was 0.079 and NRI was 0.682 with 78% of non-events and 56% of events obtaining a more correct predicted probability of 1-year mortality compared with the predictions of the baseline model (eTable 2). Performances of the CCI and the ECI were nearly identical to that of DANCAMI, except for NRI where the CCI performance was lower (Table 4). rDANCAMI performance was lower than the other three indices (Table 4). Similar to the Danish cohort, DANCAMI score categories performed almost as well in R^2 and C-statistics as the continuous score, but with a lower IDI and a higher NRI (Table 4).

Sensitivity Analyses

The sensitivity analyses showed that (1) changing the inclusion threshold to 1.20 (ie, removing all comorbidities with a score of one) or (2) changing severity weights to precise beta-coefficients had limited effect on the model performance (eTable 3); (3) using HRs as severity weights worsened all performance measures (eTable 3); and (4) 1-year mortality was higher in the derivation cohort (26%) than in the validation split-sample cohort (21%), although baseline characteristics were similar (eTable 4a). The number of comorbidities obtaining different severity weights was 7 in the refitted DANCAMI and 5 in the refitted rDANCAMI. Still, both refitted models performed better than the CCI and the ECI when tested in the validation cohort (eTable 4b).

Among patient subgroups (eTables 5–7), the models performed best for (5) patients surviving the initial MI hospitalization (6) younger age groups <75 years: (7) males (mostly attributable to the baseline model and not the added comorbidity score); and (8), European ethnicity (while the ECI was best in the other ethnic groups).

Discussion

We developed and validated two comorbidity indices predicting 1-year mortality for Danish patients after their first hospital admission for MI based on any type of comorbidity (DANCAMI) or non-cardiovascular comorbidities (rDANCAMI). The new indices included multiple variables not included in the current comorbidity indices and outperformed both the CCI and the ECI. The DANCAMI/rDANCAMI score categories performed almost equally as well as the continuous scores.

Previous Literature

In contrast to previous studies, DANCAMI was developed in a contemporary cohort with contemporary comorbidities (eg, exclusion of AIDS as a comorbidity and inclusion of psychiatric disorders). The rDANCAMI is the first comorbidity index for MI patients to include only non-cardiovascular comorbidities. However, other comorbidity indices have been developed specifically for MI patients. A 1994 US study used Medicare data to develop a comorbidity index predicting 2-year MI mortality.[2] However, the patients were diagnosed in 1987 and were all 30-day survivors; and therefore not generalizable to all MI patients. A Chinese comorbidity index was developed in 2016 to predict in-hospital mortality in MI patients admitted to a Beijing hospital during 2006–2010.[3] The study aimed to develop a method to adjust for heterogeneity between Chinese hospitals. In contrast to DANCAMI, the Chinese

Table 4 Performance of the Continuous and Categorical Scores of DANCAMI and Other Comorbidity Indices in the Danish (Development) and New Zealand (Validation) Cohorts of Patients with First-Time Myocardial Infarction

Discrimination Measures	Continuous Comorbidity Index Scores				Categorical Comorbidity Index Scores			
	Danish Cohort		New Zealand Cohort		Danish Cohort		New Zealand Cohort	
R^2								
Baseline*	0.28 (0.27–0.29)	Ref.	0.28 (0.28–0.29)	Ref.	0.28 (0.27–0.29)	Ref.	0.28 (0.28–0.29)	Ref.
DANCAMI†	0.33 (0.32–0.34)	1.20‡	0.37 (0.37–0.38)	1.32‡	0.32 (0.31–0.33)	1.14‡	0.36 (0.35–0.37)	1.29‡
rDANCAMI†	0.32 (0.31–0.33)	1.15‡	0.36 (0.35–0.37)	1.28‡	0.31 (0.30–0.32)	1.11‡	0.35 (0.34–0.36)	1.25‡
CCI†	0.32 (0.31–0.33)	1.14‡	0.37 (0.37–0.38)	1.32‡	0.31 (0.30–0.32)	1.11‡	0.36 (0.36–0.37)	1.29‡
ECI†	0.31 (0.30–0.32)	1.13‡	0.38 (0.37–0.38)	1.33‡	0.31 (0.30–0.32)	1.11‡	0.38 (0.37–0.39)	1.36‡
Harrell's C								
Baseline*	0.73 (0.72–0.73)	Ref.	0.73 (0.72–0.73)	Ref.	0.73 (0.72–0.73)	Ref.	0.73 (0.72–0.73)	Ref.
DANCAMI†	0.75 (0.75–0.76)	1.04§	0.77 (0.77–0.78)	1.07§	0.75 (0.74–0.75)	1.03§	0.77 (0.76–0.77)	1.05§
rDANCAMI†	0.75 (0.74–0.75)	1.03§	0.77 (0.76–0.77)	1.05§	0.74 (0.74–0.75)	1.01§	0.76 (0.76–0.77)	1.04§
CCI†	0.74 (0.74–0.75)	1.03§	0.77 (0.77–0.78)	1.07§	0.74 (0.74–0.75)	1.01§	0.77 (0.77–0.77)	1.05§
ECI†	0.74 (0.74–0.75)	1.02§	0.77 (0.77–0.78)	1.07§	0.74 (0.74–0.75)	1.01§	0.78 (0.77–0.78)	1.07§
IDI								
Baseline* vs DANCAMI†	0.054	–	0.079	–	0.044	–	0.061	–
Baseline* vs rDANCAMI†	0.038	–	0.068	–	0.033	–	0.057	–
Baseline* vs CCI†	0.038	–	0.077	–	0.034	–	0.066	–
Baseline* vs ECI†	0.029	–	0.081	–	0.029	–	0.081	–
NRI								
Baseline* vs DANCAMI†	0.52	–	0.68	–	0.55	–	0.72	–
Baseline* vs rDANCAMI†	0.43	–	0.57	–	0.41	–	0.53	–
Baseline* vs CCI†	0.41	–	0.58	–	0.46	–	0.71	–
Baseline* vs ECI†	0.40	–	0.68	–	0.47	–	0.69	–

Notes: *Baseline model defined as a Cox model including sex and age. †Model performances were examined in a Cox model including sex, age and the individual continuous/categorical comorbidity index scores. ‡Relative difference in R^2 compared to baseline model. §Relative difference in Harrell's C compared to baseline model.
Abbreviations: CCI, Charlson Comorbidity Index; DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction; ECI, Elixhauser Comorbidity Index; rDANCAMI, DANCAMI restricted to non-cardiovascular comorbidities; Ref., Reference.

index included potential complications of MI such as cardiac arrest and shock. In 2011, a Spanish comorbidity index was developed for patients hospitalized during 2002–2008 with non-ST-segment elevation MI.[4] This index included only 1017 patients and may not generalize to all MI patients. A 2001 Canadian study developed two separate comorbidity indices predicting 30-day and 1-year mortality among MI patients with age group and sex included in the indices.[5] Unfortunately, the authors only reported regression coefficients and odds ratios with 95% CIs and did not generate a simpler scoring system.[5] Finally, a Canadian comorbidity index developed in 2019 included a study population of patients undergoing diagnostic and/or therapeutic cardiac catheterization.[6] The difference between this and our MI study populations complicates comparison.

Unlike most other comorbidity indices, the DANCAMI and the rDANCAMI include multiple mental and behavioural health disorders such as alcohol/drug abuse, schizophrenia, and affective disorders, which were assigned relatively high weights of 3 to 5 in our study. In some indices, these disorders were not included or not considered for inclusion.[3–7] The ECI[8] and the 1994 US study[2] both included psychiatric diagnoses. In the ECI, drug abuse and depression scored less than zero, while alcohol abuse and psychoses scored zero. In the US study, the prevalence of these disorders was very low compared with our Danish cohort. This discrepancy could be due to use of different definitions of these diagnoses. The high prevalence and significant HRs of the psychiatric diagnoses in DANCAMI and rDANCAMI indicate that these variables are important predictors of mortality. This assumption is supported by our analysis showing that all novel variables in DANCAMI, including the mental and behavioural disorders, where significant predictors of mortality in the Danish cohort after adjusting for the CCI variables. The novel variables were also significant

Table 5 Adjusted Hazard Ratios for the Charlson Comorbidity Index and Additional DANCAMI Variables, Derived in the Danish and New Zealand Myocardial Infarction Cohorts

Covariables	Hazard Ratio (95% Confidence Interval)	
	Danish Cohort	New Zealand Cohort
Charlson Comorbidity Index		
Congestive heart failure	1.37 (1.28–1.46)	1.51 (1.44–1.58)
Peripheral vascular disease	1.38 (1.29–1.47)	1.38 (1.30–1.45)
Cerebrovascular disease	1.24 (1.17–1.31)	0.95 (0.90–1.01)
Dementia	1.36 (1.20–1.54)	1.80 (1.70–1.89)
Chronic pulmonary disease	1.36 (1.28–1.44)	1.44 (1.38–1.51)
Connective tissue disease	1.03 (0.93–1.15)	1.18 (1.07–1.30)
Ulcer disease	1.19 (1.08–1.31)	1.08 (0.99–1.18)
Mild liver disease	1.33 (1.03–1.71)	1.11 (0.97–1.29)
Diabetes	1.03 (0.94–1.12)	1.03 (0.99–1.08)
Hemiplegia	1.71 (1.19–2.45)	1.65 (1.55–1.76)
Moderate or severe renal disease	1.37 (1.26–1.49)	1.81 (1.74–1.88)
Diabetes with end organ damage	1.31 (1.21–1.41)	1.18 (1.07–1.30)
Any tumor	1.31 (1.22–1.40)	1.24 (1.18–1.30)
Leukemia	1.51 (1.14–1.98)	2.17 (1.84–2.57)
Lymphoma	1.68 (1.37–2.06)	1.69 (1.48–1.93)
Moderate or severe liver disease	1.86 (1.28–2.70)	2.87 (2.50–3.30)
Metastatic solid tumor	3.33 (2.91–3.80)	3.48 (3.26–3.71)
AIDS	0.43 (0.06–3.05)	0.33 (0.05–2.35)
DANCAMI additional variables*		
Valvular heart disease	1.25 (1.14–1.35)	1.29 (1.20–1.38)
Coagulopathy	1.13 (1.05–1.22)	1.13 (1.09–1.18)
Alcohol and drug abuse	1.35 (1.15–1.58)	1.20 (1.11–1.31)
Schizophrenia	1.60 (1.46–1.76)	1.21 (0.99–1.48)
Affective disorder	1.29 (1.22–1.36)	1.21 (1.10–1.32)
Epilepsy	1.26 (1.05–1.50)	1.20 (1.01–1.42)
Neurodegenerative disorder	1.30 (1.10–1.54)	1.40 (1.28–1.54)
Chronic pancreatitis	1.71 (1.14–2.56)	1.31 (0.91–1.87)

Notes: *Hazard ratios for the non-overlapping DANCAMI variables adjusted for the Charlson Comorbidity Index variables.
Abbreviations: DANCAMI, DANish Comorbidity index for Acute Myocardial Infarction.

predictors of mortality in the New Zealand MI cohort. These results indicate that the inclusion of these additional predictors in the comorbidity indices are important for accurate outcome prediction. The value of these added predictors is not clearly reflected in the standard performance measures (eg, R^2 and C-statistic), which was not surprising as these are global measures that are relatively insensitive to the addition of new variables.[20]

Both DANCAMI and rDANCAMI showed higher discrimination in the New Zealand validation cohort than in the Danish development cohort, which was unexpected. However, the CCI and the ECI also showed higher discrimination in the New Zealand cohort. These findings likely reflect different case mixes in the two nationwide cohorts, eg, a more ethnically diverse population in New Zealand than in Denmark. DANCAMI was slightly superior in the subgroup of the New Zealand cohort with European ethnicity that is likely to be more comparable to the Danish population.

The CCI and the ECI have previously been validated in MI patient populations. In studies performed in the US,[24] Taiwan,[25] and five different European countries,[26] the ECI outperformed the CCI in predicting in-hospital[24–26] and 1-year mortality.[25] These studies differ from our study as they included comorbidities as separate variables in their performance analyses instead of using a summary score. A Japanese study compared the performance of the CCI and the ECI using individual comorbidities vs. a summary score, and found that the ECI performed better with individual comorbidities.[27] However, the CCI and the ECI performed similar when the summary score was applied. This finding demonstrates that performance of individual

comorbidity indices can vary depending on their application. In our performance analyses of the summary scores, the CCI showed better performance than the ECI in the Danish cohort. In contrast, the ECI performed marginally better than the CCI in the New Zealand cohort.

Despite the concerns of information loss that may arise with the simplification of summary scores,[20] they can be a useful tool to adjust for comorbidity burden in observational studies in which multiple variables often are included in regression analyses. The same applies when categorizing summary scores. The categorized groups are a simple and easily accessible method to illustrate and adjust for comorbidity burden. However, they provide further simplification of the original prediction model since they assign the same predicted risk to patients with different comorbidity scores.[20] Moreover, there is no clear consensus on the method behind the categorization of summary scores.[20] We created four categories by examining the survival curves of the individual DANCAMI and rDANCAMI scores. In our performance analyses, the DANCAMI score categories performed almost as good as the continuous scores. Similar results were found for the ECI where the continuous scores and categories performed similar in C-statistics.[8]

Strength and Limitations

Study strengths include the nationwide population-based design (reducing selection bias) and large sample size (reducing random error). Furthermore, rDANCAMI allows researchers to study the effect of individual cardiovascular diseases separately while adjusting for non-cardiovascular comorbidity burden. We used recommended methods to generate summary scores in our final indices[20] and considered a variety of variables for both indices, including psychiatric diagnoses, which have previously been overlooked.

Although we used a five-year look-back period to identify comorbidities and defined variables from algorithms including both diagnoses, prescriptions, and laboratory data, misclassification of some conditions is unavoidable.[28] However, the positive predictive values have been reported to be high for both cardiac[14,29] and CCI comorbidities (98% overall).[30] Like previous studies,[2,8] we found several comorbidities that were associated with a decreased 1-year mortality (eg, stable angina pectoris and anxiety) in our multivariable model. These seemingly protective comorbidities could result from a bias in coding in which severity of overall patient illness may inversely affect the coding of chronic and nonfatal comorbidities.[8] We therefore excluded these comorbidities from our final indices.

We lacked detailed clinical information, eg, electrocardiogram results and cardiac biochemical markers, which may be important predictors particularly of short-term mortality. This is evident in clinical risk prediction models, such as the Global Registry of Acute Coronary Events (GRACE) risk score,[31] and may explain the superior performance of our indices among patients surviving hospital admission. However, detailed clinical information is often not available in routine secondary care data which makes it less useful as predictors in this setting.

Our robust external validation indicated that both DANCAMI and rDANCAMI generalize well outside the Danish cohort. Still, it should be noted that DANCAMI was developed and validated in patients with MI. Thus, its performance in patients with other cardiovascular diseases remains to be examined.

Conclusions

Comorbidity burden was a strong predictor of mortality in MI patients and must be controlled for accurately when studying outcomes in MI patients. We developed two separate comorbidity indices with (DANCAMI) and without (rDANCAMI) cardiovascular comorbidities to predict 1-year mortality following first-time MI. The indices were based on comorbidities in contemporary MI patients. DANCAMI performed better than the previous most commonly used comorbidity indices and included novel comorbidities with incremental ability to predict mortality. Both indices can be used to control for comorbidity burden in MI patients either by applying the continuous or the categorized summary score. The indices are likely generalizable to MI patients in other Western countries similar to Denmark and New Zealand. We therefore recommend DANCAMI as a standard approach for comorbidity adjustment in studies of MI prognosis.

Data Permission

The study was approved by the Danish Data Protection Agency (record number 2013-41-1924). The use of New Zealand data was approved by the Northern Ethics Committee Y in 2003 (AKY/03/12/314), with annual approval by the National Multi-Region Ethics Committee since 2007 (MEC07/19/EXP).

Ethics Committee Approval

No ethical committee approval was needed.

Patient Involvement Statement

No patient involvement.

Transparency Declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Author Contributions

MS and HTS conceived the study idea and designed the study together with co-authors. LWA and MS assembled the list of potential comorbidities from review of existing indices and medical conditions included in the ICD-10. MS, UHJ, RJ and LWA directed the analyses, which were carried out by LWA. LWA and MS organized the writing and wrote the initial draft, reply letter, and revised manuscript. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. LWA attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MS is the guarantor.

Funding

The study was supported by the Danish Heart Association, Department of Clinical Epidemiology's Research Foundation, Handelsgartner Ove William Buhl Olesen og ægtefælde fru Edith Buhl Olesens mindelegat, Politimester J.P.N. Colind og hustru Colinds Mindelegat and Danske lægers forsikring under SEB pension. MS was supported by the Novo Nordisk Foundation (grant NNF19OC0054908). The funding sources had no role in the design, conduct, analysis, or reporting of the study.

Disclosure

Lisbeth Wellejus Albertsen reports grants from The Danish Heart Association, Department of Clinical Epidemiology's Research Foundation, Handelsgartner Ove William Buhl Olesen og ægtefælde fru Edith Buhl Olesens mindelegat, Politimester J.P.N. Colind og hustru Colinds Mindelegat, and Danske lægers forsikring under SEB pension, during the conduct of the study. Corina Grey is supported by a grant from Heart Foundation of New Zealand, during the conduct of the study. Morten Schmidt is supported by the Novo Nordisk Foundation (grant NNF19OC0054908). The authors report no other potential conflicts of interest for this work.

References

1. Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long-term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344(jan25 2):e356. doi:10.1136/bmj.e356
2. Normand SL, Morris CN, Fung KS, McNeil BJ, Epstein AM. Development and validation of a claims based index for adjusting for risk of mortality: the case of acute myocardial infarction. *J Clin Epidemiol*. 1995;48(2):229–243. doi:10.1016/0895-4356(94)00126-B
3. Qu Z, Zhao LP, Ma X, Zhan S. Building a patient-specific risk score with a large database of discharge summary reports. *Med Sci Monit*. 2016;22:2097–2104. doi:10.12659/MSM.899262
4. Sanchis J, Nunez J, Bodi V, et al. Influence of comorbid conditions on one-year outcomes in non-ST-segment elevation acute coronary syndrome. *Mayo Clin Proc*. 2011;86(4):291–296. doi:10.4065/mcp.2010.0702
5. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol*. 2001;37(4):992–997. doi:10.1016/S0735-1097(01)01109-3
6. Azzalini L, Chabot-Blanchet M, Southern DA, et al. A disease-specific comorbidity index for predicting mortality in patients admitted to hospital with a cardiac condition. *CMAJ*. 2019;191(11):E299–E307. doi:10.1503/cmaj.181186
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
8. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009;47(6):626–633. doi:10.1097/MLR.0b013e31819432e5
9. Li P, Kim MM, Doshi JA. Comparison of the performance of the CMS Hierarchical Condition Category (CMS-HCC) risk adjuster with the Charlson and Elixhauser comorbidity measures in predicting mortality. *BMC Health Serv Res*. 2010;10:245. doi:10.1186/1472-6963-10-245
10. Holman CD, Preen DB, Baynham NJ, Finn JC, Semmens JB. A multipurpose comorbidity scoring system performed better than the Charlson index. *J Clin Epidemiol*. 2005;58(10):1006–1014. doi:10.1016/j.jclinepi.2005.01.020
11. Stirland LE, Gonzalez-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ*. 2020;368:m160. doi:10.1136/bmj.m160
12. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563–591. doi:10.2147/CLEP.S179083
13. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549. doi:10.1007/s10654-014-9930-3

14. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi:10.2147/CLEP.S91125
15. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol*. 2010;2:273–279. doi:10.2147/CLEP.S13458
16. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol*. 2011;3:133–138. doi:10.2147/CLEP.S17901
17. National Health Board. *National Minimum Dataset (Hospital Events) Data Dictionary*. Ministry of Health Wellington; 2014.
18. Ministry of Health. *Mortality Collection Data Dictionary*. Ministry of Health Wellington; 2009.
19. Ministry of Health. *Pharmaceutical Claims Data Mart Data Dictionary*. Ministry of Health Wellington, 2017.
20. Moons KG, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1–W73. doi:10.7326/M14-0698
21. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239–241. doi:10.1093/biomet/69.1.239
22. Mehta HB, Mehta V, Girman CJ, Adhikari D, Johnson ML. Regression coefficient-based scoring system should be used to assign weights to the risk index. *J Clin Epidemiol*. 2016;79:22–28. doi:10.1016/j.jclinepi.2016.03.031
23. Knottnerus JA, Tugwell P, Wells G. Editorial comment: ratios should be multiplied, not added. *J Clin Epidemiol*. 2016;79:30. doi:10.1016/j.jclinepi.2016.11.007
24. Stukenborg GJ, Wagner DP, Connors AF Jr. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. *Med Care*. 2001;39(7):727–739. doi:10.1097/00005650-200107000-00009
25. Chu Y, Ng Y, Wu S. Comparison of different comorbidity measures for use with administrative data in predicting short- and long-term mortality. *BMC Health Serv Res*. 2010;10(1). doi:10.1186/1472-6963-10-140
26. Gutacker N, Bloor K, Cookson R. Comparing the performance of the Charlson/Deyo and Elixhauser comorbidity measures across five European countries and three conditions. *Eur J Public Health*. 2015;25(Suppl 1):15–20. doi:10.1093/eurpub/cku221
27. Yamana H, Matsui H, Sasabuchi Y, Fushimi K, Yasunaga H. Categorized diagnoses and procedure records in an administrative database improved mortality prediction. *J Clin Epidemiol*. 2015;68(9):1028–1035. doi:10.1016/j.jclinepi.2014.12.004
28. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano W, Silliman RA. Methodology, design, and analytic techniques to address measurement of comorbid disease. *J Gerontol a Biol Sci Med Sci*. 2007;62(3):281–285.
29. Sundboll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11):e012832. doi:10.1136/bmjopen-2016-012832
30. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of patients. *BMC Med Res Methodol*. 2011;11:83. doi:10.1186/1471-2288-11-83
31. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345–2353. doi:10.1001/archinte.163.19.2345

Paper VI

BMJ Open

Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin–angiotensin system blockade: a UK general practice-based cohort study

Morten Schmidt,[1,2,3] Kathryn E Mansfield,[1] Krishnan Bhaskaran,[1] Dorothea Nitsch,[1] Henrik Toft Sørensen,[2] Liam Smeeth,[1] Laurie A Tomlinson[1]

To cite: Schmidt M, Mansfield KE, Bhaskaran K, *et al*. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin–angiotensin system blockade: a UK general practice-based cohort study. *BMJ Open* 2017;**7**:e012818. doi:10.1136/bmjopen-2016-012818

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012818).

Received 27 May 2016
Revised 5 August 2016
Accepted 12 October 2016

For numbered affiliations see end of article.

Correspondence to
Dr Morten Schmidt;
morten.schmidt@clin.au.dk

ABSTRACT

Objectives: To examine adherence to serum creatinine and potassium monitoring and discontinuation guidelines following initiation of treatment with ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs); and whether high-risk patients are monitored.

Design: A general practice-based cohort study using electronic health records from the UK Clinical Practice Research Datalink and Hospital Episode Statistics.

Setting: UK primary care, 2004–2014.

Subjects: 223 814 new ACEI/ARB users.

Main outcome measures: Proportion of patients with renal function monitoring before and after ACEI/ARB initiation; creatinine increase ≥30% or potassium levels >6 mmol/L at first follow-up monitoring; and treatment discontinuation after such changes. Using logistic regression models, we also examined patient characteristics associated with these biochemical changes, and with follow-up monitoring within the guideline recommendation of 2 weeks after treatment initiation.

Results: 10% of patients had neither baseline nor follow-up monitoring of creatinine within 12 months before and 2 months after initiation of an ACEI/ARB, 28% had monitoring only at baseline, 15% only at follow-up, and 47% both at baseline and follow-up. The median period between the most recent baseline monitoring and drug initiation was 40 days (IQR 12–125 days). 34% of patients had baseline creatinine monitoring within 1 month before initiating therapy, but <10% also had the guideline-recommended follow-up test recorded within 2 weeks. Among patients experiencing a creatinine increase ≥30% (n=567, 1.2%) or potassium level >6 mmol/L (n=191, 0.4%), 80% continued treatment. Although patients with prior myocardial infarction, hypertension or baseline potassium >5 mmol/L were at high risk of ≥30% increase in creatinine after ACEI/ARB initiation, there was no evidence that they were more frequently monitored.

Conclusions: Only one-tenth of patients initiating ACEI/ARB therapy receive the guideline-recommended creatinine monitoring. Moreover, the vast majority of the patients fulfilling postinitiation discontinuation criteria for creatinine and potassium increases continue on treatment.

Strengths and limitations of this study

- This is the largest monitoring study until now, examining both adherence to creatinine and potassium monitoring and discontinuation guidelines following initiation of ACE inhibitors or angiotensin receptor blockers in UK primary care, and whether patients are monitored in accordance with their individual risk profile.
- Use of the UK Clinical Practice Research Datalink and Hospital Episode Statistics ensured that the study was population-based and not restricted to specific demographic, hospital or insurance groups.
- Blood tests performed in hospital systems were not recorded in the Clinical Practice Research Datalink, but the results were consistent for patients with no recent hospital admissions.
- If the recording of creatinine levels was not missing completely at random, the associations between patient characteristics and creatinine increase may have been underestimated.

INTRODUCTION

Renin angiotensin system blockade using ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) is a mainstay in treatment of hypertension,[1] heart failure,[2] diabetic microalbuminuria or proteinuric

renal diseases,[3] and after myocardial infarction.[4] However, some patients experience a sudden decline in kidney function when initiating these drugs, presumably due to antagonism of the angiotensin II-mediated efferent arteriolar constriction or impaired kidney excretion of potassium.[5 6]

The potential impact on kidney function should be evaluated by comparing preinitiation and postinitiation levels of serum creatinine and potassium.[7] Discontinuation is recommended if the rise in creatinine exceeds 30% above baseline or if hyperkalaemia develops.[8] It is unclear whether these recommendations are routinely followed in clinical practice.[9]

A few studies have compared baseline and follow-up monitoring results,[9] but large studies using contemporary data with reference to current guidelines are lacking, and it is unknown whether patients' individual risk of renal impairment influences their likelihood of being monitored.[9] We therefore examined adherence to creatinine and potassium monitoring and treatment discontinuation guidelines following ACEI/ARB initiation in UK primary care, and whether patients are monitored in accordance with their individual risk profile.

METHODS

Data sources

We used the UK's Clinical Practice Research Datalink (CPRD) linked to hospital record data from the Hospital Episode Statistics (HES) database. The CPRD database contains primary care electronic health record data from 7% of the UK population (~15 million patient lives, with ~8 million currently under follow-up).[10] Patients included in the CPRD are largely representative of the UK population in terms of age, sex and ethnicity.[10 11] Information recorded in the database includes demographics such as sex and year of birth, the location of the general practice, medical diagnoses (based on 'Read' codes), drug prescriptions and a range of routine laboratory test results. HES records cover all hospital admissions for patients covered by the National Health Service (NHS) who receive treatment either from English NHS trusts or independent providers.[10 11] Fifty-eight per cent of general practices included in the CPRD have agreed to HES linkage.[10] We obtained linked data on socioeconomic status (index of multiple deprivation) based on area of residence.

Monitoring guidelines

Consistent with other international guidelines, the National Institute for Health and Care Excellence (NICE) recommends baseline testing of creatinine when initiating ACEI/ARB therapy in patients with hypertension,[1] heart failure,[2] myocardial infarction[4] or chronic kidney disease (CKD).[3] The time interval for baseline testing is not further specified.[1–4] Among patients with heart failure, myocardial infarction and CKD, NICE recommends follow-up monitoring within 2 weeks of treatment initiation,[2–4] and for patients with myocardial infarction at least annually thereafter.[4] A baseline assessment and follow-up test within 2 weeks is also recommended by the UK Renal Association,[12] as well as the frequently used online web resource General Practice (GP) Notebook.[13] GP Notebook additionally recommends monitoring 1, 3, 6 and 12 months after the first follow-up test.[13] NICE recommends not to initiate ACEI/ARBs in patients with a baseline potassium level >5 mmol/L and to discontinue therapy if potassium rises above 6 mmol/L.

ACEI/ARB initiators

We identified a cohort of all HES-linked CPRD patients aged ≥18 years, who initiated ACEI/ARB treatment between 1 January 2004 and 31 March 2014. We did not include earlier calendar periods, as laboratory data before 2004 were incomplete due to interface problems between laboratory reporting software and GP practice management software.[14] Also, creatinine testing was incentivised in 2004 with the introduction of the diabetes Quality and Outcomes Framework (QOF) and further in 2006 with the CKD QOF.[14] To rule out any potential influence of incomplete data around 2004, we also examined the most recent 5-year calendar period separately in a sensitivity analysis. New users were defined as persons with at least 1 year of continuous registration in the CPRD before their first recorded ACEI/ARB prescription.

Laboratory data

All creatinine test results were extracted from the general practice records of the study population, using creatinine-specific codes in CPRD. Cross-reference was then made to creatinine test results identified from a broad Read code search. Any irrelevant codes were excluded. Renal function testing in the UK includes creatinine and potassium, so it can be inferred that testing frequency is similar to creatinine for potassium. When we conducted analyses related to potassium levels, we repeated the procedure used to identify creatinine levels for potassium test results.

Patient characteristics

We obtained information for all patients on age, sex, calendar period of ACEI/ARB initiation (2004–2008 and 2010–2014), socioeconomic status (quintiles of the 2004 index of multiple deprivation scores), lifestyle factors (smoking, alcohol intake and body mass index), baseline potassium level (≤5 or >5 mmol/L), CKD, cardiovascular comorbidities (heart failure, myocardial infarction, hypertension, peripheral arterial disease and arrhythmia) and diabetes.[15] We used algorithms for smoking status, alcohol intake and body mass index based on the most recent records in the CPRD before ACEI/ARB initiation.[16 17] As measures of baseline creatinine and potassium levels, we used the single most recent measurement within 12 months before the first ACEI/ARB

prescription. We calculated the estimated glomerular filtration rate (eGFR) level from the most recent creatinine measurement and CKD stage from the CKD Epidemiology Collaboration (CKD-EPI) equation.[18] Cardiovascular comorbidities and diabetes were identified from both the CPRD and HES based on diagnoses recorded prior to ACEI/ARB initiation. The code lists for all variables are provided in the online supplementary appendix.

Patient involvement

The study included no patient involvement.

Statistical analysis

We described ACEI/ARB users according to patient characteristics, both overall and according to creatinine monitoring status (no baseline or follow-up monitoring, baseline only, follow-up only, and both baseline and follow-up monitoring). Baseline monitoring was defined as a test performed on the date of drug initiation or within either 12 months before (wide interval) or 1 month before initiation (more ideal interval assumed to be driven by planned ACEI/ARB initiation). To accord with the postinitiation monitoring interval recommended from previous trial data, we considered only follow-up monitoring within the first 2 months after drug initiation.[8]

We calculated the proportion of persons in the total cohort of new users who had baseline and follow-up monitoring (within 1, 3 and 12 months before drug initiation and within 2 weeks, 1 month and 2 months after initiation). We then computed the proportion of persons with both baseline and initial follow-up monitoring within the guideline-recommended interval of 2 weeks following drug initiation.

We repeated the analyses for continuing users, in order to examine adherence to the stricter guideline recommendations for ongoing monitoring (*ie*, monitoring within 1, 3, 6 and 12 months after the first retest).[13] Continuation was defined as ACEI/ARB use beyond 30 days following the monitoring date, *that is*, when the end date of the first continuous course of therapy was after the date of the first monitoring date plus 30 days (to allow for stockpiling). The end date of each prescription was calculated by adding the prescription duration (total number of tablets prescribed divided by the specified number of tablets per day) to the prescription date. In identifying continuous courses of therapy, we allowed for a 30-day gap between the end date of one prescription and the start of the next consecutive prescription.

In sensitivity analyses, we repeated the analyses (1) extending the follow-up window for the first follow-up monitoring from 2 to 3 weeks to account for minor delays; (2) including only the most recent calendar period (2009–2014) to account for temporal changes in data completeness and quality of care; (3) excluding patients with a hospital admission or discharge date within 1 month before or after their first ACEI/ARB prescription, in order to account for drug initiation and any subsequent renal function tests occurring in the hospital and therefore not captured in the CPRD; (4) focusing on specific patient subgroups (heart failure, myocardial infarction, hypertension, CKD (eGFR<60 mL/min/1.73 m^2), peripheral arterial disease and diabetes); and (5) defining drug use continuation as ACEI/ARB use beyond 90 days (instead of 30 days) after the first retest date.

We used the subcohort of patients with both baseline and follow-up monitoring to calculate the proportion of patients with creatinine increases ≥30% or potassium levels >6 mmol/L at the first follow-up monitoring within 2 months after initiation, as well as the proportion of patients continuing treatment despite these contraindications for use.

Finally, we fitted a logistic regression model to identify patient characteristics associated with a severe decline in renal function (creatinine increase ≥30% or potassium level >6 mmol/L) and compared these characteristics with those associated with receiving postinitiation follow-up monitoring within 2 weeks. The model included age, sex, CKD stage, cardiovascular comorbidities, diabetes and baseline potassium level (>5 vs ≤5 mmol/L). In three additional model-based sensitivity analyses, we repeated the analyses (1) excluding patients with a recent hospitalisation (as defined above); (2) omitting baseline potassium from the model to examine the extent of potential overfitting when both baseline potassium and CKD stage were kept in the model; and (3) also adjusting additionally for ethnicity.

All analyses were performed using the STATA 14 statistical software package.

RESULTS

Serum creatinine monitoring before and after ACEI/ARB initiation

We identified 223 814 new users of ACEI/ARB. We compared these patients in four groups: 21 411 (10%) had no baseline or follow-up creatinine tests within 12 months before and 2 months after treatment initiation, 63 359 (28%) had only a baseline test, 33 185 (15%) had only follow-up tests, and 105 859 (47%) had both baseline and follow-up tests (table 1). Median age varied only slightly between the groups (60, 62, 59 and 63 years, respectively) and there were no substantial differences in socioeconomic status, lifestyle factors or peripheral arterial disease. Compared with patients with neither preinitiation nor postinitiation monitoring, patients with both were more likely to have diagnosed hypertension (76% vs 61%) and diabetes (20% vs 7%), but less likely to have diagnosed heart failure (4% vs 7%), myocardial infarction (4% vs 18%) and arrhythmia (7% vs 10%). Among patients with baseline monitoring, 83% did not have CKD, 13% stage 3a, 3% stage 3b, 0.5% stage 4 CKD. In the same population, 7% started

Table 1 Characteristics of patients initiating ACE inhibitors or ARBs in the UK primary care during 2004–2014, by monitoring groups

	Serum creatinine monitoring*				
	No baseline or follow-up tests	Baseline test only	Follow-up test only	Baseline and follow-up tests	Total
Total number	21 411 (100)	63 359 (100)	33 185 (100)	105 859 (100)	223 814 (100)
Female sex	8882 (41)	27 722 (44)	14 570 (44)	49 109 (46)	100 283 (45)
Age (years)					
<50	5019 (23)	13 697 (22)	8732 (26)	19 910 (19)	47 358 (21)
50–59	5485 (26)	15 135 (24)	9115 (27)	24 866 (23)	54 601 (24)
60–69	4863 (23)	15 586 (25)	7776 (23)	27 790 (26)	56 015 (25)
70–79	3579 (17)	12 193 (19)	5066 (15)	22 152 (21)	42 990 (19)
80+	2465 (12)	6748 (11)	2496 (8)	11 141 (11)	22 850 (10)
Calendar period					
2004–2008	14 814 (69)	40 667 (64)	19 808 (60)	60 902 (58)	136 191 (61)
2009–2014	6597 (31)	22 692 (36)	13 377 (40)	44 957 (42)	87 623 (39)
SES quintiles					
1 (low)	5153 (24)	15 290 (24)	8533 (26)	25 577 (24)	54 553 (24)
2	4725 (22)	14 331 (23)	7887 (24)	24 851 (23)	51 794 (23)
3	4341 (20)	13 028 (21)	6890 (21)	22 629 (21)	46 888 (21)
4	4254 (20)	12 140 (19)	5931 (18)	19 318 (18)	41 643 (19)
5 (high)	2925 (14)	8508 (13)	3898 (12)	13 359 (13)	28 690 (13)
Missing	13 (0)	62 (0)	46 (0)	125 (0)	246 (0)
Smoking status					
Never	7860 (37)	22 496 (36)	12 229 (37)	36 895 (35)	79 480 (36)
Ever	13 433 (63)	40 797 (64)	20 915 (63)	68 939 (65)	144 084 (64)
Missing	118 (1)	66 (0)	41 (0)	25 (0)	250 (0)
Alcohol intake					
No use	2556 (12)	7819 (12)	3409 (10)	11 088 (10)	24 872 (11)
Current	15 495 (72)	47 322 (75)	25 656 (77)	82 870 (78)	171 343 (77)
Former	1328 (6)	4499 (7)	1933 (6)	7490 (7)	15 250 (7)
Missing	2032 (9)	3719 (6)	2187 (7)	4411 (4)	12 349 (6)
BMI groups					
Underweight	282 (1)	700 (1)	304 (1)	1008 (1)	2294 (1)
Healthy weight	5666 (26)	15 406 (24)	8089 (24)	24 972 (24)	54 133 (24)
Overweight	7677 (36)	23 755 (37)	12 484 (38)	40 556 (38)	84 472 (38)
Obesity	6009 (28)	20 660 (33)	10 527 (32)	35 887 (34)	73 083 (33)
Missing	1777 (8)	2838 (4)	1781 (5)	3436 (3)	9832 (4)
CKD (eGFR)†					
Stage ≤2 (≥60)	10 326 (48)	53 773 (85)	19 470 (59)	87 484 (83)	171 053 (76)
Stage 3a (45–59)	1137 (5)	7382 (12)	1766 (5)	13 913 (13)	24 198 (11)
Stage 3b (30–44)	217 (1)	1885 (3)	265 (1)	3854 (4)	6221 (3)
Stage 4 (15–29)	24 (0)	319 (1)	29 (0)	608 (1)	980 (0)
Not measured	9707 (45)	0 (0)	11 655 (35)	0 (0)	21 362 (10)
CV comorbidities‡					
Heart failure	1568 (7)	3270 (5)	1386 (4)	4583 (4)	10 807 (5)
Myocardial infarction	3881 (18)	4653 (7)	3203 (10)	4620 (4)	16 357 (7)
Hypertension	13 023 (61)	44 273 (70)	24 195 (73)	80 946 (76)	162 437 (73)
Peripheral arterial disease	471 (2)	1590 (3)	523 (2)	2547 (2)	5131 (2)
Arrhythmia	2057 (10)	4973 (8)	2000 (6)	7123 (7)	16 153 (7)
Diabetes mellitus	1399 (7)	13 586 (21)	1992 (6)	21 548 (20)	38 525 (17)

*Monitoring groups based on baseline (within 12 months before) and follow-up (within 2 months after) serum creatinine monitoring.
†Calculated from most recent creatinine measurement within 12 months before the first prescription date.
‡Diagnosis ever registered before ACE/ARB initiation in CRPD or HES.
ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HES, Hospital Episode Statistics; SES, socioeconomic status.

ACEI/ARB therapy despite baseline potassium above 5 mmol/L. The median number of days between baseline monitoring and first prescription date was 40 days (IQR 12–125 days).

Among all patients initiating ACEI/ARB therapy, the proportion of patients receiving creatinine testing before initiation was 76% within 12 months of treatment initiation, declining to 34% within 1 month before initiation

Table 2 Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating ACE inhibitors or angiotensin receptor blockers, 2004–2014

Total number	Serum creatinine, ≥1 test n=223 814 (100%)
Baseline testing	
≤12 months before	169 218 (76%)
≤3 months before	115 348 (52%)
≤1 month before	75 476 (34%)
Follow-up testing	
≤2 weeks after	65 090 (29%)
≤1 month after	114 244 (51%)
≤2 months after	139 044 (62%)

(table 2). The proportion with follow-up testing after treatment initiation was 29% within 2 weeks, increasing to 62% within 2 months. Among ACEI/ARB initiators who had a baseline test within 12 months, 21% also had a follow-up test within 2 weeks after starting treatment (table 3). However, among patients undergoing testing within 1 month prior to treatment initiation, only 9% had also the recommended follow-up test within 2 weeks of treatment start. When we extended the follow-up window to 3 weeks, this proportion increased to only 14% (table 3). Among patients continuing treatment, only 1% had follow-up measurements at 1, 3, 6 and 12 months after the first retest, in compliance with the strictest recommendation (eTable 1). These results were unchanged when the analysis was restricted to the most recent calendar period (eTables 1–2) and to patients with heart failure, myocardial infarction, hypertension, peripheral arterial disease, diabetes or no recent hospitalisation (eTable 3). Only patients with CKD received a slightly higher degree of monitoring (13%) within 2 weeks following treatment initiation (eTable 3). The proportion with follow-up testing after treatment initiation was also unchanged when results were stratified by date of ACEI/ARB initiation in 2-year intervals (eTable 4).

Serum creatinine and potassium changes after ACEI/ARB initiation

Among patients receiving the recommended renal function monitoring, 567 (1.2%) experienced a creatinine increase ≥30% and 191 (0.4%) a potassium level >6 mmol/L at their first follow-up test within 2 months of treatment initiation (1.4% experienced the increase in creatinine and/or potassium) (table 4). Among these patients, 80% continued treatment beyond 30 days following the monitoring date (table 4). The sensitivity analysis showed that 65% of patients with a creatinine increase ≥30% and 60% of those with a potassium level >6 mmol/L also continued treatment beyond 90 days after the monitoring date (eTable 5). The results remained consistent for longer baseline monitoring intervals (eTable 5).

Patients at high risk for creatinine increases ≥30%

When we examined patient characteristics associated with a creatinine increase ≥30% and adjusted for the

Table 3 Prevalence of baseline and follow-up serum creatinine monitoring among patients initiating ACE inhibitors or angiotensin receptor blockers according to clinical guideline recommendations

	Clinical guidelines					All initiators n=223 814 (100%)	
	NICE heart failure	NICE MI	NICE/UKRA hypertension	NICE CKD	GP Notebook	Wide baseline interval (≤12-months)	Ideal baseline interval (≤1 month)
Baseline testing	x	x	x	x	x	169 218 (76%)	75 476 (34%)
+Follow-up test ≤2 weeks*	x	NA	x	x	x	46 486 (21%)	19 679 (9%)
+Follow-up test ≤3 weeks†						70 792 (32%)	30 451 (14%)

*Follow-up test among those with baseline measurements.
†Sensitivity analysis illustrating the importance of 2-week vs 3-week cut-off interval in follow-up test intervals.
CKD, chronic kidney disease; GP, general practice; MI, myocardial infarction; NA, not applicable; NICE, National Institute for Health and Care Excellence; UKRA, United Kingdom Renal Association.

Table 4 Proportion of new users of ACE inhibitors or angiotensin receptor blockers who continue or discontinue treatment according to guideline recommended cut-off levels of serum creatinine and potassium at follow-up testing*

	Continuation†	Discontinuation†	Total
Total number, %	42 942 (93.1)	3178 (6.9)	46 120 (100)
Serum creatinine increase ≥30%, n (%)	462 (81.5)	105 (18.5)	567 (100)
Serum potassium >6 mmol/L, n (%)	150 (78.5)	41 (21.5)	191 (100)

*Calculated from the most recent measurements within 1 month before and 2 months after drug initiation.
†A patient was considered a continuous user when the end date of the first continuous course of therapy was larger than the date of the first follow-up monitoring +30 days (to allow for stockpiling and irregular use).

Table 5 Association between patient characteristics and serum creatinine increase ≥30% and follow-up monitoring within 2 weeks following initiation of ACE inhibitors or angiotensin receptor blockers

	OR (95% CIs)					
	Serum creatinine monitoring ≤2 weeks		Serum creatinine increase ≥30%*		Serum potassium increase ≥30%*	
Characteristics	Age-adjusted and sex-adjusted	Fully adjusted†	Age-adjusted and sex-adjusted	Fully adjusted†	Age-adjusted and sex-adjusted	Fully adjusted†
Female sex	1.07 (1.04 to 1.10)	1.07 (1.04 to 1.09)	1.39 (1.26 to 1.53)	1.63 (1.47 to 1.80)	0.87 (0.66 to 1.16)	0.94 (0.70 to 1.26)
Age (years)						
<50	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50–59	0.98 (0.94 to 1.01)	0.98 (0.95 to 1.02)	0.88 (0.74 to 1.05)	0.86 (0.72 to 1.03)	1.29 (0.79 to 2.11)	1.10 (0.67 to 1.81)
60–69	1.05 (1.02 to 1.09)	1.05 (1.01 to 1.09)	1.03 (0.88 to 1.21)	1.00 (0.85 to 1.19)	1.35 (0.84 to 2.17)	0.97 (0.60 to 1.58)
70–79	1.18 (1.14 to 1.23)	1.18 (1.13 to 1.23)	1.49 (1.27 to 1.74)	1.36 (1.15 to 1.61)	1.65 (1.02 to 2.66)	0.74 (0.43 to 1.26)
80+	1.20 (1.14 to 1.25)	1.17 (1.11 to 1.23)	2.72 (2.32 to 3.20)	2.02 (1.68 to 2.44)	2.75 (1.67 to 4.53)	0.73 (0.41 to 1.32)
CKD stage						
No CKD (≥60)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Stage 3a (45–59)	1.00 (0.96 to 1.04)	1.00 (0.96 to 1.04)	0.62 (0.53 to 0.73)	0.60 (0.51 to 0.70)	2.48 (1.66 to 3.71)	2.06 (1.36 to 3.11)
Stage 3b (30–44)	0.99 (0.93 to 1.06)	1.01 (0.94 to 1.08)	1.01 (0.82 to 1.24)	0.88 (0.71 to 1.09)	7.51 (4.75 to 11.9)	5.10 (3.16 to 8.22)
Stage 4 (15–29)	1.42 (1.21 to 1.67)	1.41 (1.20 to 1.66)	2.16 (1.52 to 3.05)	1.72 (1.18 to 2.51)	24.0 (13.5 to 42.6)	11.4 (6.07 to 21.4)
Comorbidities*						
Heart failure	1.15 (1.09 to 1.23)	1.16 (1.08 to 1.23)	4.00 (3.49 to 4.58)	2.93 (2.51 to 3.42)	2.90 (1.90 to 4.42)	2.22 (1.38 to 3.58)
MI	0.80 (0.75 to 0.85)	0.77 (0.72 to 0.82)	2.33 (1.98 to 2.74)	1.57 (1.32 to 1.87)	2.12 (1.33 to 3.39)	1.35 (0.80 to 2.25)
Hypertension	1.00 (0.97 to 1.02)	1.05 (1.00 to 1.11)	0.62 (0.56 to 0.68)	1.58 (1.36 to 1.84)	0.60 (0.45 to 0.80)	1.02 (0.63 to 1.65)
PAD	1.09 (1.01 to 1.18)	1.11 (1.02 to 1.20)	2.10 (1.70 to 2.60)	1.87 (1.50 to 2.33)	2.14 (1.18 to 3.86)	1.53 (0.82 to 2.88)
Arrhythmia	1.09 (1.03 to 1.14)	0.98 (0.95 to 1.01)	2.37 (2.07 to 2.71)	0.77 (0.69 to 0.86)	1.41 (0.90 to 2.21)	0.77 (0.56 to 1.05)
Diabetes mellitus	0.93 (0.90 to 0.96)	0.93 (0.90 to 0.96)	1.09 (0.97 to 1.22)	1.04 (0.92 to 1.18)	0.97 (0.69 to 1.36)	0.90 (0.63 to 1.29)
Baseline K>5 mmol/L	1.04 (1.00 to 1.10)	1.04 (0.99 to 1.09)	1.04 (0.86 to 1.25)	0.97 (0.80 to 1.17)	8.22 (6.14 to 11.0)	6.68 (4.94 to 9.02)

*The increase was based on the difference between the most recent baseline measurements within 12 months before and first follow-up measurement within 2 months after drug initiation. All analyses were restricted to those with both baseline and follow-up measurements (n=105 859).
†Adjusted for sex, age, CKD, heart failure, MI, hypertension, PAD, arrhythmia, diabetes and calendar period of prescription start.
CKD, chronic kidney disease; K, potassium; MI, myocardial infarction; PAD, peripheral arterial disease.

other characteristics in a multivariable analysis (table 5), we found an increased OR for women (1.6-fold increased), for age above 70 years (at least 1.3-fold increased), for CKD stage 4 (1.6-fold increased), heart failure (2.9-fold increased), peripheral arterial disease (1.9-fold increased), myocardial infarction (1.6-fold increased) and hypertension (1.6-fold increased).

Patients at high risk for potassium >6 mmol/L

Baseline potassium level and CKD stage, but not age and sex, were associated with potassium levels >6 mmol/L after ACEI/ARB initiation. Thus, the OR was sevenfold increased for baseline potassium >5 mmol/L, twofold increased for CKD stage 3a, fivefold increased for stage 3b, and 11-fold increased for stage 4 (table 5). Among cardiovascular comorbidities, heart failure was associated with the strongest OR of a potassium level >6 mmol/L (2.22, 95% CI 1.38 to 3.58).

Monitoring high-risk patients

Some characteristics associated with increased odds of having ≥30% rise in creatinine were also associated with a greater likelihood of having a follow-up test within 2 weeks following drug initiation. These included older age: persons aged 70 years or above compared with ≤50 years (1.18, 95% CI 1.13 to 1.23 for 70–79 years and 1.17, 95% CI 1.11 to 1.23 for 80+ years), CKD stage 4 compared with no CKD (1.41, 95% CI 1.20 to 1.66), heart failure (1.16, 95% CI 1.08 to 1.23) and peripheral arterial disease (1.11, 95% CI 1.02 to 1.20). However, other characteristics associated with increased odds of having ≥30% rise in creatinine were not associated with a greater likelihood of having a follow-up test within 2 weeks following drug initiation: there was no substantially increased OR (>10%) associated with female sex (1.07, 95% CI 1.04 to 1.09), prior history of myocardial infarction (0.77, 95% CI 0.72 to 0.82), hypertension (1.05, 95% CI 1.00 to 1.11) or baseline potassium >5 mmol/L (1.04, 95% CI 0.99 to 1.09). When we excluded patients with a recent hospital admission, the reduced OR for myocardial infarction was no longer observed (0.93, 95% CI 0.80 to 1.08) (eTable 6). Finally, the results remained consistent when we omitted adjustment for baseline potassium (data not shown) and when we adjusted additionally for ethnicity (eTable 6).

DISCUSSION

Only one-tenth of patients initiating ACEI/ARBs in UK primary care appear to receive the guideline-recommended creatinine monitoring. One in 15 patients started ACEI/ARBs despite baseline potassium above the recommended level, which was also shown to be a strong predictor for severe postinitiation hyperkalaemia. Among monitored patients, a creatinine increase ≥30% or a potassium level >6 mmol/L occurred in almost 1.5% of patients, and most did not discontinue therapy despite guideline recommendations to stop. Although patients with prior myocardial infarction, hypertension or a high baseline potassium level were at higher risk of sudden decline in kidney function after ACEI/ARB initiation, there was no evidence that these patient groups were monitored more frequently while initiating the drugs.

Strengths and limitations

Several issues should be considered when interpreting our study results. Its large sample size increased precision. Use of the CPRD ensured that the study was general practice-based and not restricted to specific demographic, hospital or insurance groups.

Over the time course of this study, multiple factors have impacted on the prescribing of ACEI/ARB and measurement of renal function in primary care, for example, the introduction of the relevant NICE guidelines, and QOF reimbursement for testing in certain subgroups. We also did not have information about clinical initiatives such as heart failure nurses and ACEI/ARB stopping rules ('sick-day rules'). While our main results provide summary measures over a 10-year period, sensitivity analyses confirm that despite these changes, the proportion receiving the guideline suggested that biochemical monitoring does not vary during the study period. We did not have access to blood tests performed in hospital systems, which may have been reported to GPs, but not recorded in CPRD. However, restricting the analysis to patients with no recent hospital admissions who were most likely to have had renal function measured and acted on in secondary care had little effect on our findings. We did not examine testing during initiation of dual blockade with ACEI and ARB as this combination is now used very infrequently for patients with severe comorbidities who are likely to be monitored in secondary care. Although some patients may also have been seen in outpatient specialty clinics, it is common practice for specialists to ask GPs to initiate new drugs such as ACEI/ARBs, with local biochemical monitoring, limiting misclassification.

Consistent with findings from other studies,[19] we found that ~50% of all ACEI/ARB initiators were monitored both before and after treatment start. If GPs are retesting renal function in patients at higher risk of substantial biochemical changes, we may have overestimated the proportion of patients with high potassium levels or creatinine increases compared with the untested lower-risk general population.

GP system software is used for issuing prescriptions, ensuring the accuracy of prescription data. However, it cannot be inferred that all patients actually redeemed their prescription at the pharmacy and started medication on the same day that it was prescribed.[18 20] Similarly, the estimated coverage of prescriptions may not be completely accurate due to such factors as stockpiling and irregular use. We also do not know whether GPs contacted patients with elevated laboratory results to advise them to stop taking the medication prior to the end of their prescriptions. However, 80% of patients

who developed creatinine increase ≥30% after ACEI/ARB initiation were still issued a subsequent ACEI/ARB prescription.

We aimed to detect discontinuation related closely in time to the first follow-up monitoring and hence most likely resulting from an elevated creatinine or potassium result. We therefore defined continuation as ACEI/ARB use beyond 30 days (the median prescription duration) after the monitoring date. Extending the definition of continuous use beyond 90 days reduced the risk of misclassifying patients as continuing treatment when they had in fact stopped. However, extending the duration also increased the risk of identifying discontinuation due to other reasons than creatinine/potassium increase, for example, death or cough. Diagnoses recorded in the CPRD generally have been found to have adequate validity for research purposes,[21 22] particularly in the domains assessed by the QOF.[23 24]

In the logistic regression analysis to estimate factors associated with creatinine increase ≥30%, we excluded patients without pre and post measurements (complete case analysis). If the recording of creatinine levels was not missing completely at random, the associations between patient characteristics and creatinine increase may have been underestimated.[25] While this assumption could not be tested directly, examination of baseline characteristics revealed no major differences in age, sex, socioeconomic status, and lifestyle between patients with and without premonitoring and postmonitoring. Furthermore, the results were consistent for each individual patient group examined. Patients with no testing before or after treatment initiation (including those with potentially haemolysed samples) only accounted for 10% of all ACEI/ARB initiators.

Comparison with other studies

To the best of our knowledge, this is the largest study conducted until now on adherence to monitoring and discontinuation guidelines after ACEI/ARB initiation. Only one previous study[19] examined monitoring according to guideline-recommended intervals (<14 days). All others have used longer intervals (*eg*, 30 days[26] or 6 months[27 28]), which make interpretations and implications for clinical practice less clear. Poor adherence to monitoring guidelines after ACEI/ARB initiation is not restricted to the UK,[19 28 29] but has also been reported in the USA,[30–32] Canada[33] and the Netherlands.[26 34] Owing to our sample size, we were able to show that the lack of monitoring occurred in all patient groups with an indication for ACEI/ARB therapy.

A recent Dutch study, including 3353 patients initiating ACEI/ARBs between 2005 and 2011, found that 19% had creatinine measured within 30 days and 66% within 1 year.[26] Creatinine increases above 30% occurred in 1.6% of patients, and among these 70% did not discontinue treatment.[26] A Scottish study of 4056 patients with type 2 diabetes, prescribed an ACEI/ARB between 2005 and 2009, found that 19% had both a baseline (within 90 days) and follow-up measurement (within 2 weeks) of initiation. Within this cohort, 1.7% had both a creatinine increase of ≥30% and potassium level ≥5.6 mmol/L.

The magnitude of the risk of severe renal impairment, as measured by creatinine increase in these observational studies, was consistent with our findings, but substantially higher than reported in clinical trials (*eg*, 0.2% in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)).[35] It is not clear from the literature how often harm occurs around the time of initiation, when the risk of nephrotoxicity is thought to be greatest.[8] If physicians are to understand why follow-up monitoring within 2 weeks of treatment start matters, the short-term risks need to be clarified. Until now, most studies have reported only on cumulative risk over entire courses of treatment, such as the 1.1% 2-year risk for potassium of >6 mmol/L in the Studies of Left Ventricular Dysfunction (SOLVD) trials of patients with heart failure.[36] In contrast to clinical trial reviews, reporting a 0.2% (3/1818) risk of potassium >6 mmol/L, we found a 0.4% risk of hyperkalaemia already at the time of first retesting after ACEI initiation.

Extending the previous literature, our results support that advanced age, advanced CKD and heart failure, but not sex, increase the likelihood of being monitored.[19 26 30] Consistent with some,[26 30] but not all, previous studies,[28] we found no association for diabetes. However, these previous studies reporting an association for diabetes focused on monitoring within broader intervals (*eg*, 6 months),[28] where patients with diabetes, irrespective of ACEI/ARB initiation, were likely to receive blood testing owing to the diabetes QOF programme.

Determinants of increases in creatinine levels after ACEI/ARB initiation are less well understood than for hyperkalaemia, but increasing age is a consistently reported factor.[19] Advanced CKD and a range of cardiovascular comorbidities (mostly associated with atherosclerosis) were also important determinants in our patient cohort. Consistent with previous studies, we found that the risk of hyperkalaemia was associated with CKD (most likely due to the impaired ability of the cortical collecting tubule to secrete potassium), heart failure (most likely due to the decreased delivery of sodium to the distal nephron), and high pretreatment potassium levels.[6 8 19 37] We did not observe an association with diabetes or increasing age, as could have been expected due to diabetic nephropathy or age-dependent hyporeninaemic hypoaldosteronism.[6]

Clinical relevance

Several possible explanations exist for the divergence between the clinical guideline recommendations and the observed monitoring and response patterns in clinical practice. The first is *clinician non-adherence* to ordering tests. This may be due to inconsistent

recommendations for timing and frequency of monitoring over time,[6] consensus-based (rather than evidence-based) monitoring guidelines, and a lack of guidelines tailored to particular high-risk patients, such as those with CKD and heart failure. Although we found that follow-up monitoring correlated well with the risk of renal impairment after ACEI/ARB initiation for most patient groups, it was not observed for patients with myocardial infarction or preinitiation high potassium. The second explanation may be *patient non-adherence* to ordered tests. This is particularly salient in UK primary care where blood samples may be taken in phlebotomy clinics that the patient has to visit rather than the GP practice. Patients may find it burdensome to have blood tests, and GPs have no direct economic incentives to ensure that they are done. A third barrier is *lack of evidence of the clinical importance* of monitoring and its cost-effectiveness. ACEI/ARB-induced renal impairment is rare in clinical trials, even among patients with multiple risk factors for atherosclerotic renal artery stenosis.[8 38] Trial results may therefore have led to a general perception that the rarity of renal impairment obviates the need for close monitoring. However, as observed in our data, the risks in real-world practice may be somewhat higher and non-negligible. In addition, previous research has shown that potassium monitoring in high-risk patients with CKD and diabetes may reduce serious hyperkalaemia-associated adverse events.[39] Still, the extent to which an initial creatinine increase ≥30% translates into adverse long-term outcomes in real-world patients remains to be clarified in future studies.

Generalisability, implications and conclusions

The majority of patients initiating treatment with ACEI/ARBs experience only minor changes in renal function. However, substantial increases in creatinine levels after ACEI/ARB initiation may not be as rare as previously suggested, reinforcing the need for adherence to clinical guidelines for both pre-initiating and post-initiating monitoring. Moreover, the postinitiation creatinine increase and potassium levels used in this study are widely recognised cut-off levels, making the results internationally applicable. The comparison with the previous literature also confirms that the lack of systematic monitoring is not exclusive to the UK. Of particular concern was that even when appropriate monitoring was performed, severe renal impairment only rarely led to treatment discontinuation. Individual patient counselling may also be helpful to ensure that those at highest risk are closely monitored. More work is needed to determine the prognostic importance of the changes in renal function that we have observed.

Author affiliations
[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Internal Medicine, Regional Hospital of Randers, Denmark

Twitter Follow Kathryn Mansfield @AnimaSophia

Contributors LAT conceived the study idea and acquired data permissions. MS, KEM and LAT designed the study. MS and KEM performed data management and established the cohort. MS, KEM and LAT reviewed the literature. The analyses were carried out by MS. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. MS is the guarantor.

Funding MS was supported by the A.P. Møller Foundation for the Advancement of Medical Science, Snedkermester Sophus Jacobsen & Hustru Astrid Jacobsens Fond, and Christian og Ottilia Brorsons Rejselegat for yngre videnskabsmænd og–kvinder. HTS was supported by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation. KB holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (grant number 107731/Z/15/Z). LAT and KEM are funded by a Wellcome Trust intermediate clinical fellowship to LAT (101143/Z/13/Z).

Disclaimer None of these funding sources had a role in the design, conduct, analysis or reporting of the study.

Competing interests None declared.

Ethics approval London School of Hygiene and Tropical Medicine Ethics Committee (Approval number 6536) and the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (Approval number 16_025).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. National Institute for Health and Clinical Excellence (NICE). Hypertension in adults: diagnosis and management. 2011. https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance#initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2 (accessed 1 Apr 2016).
2. National Institute for Health and Clinical Excellence (NICE). Chronic heart failure in adults: management. 2010. http://pathways.nice.org.uk/pathways/chronic-heart-failure (accessed 1 Apr 2016).
3. National Institute for Health and Clinical Excellence (NICE). Management of chronic kidney disease. 2014. http://pathways.nice.org.uk/pathways/chronic-kidney-disease#path=view%3A/pathways/chronic-kidney-disease/management-of-chronic-kidney-disease.xml&content=view-node%3Anodes-blood-pressure-control-and-antihypertensive-treatment (accessed 1 Apr 2016.
4. National Institute for Health and Clinical Excellence (NICE). Myocardial infarction: secondary prevention. 2013. http://pathways.nice.org.uk/pathways/myocardial-infarction-secondary-prevention (accessed 1 Apl 2016).
5. Lesogor A, Cohn JN, Latini R, *et al*. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. *Eur J Heart Fail* 2014;15:1236–44.
6. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Cardiovasc Ther* 2012;30:e156–66.
7. McDowell SE, Thomas SK, Coleman JJ, *et al*. A practical guide to monitoring for adverse drug reactions during antihypertensive drug therapy. *J R Soc Med* 2013;106:87–95.
8. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685–93.

9. McDowell SE, Ferner RE. Biochemical monitoring of patients treated with antihypertensive therapy for adverse drug reactions. *Drug Saf* 2011;34:1049–59.
10. Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
11. Health & Social Care Information Centre. Hospital Episode Statistics. http://www.hscic.gov.uk/hes (accessed 1 May 2016).
12. UK Renal Association. Hypertension. http://www.renal.org/information-resources/the-uk-eckd-guide/hypertension#sthash.QNqnBcyh.dpbs (accessed 1 Apr 2016).
13. GP Notebook. General Practice Notebook—a UK medical reference. http://www.gpnotebook.co.uk (accessed 1 Apr 2016).
14. McDonald HI. *The epidemiology of infections among older people with diabetes mellitus and chronic kidney disease*. London School of Hygiene and Tropical Medicine. 2015.
15. McDonald HI, Thomas SL, Millett ERC, *et al*. CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. *Am J Kidney Dis* 2015;66:60–8.
16. Bhaskaran K, Douglas I, Forbes H, *et al*. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet* 2014;384:755–65.
17. Bhaskaran K, Forbes HJ, Douglas I, *et al*. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open* 2013;3:e003389.
18. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
19. Mathieson L, Severn A, Guthrie B. Monitoring and adverse events in relation to ACE inhibitor/angiotensin receptor blocker initiation in people with diabetes in general practice: a population database study. *Scott Med J* 2013;58:69–76.
20. Tomlinson LA, Riding AM, Payne RA, *et al*. The accuracy of diagnostic coding for acute kidney injury in England—a single centre study. *BMC Nephrol* 2013;14:58.
21. Herrett E, Thomas SL, Schoonen WM, *et al*. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14.
22. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;60:e128–36.
23. Doran T, Kontopantelis E, Valderas JM, *et al*. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. *BMJ* 2011;342:d3590.
24. Barbour SJ, Schachter M, Er L, *et al*. A systematic review of ethnic differences in the rate of renal progression in CKD patients. *Nephrol Dial Transplant* 2010;25:2422–30.
25. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med* 2010;29:2920–31.
26. van Blijderveen JC, Straus SM, de Ridder MA, *et al*. Adherence to renal function monitoring guidelines in patients starting antihypertensive therapy with diuretics and RAAS inhibitors: a retrospective cohort study. *Drug Saf* 2014;37:369–77.
27. McDowell SE, Coleman JJ, Evans SJW, *et al*. Laboratory monitoring and adverse patient outcomes with antihypertensive therapy in primary care. *Pharmacoepidemiol Drug Saf* 2010;19:482–9.
28. Coleman JJ, McDowell SE, Evans SJW, *et al*. Oversight: a retrospective study of biochemical monitoring in patients beginning antihypertensive drug treatment in primary care. *Br J Clin Pharmacol* 2010;70:109–17.
29. Kalra PA, Kumwenda M, MacDowall P, *et al*. Questionnaire study and audit of use of angiotensin converting enzyme inhibitor and monitoring in general practice: the need for guidelines to prevent renal failure. *BMJ* 1999;318:234–7.
30. Raebel MA, McClure DL, Chan KA, *et al*. Laboratory evaluation of potassium and creatinine among ambulatory patients prescribed spironolactone: are we monitoring for hyperkalemia? *Ann Pharmacother* 2007;41:193–200.
31. Hurley JS, Roberts M, Solberg LI, *et al*. Brief report: laboratory safety monitoring of chronic medications in ambulatory care settings. *J Gen Intern Med* 2005;20:331–3.
32. Simon SR, Andrade SE, Ellis JL, *et al*. Baseline laboratory monitoring of cardiovascular medications in elderly health maintenance organization enrollees. *J Am Geriatr Soc* 2005;53:2165–9.
33. McAlister FA, Tu K, Majumdar SR, *et al*. Laboratory testing in newly treated elderly hypertensive patients without co-morbidities: a population-based cohort study. *Open Med* 2007;1:e60–7.
34. Bootsma JE, Warlé-van Herwaarden MF, Verbeek AL, *et al*. Adherence to biochemical monitoring recommendations in patients starting with renin angiotensin system inhibitors: a retrospective cohort study in the Netherlands. *Drug Saf* 2011;34:605–14.
35. Yusuf S, Teo KK, Pogue J, *et al*., ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–59.
36. de Denus S, Tardif JC, White M, *et al*. Quantification of the risk and predictors of hyperkalemia in patients with left ventricular dysfunction: a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Am Heart J* 2006;152:705–12.
37. Desai AS, Swedberg K, McMurray JJV, *et al*. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol* 2007;50:1959–66.
38. Pitt B, Segal R, Martinez FA, *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747–52.
39. Raebel MA, Ross C, Xu S, *et al*. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. *J Gen Intern Med* 2010;25:326–33.

Paper VII

Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study

Morten Schmidt,[1,2,3] Kathryn E Mansfield,[1] Krishnan Bhaskaran,[1] Dorothea Nitsch,[1] Henrik Toft Sørensen,[2] Liam Smeeth,[1] Laurie A Tomlinson[1]

[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Internal Medicine, Regional Hospital of Randers, Randers, Denmark
Correspondence to: M Schmidt morten.schmidt@clin.au.dk

Additional material is published online only. To view please visit the journal online.
Cite this as: *BMJ* 2017;356:j791
http://dx.doi.org/10.1136/bmj.j791
Accepted: 27 January 2017

ABSTRACT

OBJECTIVE
To examine long term cardiorenal outcomes associated with increased concentrations of creatinine after the start of angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment.

DESIGN
Population based cohort study using electronic health records from the Clinical Practice Research Datalink and Hospital Episode Statistics.

SETTING
UK primary care, 1997-2014.

PARTICIPANTS
Patients starting treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (n=122 363).

MAIN OUTCOME MEASURES
Poisson regression was used to compare rates of end stage renal disease, myocardial infarction, heart failure, and death among patients with creatinine increases of 30% or more after starting treatment against those without such increases, and for each 10% increase in creatinine. Analyses were adjusted for age, sex, calendar period, socioeconomic status, lifestyle factors, chronic kidney disease, diabetes, cardiovascular comorbidities, and use of other antihypertensive drugs and non-steroidal anti-inflammatory drugs.

RESULTS
Among the 2078 (1.7%) patients with creatinine increases of 30% or more, a higher proportion were female, were elderly, had cardiorenal comorbidity, and used non-steroidal anti-inflammatory drugs, loop diuretics, or potassium sparing diuretics. Creatinine increases of 30% or more were associated with an increased adjusted incidence rate ratio for all outcomes, compared with increases of less than 30%: 3.43 (95% confidence interval 2.40 to 4.91) for end stage renal disease, 1.46 (1.16 to 1.84) for myocardial infarction, 1.37 (1.14 to 1.65) for heart failure, and 1.84 (1.65 to 2.05) for death. The detailed categorisation of increases in creatinine concentrations (<10%, 10-19%, 20-29%, 30-39%, and ≥40%) showed a graduated relation for all outcomes (all P values for trends <0.001). Notably, creatinine increases of less than 30% were also associated with increased incidence rate ratios for all outcomes, including death (1.15 (1.09 to 1.22) for increases of 10-19% and 1.35 (1.23 to 1.49) for increases of 20-29%, using <10% as reference). Results were consistent across calendar periods, across subgroups of patients, and among continuing users.

CONCLUSIONS
Increases in creatinine after the start of angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment were associated with adverse cardiorenal outcomes in a graduated relation, even below the guideline recommended threshold of a 30% increase for stopping treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A sudden decline in kidney function may occur after treatment with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) is started

Increases in creatinine of up to 30% over baseline levels are generally considered safe and even a marker of long term preservation of kidney function

Long term cardiac and renal outcomes associated with more detailed categorisations of post-initiation increases in creatinine concentrations are unknown

WHAT THIS STUDY ADDS

This cohort study shows a graduated increased risk of end stage renal disease, adverse cardiac outcomes, and death for each 10% increase in creatinine, even below the 30% threshold

Whether these creatinine changes are causally related to adverse outcomes or represent a biomarker of increased risk is unclear

Increases in creatinine after starting ACEI/ARB treatment identify a high risk group needing close monitoring and in whom the risks and benefits of ACEI/ARB prescribing should be considered

Introduction

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are commonly prescribed drugs for hypertension, heart failure, diabetic microalbuminuria, and proteinuric renal disease and after myocardial infarction.[1] Patients may, however, have a sudden decline in kidney function after starting to take these drugs, owing to antagonism of angiotensin II mediated efferent arteriolar constriction.[2] Despite unambiguous recommendations to detect sudden renal impairment by monitoring serum creatinine before and after the start of ACEI/ARB treatment and to discontinue treatment if creatinine concentrations increase by 30% or more,[1] recent data show that only 10% of patients receive the recommended monitoring and only 20% of those with a creatinine increase of 30% or more after starting ACEI/ARB treatment discontinue the drugs.[3]

Clinical trial data has indicated that ACEI/ARB induced renal impairment is uncommon.[4 5] Patients seen in routine clinical practice are, however, on average older and have more comorbidity than those eligible for trials.[6] As a consequence, the absolute risk of increases in creatinine of 30% or more in the community setting is not negligible.[3] Although this level of creatinine increase after starting ACEI/ARB treatment

raises concern about the long term balance of risks and benefits, smaller increases (<30%) do not prompt consideration of treatment discontinuation according to current guidelines. The rationale for the 30% threshold in the context of adverse clinical outcomes is unclear,[4] as little evidence is available on the actual risks associated with creatinine increases of less than 30%.

Considering the high prevalence of ACEI/ARB use in general practice, any additional previously unrecognised risks would have major clinical and public health implications. We therefore used real world data to examine the cardiorenal risks associated with different levels of increase in creatinine after the start of ACEI/ARB treatment.

Methods

Data sources

We used the UK's Clinical Practice Research Datalink (CPRD), linked to hospital record data from the Hospital Episode Statistics (HES) database. The CPRD database contains data from primary care electronic health records for 7% of the UK population (approximately 15 million patient lives, with about 8 million currently followed).[7] Patients included in the CPRD are largely representative of the UK population in terms of age, sex, and ethnicity.[7 8] Information recorded in the database covers demographics such as sex and year of birth, the location of the general practice, medical diagnoses (based on Read codes), drug prescriptions, and a range of routine laboratory test results. The HES records all hospital admissions for patients covered by the National Health Service who receive treatment from either English NHS trusts or independent providers.[7 8] Fifty eight per cent of general practices included in the CPRD have agreed to HES linkage.[7] We used lists of Read codes (CPRD) and ICD-10 (international classification of diseases, 10th revision) codes (HES) to identify outcomes and covariables. We obtained linked data on socioeconomic status based on area of residence from the UK Index of Multiple Deprivation.

Study population

We identified a cohort of all HES linked CPRD patients aged 18 years or above who started ACEI/ARB treatment between 1 April 1997 and 31 March 2014. We defined new users as those with at least one year of continuous registration in the CPRD before their first recorded prescription for ACEI/ARB. We restricted our main study cohort to patients with both pre-initiation (within 12 months) and post-initiation (within two months) creatinine measurements and excluded patients with end stage renal disease diagnosed before cohort entry (n=17).

Serum creatinine

We extracted all creatinine test results from the general practice records of the study population. We calculated a change in creatinine concentrations after the start of ACEI/ARB treatment as the relative difference between the most recent baseline measurement before or on the date of starting treatment and the first follow-up measurement within two months after starting. We defined the baseline measurement as within 12 months because previous work suggested that very recent creatinine concentrations are obtained for only a small proportion of patients starting ACEI/ARBs.[3] We chose the two month post-initiation period to accord with the interval recommended in reviews of previous trial data.[4]

In our analysis, we firstly dichotomised the relative increase according to the guideline recommended cut-off levels of 30% or more versus less than 30%. Secondly, to examine whether a graduated ("dose-response") relation existed, we categorised increases in creatinine in more detail, as less than 10% (reference group), 10-19%, 20-29%, 30-39%, and 40% or more. Thirdly, we used fractional polynomials to assess the form of the association between the continuous creatinine increase variable and outcomes. Because of evidence of non-linearity in the log scale for the association with several of the outcomes, we kept to the categorical modelling.

Outcomes

We used HES and the CPRD to identify first time diagnoses of end stage renal disease, myocardial infarction, and heart failure, as well as all cause mortality. We defined end stage renal disease as the presence of a hospital or primary care morbidity code for end stage renal disease, renal transplant, peritoneal dialysis or haemodialysis, or an arteriovenous fistula (suggesting anticipation of end stage renal disease).

Patients' characteristics

We obtained information for all patients on age, sex, socioeconomic status (fifths of 2004 Index of Multiple Deprivation scores), lifestyle factors (smoking, alcohol intake, and body mass index), comorbidities (diabetes, myocardial infarction, heart failure, hypertension, arrhythmia, peripheral arterial disease, and chronic kidney disease stage), blood pressure measurements before and after starting ACEI/ARB treatment, and concomitant use of other antihypertensive drugs (β blockers, calcium channel blockers, thiazides, loop diuretics, and potassium sparing diuretics) and non-steroidal anti-inflammatory drugs at time of starting ACEI/ARB treatment.[9] We used algorithms to estimate smoking status, alcohol intake, and body mass index based on the most recent CPRD records before the start of ACEI/ARB treatment.[10 11] We calculated estimated glomerular filtration rate on the basis of the baseline creatinine concentration and the chronic kidney disease stage by using the CKD-EPI equation.[12]

We identified other comorbidities from the CPRD and HES on the basis of diagnoses recorded before the start of ACEI/ARB treatment. We defined pre-initiation and post-initiation systolic and diastolic blood pressure on the basis of the most recent measurement within 12 months before and after the start of ACEI/ARB treatment. Use of non-steroidal anti-inflammatory drugs was based on prescriptions recorded within 30 days before the start of ACE/ARB treatment. We defined concurrent use of other antihypertensive drugs by courses of continuous treatment for each class of drugs concomitant with the ACEI/ARB prescription date. In

doi: 10.1136/bmj.j791 | BMJ 2017;356:j791 | the bmj

identifying continuous courses of treatment, we calculated the end date of each prescription by adding the duration of the prescription (total number of tablets prescribed divided by the specified number of tablets per day) to the date of the prescription. We further allowed for a 30 day gap between the end date of one prescription and the start of the next consecutive prescription to allow for alternative sources of drug (eg, outpatient clinics) or stockpiling of prescriptions.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Statistical analysis

We characterised all patients starting ACEI/ARB treatment according to sex, age, comorbidities, co-medication use, socioeconomic status, lifestyle factors, and calendar period. We followed all new ACEI/ARB users with a change in creatinine concentration between baseline and the date of the first follow-up test, until the occurrence of an outcome, death, withdrawal from the general practice, or end of the follow-up period (31 March 2014), whichever occurred first. We illustrated the survival function by using the Kaplan-Meier estimator.

We used Poisson regression to examine the association between the percentage increase in creatinine concentration and long term cardiorenal risks. We modelled the cause specific hazard to account for competing risks (that is, censoring outcomes competing with the outcome of interest), which is appropriate for estimating causal effects.[13 14] We calculated rates and incidence rate ratios comparing the associations of categories of percentage creatinine increase with outcomes, using robust standard errors to account for clustering by general practice. We adjusted for age and sex in the "crude" model. In the main analysis, we also adjusted for the comorbidities listed above (including chronic kidney disease stage at baseline), use of concurrent drugs, lifestyle factors, socioeconomic status, calendar period, and time since first prescription. We included age (<50, 50-59, 60-69, 70-79, and ≥80 years), calendar period (1997-2003, 2004-08, and 2009-14) and years since first prescription (<1, 1 to <2, 2 to <5, 5 to <10, and ≥10 years) as time updated variables. To restrict assessment of outcomes to patients with incident disease, in each analysis we excluded people with a previous history (assessed at baseline) of the outcome in question. To examine whether patients' characteristics modified the incidence rate ratios, we stratified the analyses by comorbidities. We also illustrated the time dependent effect estimates for each outcome graphically and did tests for linear trends to examine whether an interaction with time since starting drug treatment existed.

To consider the effect of potential confounders, we examined whether the effect estimates differed from our main results in several sensitivity analyses. Firstly, we restricted the study period to the most recent 10 year calendar period (2004-14) to increase the completeness of covariable recording and to take into account temporal differences in patient care.[15] Secondly, we excluded patients with diabetes or chronic kidney disease stage 4 to account for measurements made at outpatient hospital clinics and therefore not available in the CPRD for these groups of patients. Thirdly, to explore the effect of drug cessation, we restricted the analysis to continuing users (irrespective of creatinine result)—that is, patients whose first continuous course of ACE/ARB treatment ended at least 90 days after the retest date. Fourthly, to consider the potential confounding effect of proteinuria, we restricted an analysis to ACEI/ARB users with diabetes, among whom we would anticipate that most have substantial protein excretion. Fifthly, we excluded patients with a potassium concentration above 6 mmol/L at the first follow-up monitoring to explore the prognostic influence of hyperkalaemia on the outcomes, particularly death. Sixthly, to gain insight into potential alternative mechanisms leading to increases in creatinine after the start of ACEI/ARB treatment, we added a post hoc analysis to estimate the relative reduction in median systolic and diastolic blood pressure after the start of treatment. Finally, we examined whether our cohort differed from other patients starting ACEI/ARB treatment who did not have both pre-initiation and post-initiation creatinine monitoring. For this purpose, we resampled all patients starting ACEI/ARB treatment in the study period to compare baseline characteristics and cumulative mortality risk among those with complete versus incomplete pre-initiation and post-initiation monitoring. We used the STATA 14 statistical software package for all analyses.

Results

Patients' characteristics

Among 303 451 patients who started ACEI/ARB treatment during 1997-2014, 122 363 (40%) had both baseline and follow-up creatinine monitoring and were included in the study (table 1). Among these, 2078 (1.7%) had an increase in creatinine of 30% or more (median age 68 years) and 120 285 (98.3%) had an increase of less than 30% (median age 63 years). More detailed categorisation showed that the creatinine increase was less than 10% for 102 445 (83.7%) patients, 10-19% for 14 301 (11.7%) patients, 20-29% for 3539 (2.9%) patients, 30-39% for 1099 (0.9%) patients, and 40% or more for 979 (0.8%) patients.

Compared with patients with a creatinine increase of less than 30%, a higher proportion of those with an increase of 30% or more were female (56.1% *v* 46.1%) or had moderate to severe chronic kidney disease (stage 3b or 4) (8.9% *v* 4.3%), previous myocardial infarction (10.5% *v* 4.5%), heart failure (19.0% *v* 4.8%), arrhythmia (17.2% *v* 6.8%), or peripheral arterial disease (6.0% *v* 2.5%). Patients with an increase of 30% or more were four times more likely to use loop diuretics (28.6% *v* 7.2%) or potassium sparing diuretics (8.8% *v* 2.0%) but also

Table 1 | Patients' characteristics according to guideline recommended discontinuation level of creatinine increases (≥30%) after renin-angiotensin system blockade. Values are numbers (percentages) unless stated otherwise

Characteristic	Serum creatinine elevation after starting ACEI/ARB	
	≥30% (n=2078)	<30% (n=120 285)
Female sex	1166 (56.1)	55 482 (46.1)
Age, years:		
<50	292 (14.1)	21 959 (18.3)
50-59	322 (15.5)	27 955 (23.2)
60-69	452 (21.8)	31 820 (26.5)
70-79	540 (26.0)	25 908 (21.5)
≥80	472 (22.7)	12 643 (10.5)
Comorbidities*		
Diabetes mellitus	494 (23.8)	26 433 (22.0)
Myocardial infarction	219 (10.5)	5468 (4.5)
Heart failure	395 (19.0)	5756 (4.8)
Hypertension	1333 (64.1)	91 042 (75.7)
Arrhythmia	358 (17.2)	8122 (6.8)
Peripheral arterial disease	124 (6.0)	3044 (2.5)
Chronic kidney disease (eGFR)†:		
Stage ≤2 (≥60)	1612 (77.6)	98 702 (82.1)
Stage 3a (45-59)	281 (13.5)	16 387 (13.6)
Stage 3b (30-44)	143 (6.9)	4502 (3.7)
Stage 4 (15-29)	42 (2.0)	694 (0.6)
Co-medications		
β blockers	493 (23.7)	20 474 (17.0)
Calcium channel blockers	352 (16.9)	22 700 (18.9)
Thiazides	435 (20.9)	25 281 (21.0)
Loop diuretics	594 (28.6)	8693 (7.2)
Potassium sparing diuretics	183 (8.8)	2354 (2.0)
NSAIDs	706 (34.0)	28 306 (23.5)
Blood pressure, median (IQR)‡:		
Pre-initiation systolic	150 (135-168)	155 (142-169)
Pre-initiation diastolic	84 (75-95)	90 (80-98)
Post-initiation systolic	140 (125-158)	144 (132-158)
Post-initiation diastolic	80 (70-90)	83 (76-90)
Socioeconomic status, fifths:		
1 (lowest)	468 (22.5)	29 144 (24.2)
2	469 (22.6)	28 463 (23.7)
3	460 (22.1)	25 681 (21.4)
4	388 (18.7)	21 799 (18.1)
5 (highest)	287 (13.8)	15 040 (12.5)
Missing	6 (0.3)	158 (0.1)
Smoking status:		
Never	687 (33.1)	41 528 (34.5)
Ever	1373 (66.1)	78 574 (65.3)
Missing	18 (0.9)	183 (0.2)
Alcohol intake:		
No use	276 (13.3)	12 951 (10.8)
Current	1488 (71.6)	94 129 (78.3)
Former	162 (7.8)	8146 (6.8)
Missing	152 (7.3)	5059 (4.2)
Body mass index group:		
Underweight	47 (2.3)	1115 (0.9)
Healthy weight	560 (26.9)	28 676 (23.8)
Overweight	717 (34.5)	46 231 (38.4)
Obesity	603 (29.0)	40 116 (33.4)
Missing	151 (7.3)	4147 (3.4)
Calendar period:		
1997-2003	364 (17.5)	16 157 (13.4)
2004-08	983 (47.3)	59 915 (49.8)
2009-14	731 (35.2)	44 213 (36.8)

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFR=estimated glomerular filtration rate; IQR=interquartile range; NSAID=non-steroidal anti-inflammatory drug.
*Diagnosis ever registered in Clinical Practice Research Datalink or Hospital Episode Statistics before start of treatment with ACEI or ARB.
†Calculated from most recent creatinine measurement within 12 months before first prescription date; eGFR given in mL/min/1.73 m^2.
‡16 365 (13%) patients had no pre-initiation blood pressure measurement within 12 months before starting ACEI/ARB treatment (18% among those with ≥30% increase in creatinine and 13% among those with <30% increase). Also, 17 190 (14%) patients had no post-initiation blood pressure measurement in 12 months after starting drug treatment (19% among those with ≥30% increase in creatinine and 14% among those with <30% increase).

more often used β blockers (23.7% *v* 17.0%) and non-steroidal anti-inflammatory drugs (34.0% *v* 23.5%); fewer had hypertension (64.1% *v* 75.7%), calcium channel blocker use (16.9% *v* 18.9%), current alcohol consumption (71.6% *v* 78.3%), or obesity (29.0% *v* 33.4%). The overall blood pressure response was similar in the two groups after the start of ACEI/ARB treatment, both having a 7% reduction in systolic blood pressure (from 150 to 140 mm Hg in patients with a creatinine increase of 30% or more and from 155 to 144 mm Hg in those with a less than 30% increase). Socioeconomic status, use of thiazides, prevalence of smoking, and prevalence of diabetes did not differ between the groups.

Levels of creatinine increase and clinical outcomes

Increases in creatinine of 30% or more were associated with increased rates of all outcomes (table 2). The adjusted incidence rate ratios were 3.43 (95% confidence interval 2.40 to 4.91) for end stage renal disease, 1.46 (1.16 to 1.84) for myocardial infarction, 1.37 (1.14 to 1.65) for heart failure, and 1.84 (1.65 to 2.05) for death.

When we examined interactions with time since the start of drug treatment (fig 1 and supplementary table A), we observed a pronounced effect of time for end stage renal disease, with increases in incidence rate ratios falling from 12.2-fold during the first year to 3.7-fold within the second year, to 1.7-fold within 2 to <5 years, and to 2.5-fold within 5 to <10 years after the start of treatment. However, confidence intervals were wide, reflecting the relatively small number of end stage renal disease events (P for trend=0.094). We observed similar trends of decreasing risk over time for heart failure (P for trend=0.025) and mortality (P for trend<0.001), although effect sizes were smaller. The incidence rate ratio for heart failure fell from a 1.9-fold increase within the first year to a 1.5-fold increase within the second year and remained neutral in risk thereafter. The mortality rate ratio declined from a 3.5-fold increase within the first year and remained approximately 50% increased thereafter.

The more detailed categorisation of creatinine increases showed graduated effects for all outcomes. This is illustrated by the survival function in figure 2. The absolute one year risk of dying was 2% in the group with less than 10% increase, 2% for 10-19%, 4% for 20-29%, 7% for 30-39%, and 16% for 40% or above; the corresponding risks were 9%, 12%, 16%, 24%, and 37% at five years and 22%, 26%, 33%, 42%, and 57% at 10 years. This "dose-response" relation also held for all outcomes after adjustment for possible confounders (fig 3). Using creatinine increase less than 10% as reference, incidence rate ratios increased steadily among patients with creatinine increases of 10-19% up to those with creatinine increases of 40% or more for end stage renal disease (1.73 to 4.04; P for trend<0.001), for myocardial infarction (1.12 to 1.59; P<0.001), for heart failure (1.14 to 1.42; P<0.001), and for death (1.15 to 2.11; P<0.001).

Patient subgroups

Among subgroups of patients (table 3), the risk of adverse renal or cardiac outcomes associated with

Table 2 | Creatinine increases of ≥30% after renin-angiotensin system blockade and risk of adverse cardiorenal events*

Serum creatinine increase†	No of events	Risk, % (95% CI)‡ 1 year	5 years	10 years	Rate per 1000 person years	Incidence rate ratio (95% CI) Age and sex adjusted	Fully adjusted§
End stage renal disease:							
<30%	762	0.05 (0.04 to 0.07)	0.33 (0.29 to 0.37)	0.77 (0.68 to 0.86)	1.3	1.00 (reference)	1.00 (reference)
≥30%	45	0.30 (0.13 to 0.63)	0.74 (0.41 to 1.25)	1.92 (1.02 to 3.30)	5.2	4.06 (3.01 to 5.48)	3.43 (2.40 to 4.91)
Myocardial infarction:							
<30%	3334	0.41 (0.37 to 0.45)	1.75 (1.67 to 1.84)	3.68 (3.5 to 3.88)	5.9	1.00 (reference)	1.00 (reference)
≥30%	87	0.28 (0.11 to 0.64)	2.19 (1.51 to 3.07)	3.80 (2.69 to 5.19)	11.0	1.73 (1.41 to 2.13)	1.46 (1.16 to 1.84)
Heart failure:							
<30%	6892	0.95 (0.90 to 1.01)	3.22 (3.10 to 3.34)	7.28 (7.00 to 7.56)	12.4	1.00 (reference)	1.00 (reference)
≥30%	208	2.94 (2.19 to 3.85)	5.89 (4.73 to 7.23)	9.01 (7.17 to 11.1)	28.9	2.12 (1.82 to 2.47)	1.37 (1.14 to 1.65)
All cause mortality:							
<30%	13281	1.74 (1.67 to 1.82)	9.68 (9.48 to 9.88)	22.5 (22.1 to 23.0)	22.4	1.00 (reference)	1.00 (reference)
≥30%	640	11.1 (9.77 to 12.5)	29.8 (27.6 to 32.1)	49.2 (45.5 to 53.0)	72.7	2.68 (2.47 to 2.91)	1.84 (1.65 to 2.05)

*Among patients with at least one creatinine measurement within 12 months before and 2 months after starting drug and who continued treatment after first follow-up measurement.
†Increase calculated as difference between most recent baseline measurement within 12 months before starting drug and first follow-up measurement within 2 months after starting drug.
‡Cumulative incidence proportions of non-fatal outcomes calculated taking into account death as competing risk.
§Adjusted for age, sex, comorbidities (diabetes mellitus, myocardial infarction, heart failure, hypertension, arrhythmia, peripheral arterial disease, and chronic kidney disease stage), co-medications (β blockers, calcium channel blockers, thiazides, loop diuretics, potassium sparing diuretics, and non-steroidal anti-inflammatory drugs), lifestyle factors (smoking status, alcohol intake, and body mass index), socioeconomic status, calendar period, and time since first prescription.

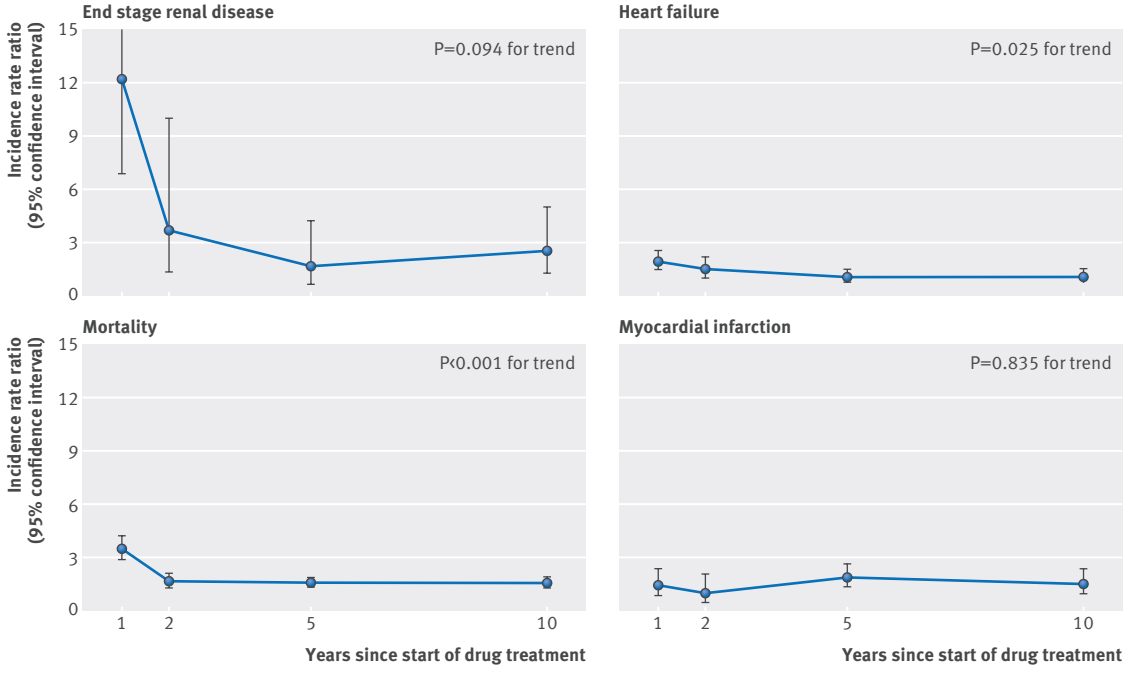


Fig 1 | Time dependent cardiorenal risks associated with creatinine increases ≥30% after renin-angiotensin system blockade

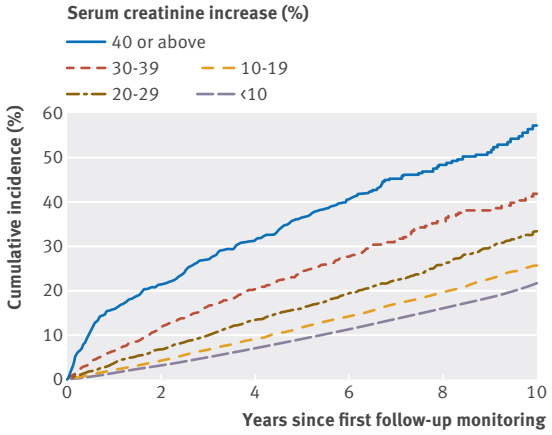


Fig 2 | Cumulative mortality according to levels of creatinine increase after renin-angiotensin system blockade

creatinine increases of 30% or more was higher in men than in women. The precision of estimates for non-fatal outcomes varied by subgroups, but without substantial modification of the incidence rate ratios. Importantly, the incidence rate ratio for death had high precision for all subgroups and was consistently increased in patients with and without individual comorbidities, including diabetes.

Sensitivity analyses

The sensitivity analysis comparing the baseline characteristics of patients with and without complete monitoring of creatinine concentrations showed no major differences in age, sex, blood pressure values, socioeconomic status, or lifestyle factors (supplementary table

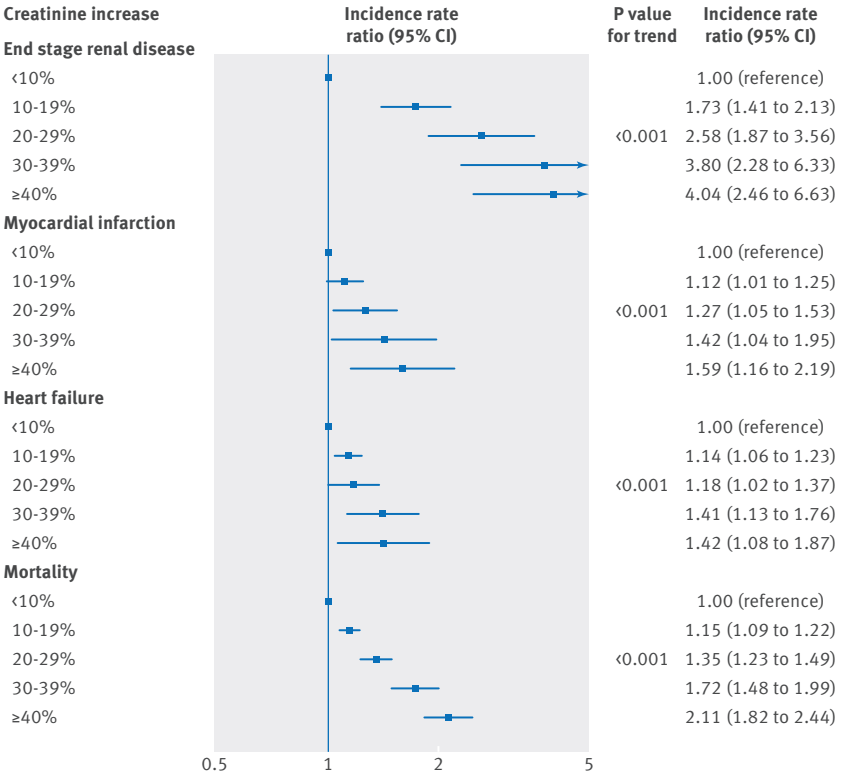


Fig 3 | Cardiorenal risks associated with levels of creatinine increase after renin-angiotensin system blockade

B). However, those with complete monitoring had a higher prevalence of non-cardiac comorbidity, in particular diabetes and chronic kidney disease. The cumulative mortality function for this group was similar to that of the group with creatinine increases between 10% and 19% (supplementary figure A). The remaining sensitivity analyses all supported the robustness of the main results (supplementary tables C and D).

Discussion

We found that patients in routine clinical care who started treatment with ACEI/ARB and whose creatinine concentration had increased by 30% or more at their first follow-up monitoring visit were at increased risk for adverse cardiac outcomes and death, compared with patients with more stable creatinine values. Our study thus confirms data from clinical trials in a real world clinical setting. Moreover, we established that risks were also substantially increased for end stage renal disease. In general, risks were highest in the first year after the start of ACEI/ARB treatment but were sustained up to 10 years later for end stage renal disease, myocardial infarction, and death. Importantly, we showed a "dose-response" relation between the level of increase in creatinine values and risk of adverse outcomes, indicating that all increases below 30% cannot be viewed as safe. Our results were consistent across calendar periods and patient subgroups in a range of sensitivity analyses. It is not clear whether increases in creatinine values after the start of ACEI/ARB treatment are due to pathophysiological processes representing a biomarker of increased risk or whether a direct causal relation exists between reduced renal function and adverse outcomes. These results therefore identify a group of patients at high risk but do not necessarily support discontinuation of ACEI/ARBs.

Strengths and limitations of study

This large population based study is the first to use data from routine clinical care to examine long term outcomes associated with changes in renal function after

Table 3 | Creatinine increases ≥30% after renin-angiotensin system blockade and risk of adverse cardiorenal events, stratified by comorbidities

Baseline characteristics	Adjusted incidence rate ratio (95% CI)			
	End stage renal disease	Myocardial infarction	Heart failure	All cause death
Sex:				
Men	4.81 (3.22 to 7.21)	1.64 (1.24 to 2.17)	1.51 (1.20 to 1.91)	1.89 (1.62 to 2.20)
Women	1.64 (0.75 to 3.58)	1.30 (0.89 to 1.88)	1.25 (0.94 to 1.65)	1.74 (1.50 to 2.03)
Diabetes mellitus	3.19 (1.81 to 5.61)	1.82 (1.28 to 2.60)	1.32 (0.95 to 1.85)	1.96 (1.66 to 2.32)
No diabetes mellitus	3.09 (1.91 to 5.01)	1.31 (0.97 to 1.78)	1.40 (1.13 to 1.73)	1.78 (1.55 to 2.04)
Previous myocardial infarction	1.12 (0.21 to 6.00)	-	1.34 (0.85 to 2.10)	1.93 (1.53 to 2.43)
No myocardial infarction	3.62 (2.50 to 5.24)	-	1.42 (1.16 to 1.75)	1.84 (1.63 to 2.06)
Heart failure	1.86 (0.40 to 8.74)	1.63 (0.96 to 2.78)	-	1.85 (1.54 to 2.23)
No heart failure	3.86 (2.70 to 5.53)	1.47 (1.12 to 1.91)	-	1.85 (1.63 to 2.10)
Hypertension	4.53 (2.99 to 6.87)	1.65 (1.22 to 2.22)	1.61 (1.30 to 1.99)	1.94 (1.69 to 2.22)
No hypertension	1.92 (0.93 to 3.97)	1.21 (0.80 to 1.84)	1.14 (0.85 to 1.51)	1.76 (1.50 to 2.07)
Cardiac arrhythmia	3.83 (1.36 to 10.8)	1.70 (0.98 to 2.94)	1.35 (0.94 to 1.93)	1.68 (1.38 to 2.04)
No cardiac arrhythmia	3.49 (2.41 to 5.05)	1.44 (1.11 to 1.87)	1.42 (1.17 to 1.74)	1.93 (1.71 to 2.19)
Peripheral arterial disease	1.03 (0.14 to 7.67)	1.59 (0.83 to 3.06)	1.78 (1.06 to 2.98)	1.86 (1.32 to 2.61)
No peripheral artery disease	3.67 (2.58 to 5.22)	1.48 (1.16 to 1.88)	1.35 (1.10 to 1.64)	1.86 (1.68 to 2.06)
Chronic kidney disease (eGFR*):				
Stage ≤2 (≥60)	2.70 (1.61 to 4.50)	1.42 (1.06 to 1.89)	1.23 (0.99 to 1.53)	1.71 (1.49 to 1.96)
Stage 3a (45-59)	5.81 (2.82 to 12.0)	2.10 (1.33 to 3.31)	1.90 (1.30 to 2.77)	2.05 (1.62 to 2.60)
Stage 3b (30-44)	2.79 (1.06 to 7.34)	1.31 (0.54 to 3.17)	1.64 (0.96 to 2.81)	2.01 (1.45 to 2.77)
Stage 4 (15-29)	7.81 (1.99 to 30.7)	0.84 (0.09 to 7.94)	0.68 (0.09 to 5.18)	2.36 (1.28 to 4.37)

See table 2 and text for definitions of study cohort, serum creatinine increases, and adjusted model.
*Estimated glomerular filtration rate (mL/min/1.73 m²).

the start of ACEI/ARB treatment. It represents an important complement to clinical trials, the participants of which may not be representative of treated patients in clinical practice.[6] The study's size and long follow-up also permitted examination of a full range of outcomes, beyond those evaluated in individual clinical trials. Importantly, this is the first study to examine the association with end stage renal disease, as clinical trials are rarely powered to examine this outcome.

Patients who had a greater fall in renal function after starting ACEI/ARB treatment had a higher proportion of comorbidities and concurrent drugs that are themselves associated with adverse renal outcomes. However, our findings were robust after adjustment for a range of potential confounders, including comorbidity, co-medication use, lifestyle factors, and socioeconomic status. Nevertheless, residual confounding cannot be excluded. We were unable to adjust for proteinuria, a potentially important confounder owing to its association with adverse cardiorenal outcomes, because of its incomplete recording. However, to provide an explanation for our results, proteinuria would need to be associated with the degree of increase in creatinine concentrations after the start of ACEI/ARB treatment. We are not aware of any evidence that this is the case. In addition, effect estimates were similar in all analyses restricted to patients with diabetes, among whom we would anticipate that a high proportion would have substantial urinary protein excretion.

The validity of the diagnosis of myocardial infarction has consistently been found to be high, with positive predictive values of 92-93% in both the CPRD and HES.[16 17] Heart failure, end stage renal disease, and mortality have not been validated individually. However, the diagnoses recorded in the CPRD, particularly in the domains assessed by the Quality and Outcomes Framework,[18 19] are in general considered to have adequate validity for research purposes, with an overall median proportion of cases with a confirmed diagnosis of 89%.[20 21]

A limitation of our study was that we could include only patients with both baseline and follow-up creatinine measurements (complete case analysis) to calculate changes in renal function. Comparison of the baseline characteristics of patients with and without complete monitoring of creatinine concentrations showed no major differences in demographics, socioeconomics, or lifestyle, although a greater proportion of those with complete monitoring had diabetes and chronic kidney disease. Therefore, the proportion of patients with a decline in renal function among those starting ACEI/ARB treatment in the population as a whole may be lower than that observed in the monitored group. This view was also supported by the cumulative mortality function in the group with incomplete monitoring, which was similar to the monitored group with less pronounced increases in creatinine. Importantly, we have no reason to suspect that the association between change in renal function and long term outcomes is not generalisable to the whole population. Also, our results were consistent within strata of patients' comorbidities and when we excluded subgroups of patients expected to have monitoring performed in outpatient hospital clinics.

Although we used the most recent blood test within 12 months, two thirds of all baseline creatinine tests were carried out within six months of the start of ACE/ARB treatment. Our study was also able to focus on participants whom we were confident continued to be prescribed ACEI/ARBs after their post-initiation blood test (regardless of creatinine results). We previously found that 80% of patients with creatinine increases of 30% or more continued treatment despite guideline recommendations to stop.[3] Our new results emphasise the clinical implications of these findings, as the adverse outcomes associated with creatinine increases also applies to continuing ACEI/ARB users.

General practice system software used for issuing prescriptions ensures the accuracy of prescription data, but we cannot be certain that patients were taking their drugs as prescribed. However, given the consistency of results for the overall cohort and for patients with prescription coverage 90 days after the monitoring date, misclassified drug use is unlikely to have affected the results substantially.

Comparison with other studies

Many post hoc analyses of clinical trials have examined the prognostic significance of a deterioration in renal function after the start of ACEI/ARB treatment. In clinical trials of patients with heart failure, deterioration in renal function after starting ACEI/ARB treatment is commonly found.[22] Although this deterioration is associated with a poorer prognosis compared with patients with preserved renal function, the overall benefits of ACEI/ARB treatment compared with placebo remain for cardiovascular outcomes and mortality.[22] Our study does not undermine that evidence but flags that the risk-benefit ratio may differ among patients with marked changes in creatinine concentrations. This is particularly the case for other prescribing indications for which the clinical trial evidence is less clear.

The recommendation in many international guidelines to stop ACEI/ARB treatment if creatinine rises by 30% or more after initiation are founded on a single review of 12 clinical trials of ACEI/ARB treatment for diabetes and heart failure.[4] Studies included in this review evaluated progression of renal disease among patients with pre-existing renal impairment. Of these studies, only six were double blinded and included a total of 1102 participants. These trials were published during 1993-97 and may not relate to patients receiving contemporary routine clinical care. The methods that define a cut-off level of creatinine increase at 30% for cessation are not clearly presented.[4] In addition, the results provided by these studies are not supported by later trials. Recent reviews have not shown the superiority of ACEI/ARBs compared with other antihypertensive drugs for treating early non-diabetic chronic kidney disease,[23] diabetes with normal renal function,[24] and diabetes and chronic kidney disease.[25] A UK multicentre interventional trial to compare the outcomes of continuation versus cessation of ACEI/ARB treatment is

under way in response to observational evidence that stopping ACEI/ARB treatment may slow progression in advanced renal disease.[26 27]

A fixed recommendation to stop ACEI/ARB treatment only if creatinine is increased by 30% or more is also hard to reconcile with the growing body of evidence related to acute kidney injury, which shows that even a small deterioration in renal function is associated with a subsequently increased risk of mortality and other adverse outcomes.[28] It is important to consider that the prognostic significance of ACEI/ARB associated renal impairment may depend on the underlying cause and on subsequent changes in renal function if ACEI/ARB treatment is continued.[4 22] Underlying causes may be different in the routine care setting, in which patients are older, have multiple comorbidities, and have more advanced kidney disease compared with patients who participated in early clinical trials.

Conclusions and implications

In routine primary care, most patients starting treatment with an ACEI/ARB have only minor changes in renal function. However, increases in creatinine concentrations of more than 10% after starting ACEI/ARB treatment affect more than 15% of patients and have important implications. We have shown that creatinine increases after the start of ACEI/ARB treatment were associated with cardiorenal risks in a "dose-response" relation, with no distinct cut-off at 30%, as previously suggested. Further investigation is needed to ascertain whether ACEI/ARB associated changes in renal function unmask underlying pathophysiology or lead directly to adverse outcomes by causing permanent renal impairment in some patients. In addition, a better understanding of the overall risk-benefit ratio of continuing treatment after loss of kidney function for different prescribing indications is needed. Most importantly, patients with substantial increases in creatinine after starting ACEI/ARB treatment should be recognised as a very high risk group needing close ongoing monitoring. Review is needed of the risks and potential benefits of continuation of drug treatment for the specific prescribing indication for each patient.

Contributors: LAT had the idea for the study and acquired data permissions. MS, KEM, and LAT designed the study. MS and KEM managed the data and established the cohort. MS, KEM, and LAT reviewed the literature. MS did the analyses. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. MS is the guarantor.

Funding: MS was supported by Aarhus University Hospital, the A.P. Møller Foundation for the Advancement of Medical Science, Snedkermester Sophus Jacobsen and Hustru Astrid Jacobsens Fond, and Christian og Ottilia Brorsons Rejselegat for yngre videnskabsmænd og –kvinder. HTS was supported by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation. KB holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (grant number 107731/Z/15/Z). LAT and KEM are funded by a Wellcome Trust intermediate clinical fellowship (101143/Z/13/Z). None of these funding sources had a role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: LAT and LS were supported by Wellcome Trust and MS by grants from A.P. Møller Foundation for the Advancement of Medical Science, Snedkermester Sophus Jacobsen and Hustru Astrid Jacobsens Fond, Christian og Ottilia Brorsons Rejseleg at for yngre videnskabsmænd og –kvinder; the Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, but none of these studies has any relation to the present study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the London School of Hygiene and Tropical Medicine Ethics Committee (No 6536) and the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (No 16_025) and made available to the journal reviewers.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

1 National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2016. http://www.nice.org.uk/guidance/cg127/chapter/1-recommendations#choosing-antihypertensive-drug-treatment-2.
2 Lesogor A, Cohn JN, Latini R, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. *Eur J Heart Fail* 2013;15:1236-44. doi:10.1093/eurjhf/hft089.
3 Schmidt M, Mansfield KE, Bhaskaran K, et al. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin-angiotensin system blockade: a UK general practice-based cohort study. *BMJ Open* 2017;7:e012818. doi:10.1136/bmjopen-2016-012818.
4 Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern?*Arch Intern Med* 2000;160:685-93. doi:10.1001/archinte.160.5.685.
5 Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52. doi:10.1016/S0140-6736(97)01187-2.
6 Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006;70:2021-30. doi:10.1038/sj.ki.5001934.
7 Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827-36. doi:10.1093/ije/dyv098.
8 Health and Social Care Information Centre. Hospital Episode Statistics. www.hscic.gov.uk/hes.
9 McDonald HI, Thomas SL, Millett ERC, Nitsch D. CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. *Am J Kidney Dis* 2015;66:60-8. doi:10.1053/j.ajkd.2014.11.027.
10 Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5•24 million UK adults. *Lancet* 2014;384:755-65. doi:10.1016/S0140-6736(14)60892-8.
11 Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open* 2013;3:e003389. doi:10.1136/bmjopen-2013-003389.
12 Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12. doi:10.7326/0003-4819-150-9-200905050-00006.
13 Bhaskaran K, Rachet B, Evans S, Smeeth L. Re: Helene Hartvedt Grytli, Morten Wang Fagerland, Sophie D. Fosså, Kristin Austlid Taskén. Association between use of β-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2013.01.007.: beta-blockers and prostate cancer survival--interpretation of competing risks models. *Eur Urol* 2013;64:e86-7. doi:10.1016/j.eururo.2013.07.004.

14 Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012;41:861-70. doi:10.1093/ije/dyr213.
15 Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. *BMJ* 2013;346:f114. doi:10.1136/bmj.f114.
16 Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* 2013;346:f2350. doi:10.1136/bmj.f2350.
17 Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2008;17:1197-201. doi:10.1002/pds.1672.
18 Doran T, Kontopantelis E, Valderas JM, et al. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. *BMJ* 2011;342:d3590. doi:10.1136/bmj.d3590.
19 Barbour SJ, Schachter M, Er L, Djurdjev O, Levin A. A systematic review of ethnic differences in the rate of renal progression in CKD patients. *Nephrol Dial Transplant* 2010;25:2422-30. doi:10.1093/ndt/gfq283.
20 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4-14. doi:10.1111/j.1365-2125.2009.03537.x.
21 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;60:e128-36. doi:10.3399/bjgp10X483562.
22 Clark H, Krum H, Hopper I. Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. *Eur J Heart Fail* 2014;16:41-8. doi:10.1002/ejhf.13.
23 Sharma P, Blackburn RC, Parke CL, McCullough K, Marks A, Black C. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. *Cochrane Database Syst Rev* 2011;10:CD007751.
24 Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016;352:i438. doi:10.1136/bmj.i438.
25 Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;385:2047-56. doi:10.1016/S0140-6736(14)62459-4.
26 Ahmed AK, Kamath NS, El Kossi M, El Nahas AM. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2010;25:3977-82. doi:10.1093/ndt/gfp511.
27 Bhandari S, Ives N, Brettell EA, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. *Nephrol Dial Transplant* 2016;31:255-61.
28 Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;53:961-73. doi:10.1053/j.ajkd.2008.11.034.

Paper VIII

AP&T Alimentary Pharmacology and Therapeutics

Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular events following coronary stent implantation

M. Schmidt*,†, M. B. Johansen*, D. J. Robertson‡, M. Maeng†, A. Kaltoft†, L. O. Jensen§, H.-H. Tilsted¶, H. E. Bøtker†, H. T. Sørensen* & J. A. Baron**

*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
†Department of Cardiology, Aarhus University Hospital, Skejby, Denmark.
‡VA Medical Center, White River Junction, VT, and Department of Medicine, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, UK.
§Department of Cardiology, Odense University Hospital, Odense, Denmark.
¶Department of Cardiology, Aarhus University Hospital, Aalborg, Denmark.
**Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA.

Correspondence to:
Dr M. Schmidt, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200, Aarhus N, Denmark.
E-mail: morten.schmidt@dce.au.dk

Publication data
Submitted 28 August 2011
First decision 15 September 2011
Resubmitted 22 September 2011
Accepted 25 September 2011
EV Pub Online 4 November 2011

SUMMARY

Background
Cytochrome P450 inhibition by proton pump inhibitors (PPIs) may attenuate the effectiveness of clopidogrel.

Aim
To examine whether PPI use modifies the association between clopidogrel use and major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) with stent implantation, using time-varying drug exposure ascertainment.

Methods
We conducted this population-based cohort study in Western Denmark (population 3 million) using medical databases. We identified all 13 001 patients with coronary stent implantation between 2002 and 2005 and ascertained their reported comorbidities. During the recommended 12-month postintervention treatment period, we tracked use of clopidogrel and PPI and the rate of MACE. We used Cox regression to compute hazard ratios (HRs), controlling for potential confounders.

Results
During follow-up, one or more prescriptions were redeemed by 91% of patients for clopidogrel and by 21% of patients for PPIs. Of the patients, 15% experienced a MACE. The adjusted HR for MACE comparing clopidogrel use with non-use was 0.57 [95% confidence interval (CI): 0.44–0.74] among PPI users and 0.47 (95% CI: 0.42–0.53) among PPI non-users, yielding an interaction effect (i.e. relative rate increase) of 1.20 (95% CI: 0.91–1.58). PPI users treated from before PCI had a 25% increased rate of MACE compared to PPI non-users, independent of clopidogrel use [adjusted HR = 1.24 (95% CI: 0.97–1.58) for clopidogrel users and 1.26 (95% CI: 0.97–1.63) for clopidogrel non-users].

Conclusions
The use of PPIs as a class did not modify the protective effect of clopidogrel, but its use was associated with major adverse cardiovascular events itself, particularly among patients having used PPIs before percutaneous coronary intervention.

Aliment Pharmacol Ther 2012; **35:** 165–174

doi:10.1111/j.1365-2036.2011.04890.x

INTRODUCTION

The thienopyridine clopidogrel is currently a mainstay in tertiary prevention of vascular events in patients with coronary artery disease or ischaemic stroke.[1] Clopidogrel is a pro-drug that is metabolized by hepatic cytochrome P450 (CYP) enzymes (primarily the 2C19 and 3A4 isoforms) to an active thiol metabolite, which irreversibly inhibits the binding of adenosine-5-diphosphate (ADP) to the platelet $P2Y_{12}$-receptor. Patients with high residual ADP-inducible platelet reactivity are at increased risk of major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI).[2]

Several proton pump inhibitors (PPIs) are metabolized by CYP2C19 and thus may interact with clopidogrel metabolism.[3] Intense debate is ongoing about whether the diminished *ex vivo* antiplatelet effect of clopidogrel through concomitant PPI use translates into adverse clinical outcomes.[3, 4] The importance of this interaction arises from the large number of PCIs performed annually, the increasing use of drug-eluting stents with the associated necessity for long-term clopidogrel treatment,[1] and the possibility of preventing an adverse interaction by avoiding co-administration of PPIs.[3]

No population-based study has examined the clinical outcome of the clopidogrel-PPI interaction in patients receiving coronary stents, with assessment of clopidogrel and PPI use in a manner that accounts for discontinuation and restart of therapy, allowing clinical quantification of the interaction effect.[5] To clarify these issues, we examined in detail whether PPI use modified the association between clopidogrel use and MACE after coronary stent implantation, and whether clopidogrel users were at increased risk of MACE when concomitantly administered a PPI.

METHODS

Setting

We conducted this population-based cohort study using medical databases in Western Denmark, which has 3 million inhabitants (55% of the Danish population). The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including clopidogrel and PPIs. Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[6]

Patients and procedures

We used the Western Denmark Heart Registry (WDHR) to identify all PCIs performed between 1 January 2002 and 30 June 2005.[7] Since 1999, this registry has collected patient and procedure data from all cardiac intervention centres in Western Denmark.[7] We defined the first PCI during the inclusion period as the 'index PCI' and the date of the procedure as the 'index date'. We did not include patients treated by balloon angioplasty without stenting.

Participating centres are high-volume facilities, each performing more than 1000 PCIs per year. The interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, pre- or postdilatation, choice of stent, use of direct stenting, and administration of periprocedural glycoprotein IIb/IIIa inhibitor) left to the operator's discretion.[7]

Medication use

We used the Danish Nationwide Prescription Database (DNPD)[8] to identify all redeemed prescriptions for clopidogrel and PPIs.[9] Thienopyridines and PPIs were available by prescription only during the study period. As no prescriptions were filled for ticlopidine, no alternative ADP receptor inhibitor was included in the study. Relevant Anatomical Therapeutic Chemical codes are provided in the Appendix S1.

The recommended daily maintenance dose of clopidogrel for secondary prevention of ischaemic vascular events in Denmark is 75 mg (one tablet) daily for up to 12 months.[9] Thus, for study purposes the number of days supplied from a dispensed clopidogrel prescription corresponded to the number of tablets per package. Packages available in the Danish market contained 28 or 84 tablets.[9] We computed the number of days exposed by adding 7 days to the number of days supplied. This buffer allowed for a 7-day gap to occur between prescription redemptions before a patient was considered to have discontinued the medication.

Use of the following PPIs was recorded in the DNPD: esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.[10] As in the case of clopidogrel, we computed the number of days exposed for PPIs. We defined current users of clopidogrel and PPI, individually, at a given point in time as patients exposed by the most recent prescription redeemed. In a time-varying manner, patients thus contributed time-at-risk as a current user or as a non-user of each drug.

Major adverse cardiovascular events

In line with the recommended duration of clopidogrel treatment, we identified MACE occurrences within 12 months after the index date.[9] We defined MACE as a first occurrence of myocardial infarction (MI), ischaemic stroke, stent thrombosis, target lesion revascularization, or cardiac death. A committee of cardiac specialists, blinded to the history of medication use, reviewed relevant records to determine the occurrence of stent thrombosis and cardiac death, diagnoses that originally were not included in Danish medical registries.[7]

Myocardial infarction and ischaemic stroke

We used the Danish National Registry of Patients (DNRP), covering all nonpsychiatric hospitals since 1977 and emergency room and outpatient clinic visits since 1995, to identify admissions for MI and ischaemic stroke.[11] Associated International Classification of Diseases (ICD) codes are provided in the Appendix S1.

Stent thrombosis and target lesion revascularization

Based on review of original medical records and catheterisation angiograms, the cardiac specialist committee adjudicated the occurrence of definite stent thrombosis as defined by the Academic Research Consortium.[7] We defined target lesion revascularization as a repeat PCI or coronary artery bypass grafting of the index lesion, identified from the WDHR.[7]

Mortality

We obtained data on all-cause mortality from the Danish Civil Registration System.[6] This registry has recorded vital statistics – including date of birth, change of address, date of emigration, and exact date of death – for the Danish population since 1968.[6] The cardiac specialist committee then reviewed original paper death certificates obtained from the National Registry of Causes of Death, which has collected data on dates and causes of death in Denmark since 1943.[12] Deaths were classified as either cardiac or noncardiac, based on the underlying cause recorded on the death certificates. Cardiac death was defined as an evident cardiac death, unwitnessed death, or death from unknown causes.[13]

Patient characteristics

We obtained information on potential confounders (diabetes, hypertension and obesity) from diagnoses recorded in the DNRP between 1977 and the index date. To ensure complete identification of patients with diabetes, we also searched the DNPD for any use of antidiabetic drugs from 1995 to the index date. From the WDHR, we retrieved procedure-specific data, including the year of index PCI, PCI indication (ST-segment elevation MI, non-ST-segment elevation MI or unstable angina pectoris, or stable angina pectoris), number of treated arteries (1, 2, or 3 or more), number of implanted stents (1, 2, or 3 or more), lesion type (A, B1, B2, or C),[14] and stent type (drug-eluting or bare-metal stent).[7] We used the DNPD to obtain information on use of the following medications: aspirin, calcium channel blockers, statins, vitamin K antagonists, nonselective nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, and systemic glucocorticoids. Associated ICD and ATC codes are provided in the Appendix S1.

Statistical analysis

We characterised the patients on the basis of medical, procedural and demographic variables. We followed all patients from the index date until the date of MACE, noncardiac death, emigration, or 12 months of follow-up, whichever came first. Among clopidogrel and PPI users, we examined the proportion taking medication at end of follow-up, based on the number of days exposed since the last prescription redemption. We stratified the analyses according to whether patients had initiated therapy before or after index PCI.

Time-varying exposure assessment allowed patients to be considered exposed to different medications over time: that is, clopidogrel plus a PPI, clopidogrel without a PPI, a PPI without clopidogrel, or no use of clopidogrel or a PPI. This approach permitted comparison of MACE frequency per cumulative time-at-risk associated with each of the four exposure categories. We illustrated graphically how the event rates associated with these four categories progressed relative to each other over time.

We examined whether PPIs as a class modified the association between clopidogrel and MACE, by comparing current use of clopidogrel with non-use, in subgroups of patients with or without concomitant PPI use. We used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs). The 'interaction effect' is the exponentiated coefficient for the interaction term in the model, that is, the ratio of the stratum-specific HRs.[5] The interaction effect estimates the relative hazard rate increase (or decrease) in patients with concomitant use of clopidogrel and a PPI, beyond that expected from the independent effects of each drug alone.[5] An interaction effect other than 1.0 suggests that concomitant PPI use modifies any

Table 1 | Characteristics of the entire cohort receiving stents and the subgroup experiencing major adverse cardiovascular events (MACE)

	All patients (n = 13 001)	MACE patients* (n = 1890)
	N (%)	%
Female	3599 (27.7)	533 (28.2)
Age group		
<60 years	4763 (36.6)	585 (31.0)
60–69 years	3949 (30.4)	825 (27.9)
≥70 years	4289 (33.0)	777 (41.1)
Medication use†		
Clopidogrel	11 859 (91.2)	1097 (58.0)
Proton pump inhibitors	2742 (21.1)	271 (14.3)
Esomeprazole	1260 (9.7)	119 (6.3)
Lansoprazole	719 (5.5)	60 (3.2)
Omeprazole	421 (3.2)	45 (2.4)
Pantoprazole	765 (5.9)	65 (3.4)
Rabeprazole	18 (0.1)	1 (0.1)
Aspirin	11 231 (86.4)	906 (47.9)
Vitamin K antagonists	889 (6.8)	93 (4.9)
Nonselective NSAIDs	1409 (10.8)	75 (4.0)
COX-2 inhibitors	1322 (10.2)	78 (4.1)
Oral glucocorticoids	943 (7.3)	70 (3.7)
Calcium channel blockers	3016 (23.2)	244 (12.9)
Statins	9720 (74.8)	763 (40.4)
Comorbidities‡		
Diabetes	1390 (10.7)	267 (14.1)
Hypertension	389 (3.0)	76 (4.0)
Obesity	82 (0.6)	12 (0.6)
Procedure data		
Year of study entry		
2002	3112 (23.9)	496 (26.2)
2003	3722 (28.6)	561 (29.7)
2004	3986 (30.7)	542 (28.7)
2005	2181 (16.8)	291 (15.4)
PCI indication		
STEMI	3790 (29.2)	862 (45.6)
Non-STEMI or unstable angina pectoris	3987 (30.7)	508 (26.9)
Stable angina pectoris	4876 (37.5)	461 (24.4)
Other	348 (2.7)	59 (3.1)
Number of treated arteries§		
1	10 184 (78.3)	1472 (77.9)
2	2366 (18.2)	356 (18.8)
≥3	339 (2.6)	47 (2.5)
Number of stents§		
1	10 761 (82.8)	1483 (78.5)
2	1720 (13.2)	308 (16.3)
≥3	458 (3.5)	93 (4.9)
Lesion type§¶		
A	2684 (20.6)	310 (16.4)
B	7884 (60.6)	1200 (63.5)
C	2427 (18.7)	380 (20.1)
Stent type		
BMS	8847 (68.0)	1428 (75.6)
DES	3548 (27.3)	378 (20.0)
BMS and DES	606 (4.7)	84 (4.4)

BMS, bare-metal stent; COX, cyclooxygenase; DES, drug-eluting stent; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

* Patients with myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization, or cardiac death during the 12-month follow-up period.

† Any prescription redemption during follow-up.

‡ Registered between 1977 and the index PCI.

§ Data were not available on the number of treated arteries for 112 patients, on the number of stents for 62 patients, and on the lesion type for six patients.

¶ Lesion classification: A, noncomplicated, length <10 mm; B, irregular, length 10–20 mm; C, irregular, side branch, 90 degrees, chronic occlusion, length >20 mm.[14]

protective effect of clopidogrel. We used the Wald χ^2 test to assess the null hypothesis of no interaction.

In regression analyses, we adjusted for the following potential confounders: age, gender, diabetes, hypertension, obesity and time-varying use (calculated from the number of days exposed) of aspirin and of calcium channel blockers and lipophilic statins (drugs with potential for interaction with clopidogrel).[15] To examine the confounding impact of our measures of diabetes, hypertension, and obesity, we fit a minimally adjusted model omitting these variables. As the results from the minimally adjusted model were similar to those from the fully adjusted model, they are not further reported. We repeated the analyses stratifying by age, gender, PCI

indication, and presence/absence of diabetes. We also repeated the analyses for the most commonly used PPIs (esomeprazole, lansoprazole, omeprazole and pantoprazole) for the individual outcomes included in MACE, and for presence of upper gastrointestinal bleeding. Because there were few instances of stent thrombosis, ischaemic stroke, and upper gastrointestinal bleeding, we do not report further on these individual outcomes.

Finally, we examined whether clopidogrel modified the association between PPI use and MACE, by comparing current PPI use with non-use, in subgroups of patients with or without concomitant clopidogrel use. To examine the impact of new use (starting after PCI) and longer term PPI use (starting before PCI),[16] we repeated the analysis in subgroups of patients with or without one or more filled PPI prescriptions before index PCI.

RESULTS

Patient characteristics

We identified 13 001 patients who had undergone coronary stent implantation (Table 1). The median age on the index date was 64 years and 28% were women. The indications for PCI were STEMI for 3790 (29%) patients, non-STEMI or unstable angina pectoris for 3987 (31%) patients, and stable angina pectoris for 4876 (37.5%) patients. During follow-up, 11 859 (91%) patients filled at least one prescription for clopidogrel and 2742 (21%) filled at least one prescription for a PPI. Among patients using clopidogrel after PCI, only 45% continued treatment until end of follow-up (Table 2). This proportion was 54% among PPI users, highest among longer-term users (64%) and lowest among new users (39%).

Clinical outcomes

Overall, 1890 (15%) patients experienced a MACE during the 12-month follow-up. The rates of MACE per 1000 person years were 154 for concomitant clopidogrel and PPI use, 104 for clopidogrel without PPI use, 267 for PPI without clopidogrel use, and 263 for no use of either drug (Table 3 and Figure 1).

The adjusted HR for MACE comparing clopidogrel use with non-use was 0.57 (95% CI: 0.44–0.74) among PPI users and 0.47 (95% CI: 0.42–0.53) among PPI

Table 2 | The proportion of clopidogrel and proton pump inhibitor (PPI) users who continued therapy until the end of follow-up*

		Drug use at end of follow-up*	
	N	No (%)	Yes (%)
Ever use of clopidogrel after PCI†	11 859	6557 (55.3)	5302 (44.7)
Ever use of clopidogrel before PCI‡	1698	811 (47.8)	887 (52.2)
No clopidogrel prescription before PCI	10 161	5746 (56.5)	4415 (43.5)
No clopidogrel prescription after PCI	1142	1102 (96.5)	40 (3.5)§
Ever use of clopidogrel before PCI‡	169	129 (76.3)	40 (23.7)§
No clopidogrel prescription before PCI	973	973 (100)	–
Ever use of a PPI after PCI†	2742	1263 (46.1)	1479 (53.9)
Ever use of a PPI before PCI‡	1622	578 (35.6)	1044 (64.4)
No PPI prescription before PCI	1120	685 (61.2)	435 (38.8)
No PPI prescription after PCI	10 259	10 183 (99.3)	76 (0.7)§
Ever use of a PPI before PCI‡	1432	1356 (94.7)	76 (5.3)§
No PPI prescription before PCI	8827	8827 (100)	–

PCI, percutaneous coronary intervention.

* End of follow-up was defined by a major adverse cardiovascular event, noncardiac death, emigration, or 12 months of follow-up, whichever came first. Patients were considered drug users at end of follow-up if they were covered by the number of days exposed from their last prescription redemption.

† At least one prescription redemption within follow-up.

‡ At least one prescription redemption within 5 years before PCI.

§ Patients who at time of death were covered by the number of days exposed from their last prescription redemption before PCI and who did not live to fill a new prescription after PCI.

Table 3 | Hazard ratio for major adverse cardiovascular events*, comparing clopidogrel use with non-use, with or without concomitant use of proton pump inhibitors

		Clopidogrel use									
		Number†		Rates†		Unadjusted hazard ratio (95% CI)	Interaction effect‡ (95% CI)	*P*§	Adjusted hazard ratio¶ (95% CI)	Interaction effect‡ (95% CI)	*P*§
		–	+	–	+						
Any PPI**	–	973	677	263	104	0.38 (0.34–0.42)	1.28 (0.97–1.69)	0.08	0.47 (0.42–0.53)	1.20 (0.91–1.58)	0.19
	+	102	138	267	154	0.48 (0.37–0.63)			0.57 (0.44–0.74)		
Esomeprazole	–	1039	759	264	108	0.39 (0.35–0.43)	1.30 (0.85–2.00)	0.23	0.39 (0.35–0.43)	1.32 (0.86–2.03)	0.20
	+	36	56	238	153	0.50 (0.33–0.77)			0.51 (0.34–0.78)		
Lansoprazole	–	1050	787	263	109	0.39 (0.35–0.44)	1.06 (0.61–1.83)	0.85	0.39 (0.35–0.44)	1.09 (0.63–1.89)	0.75
	+	25	28	289	138	0.41 (0.24–0.71)			0.43 (0.25–0.74)		
Omeprazole	–	1053	796	263	110	0.39 (0.35–0.44)	1.01 (0.54–1.87)	0.99	0.39 (0.36–0.44)	1.00 (0.54–1.87)	0.99
	+	22	19	288	145	0.40 (0.21–0.73)			0.40 (0.21–0.73)		
Pantoprazole	–	1056	782	264	109	0.39 (0.35–0.43)	1.45 (0.82–2.56)	0.21	0.39 (0.35–0.43)	1.47 (0.83–2.60)	0.19
	+	19	33	254	154	0.56 (0.32–0.99)			0.57 (0.32–1.01)		

* Composite of myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization, and cardiac death within 12 months after coronary stent implantation.

† Numbers reflect exposure status at time of outcome. Rates are number of events per 1000 person years.

‡ The ratio of the stratum-specific hazard ratios, which estimates the increase in hazard ratio associated with concomitant use of clopidogrel and proton pump inhibitors, beyond that expected from the independent effects of these drugs alone.

§ Wald χ^2 test for no interaction in the model.

¶ Adjusted for age, gender, diabetes, hypertension, obesity, and time-varying use of aspirin, calcium channel blockers, and statins.

** Any use of esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole.

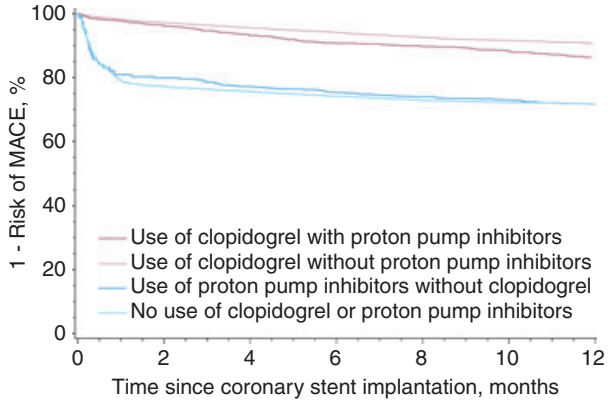


Figure 1 | Survival function for major adverse cardiovascular event (MACE) associated with time-dependent categories of clopidogrel and proton pump inhibitor use.

non-users (Table 3), yielding an interaction effect of 1.20 (95% CI: 0.91–1.58). The results were consistent for MI, TLR, and cardiac death, as separate outcomes (Table S1). We observed no substantial difference from the overall results in subgroups based on age, gender, PCI indication, or presence/absence of diabetes (data not shown).

The adjusted HR for MACE, comparing use of PPIs as a class with non-use, was 1.40 (95% CI: 1.17–1.68) among clopidogrel users and 1.16 (95% CI: 0.95–1.43) among clopidogrel non-users (Table 4). The results were similar for individual PPIs among clopidogrel users (Table S2). The adjusted HR comparing new PPI use with non-use was 1.61 (95% CI: 1.13–2.29) among clopidogrel users and 0.98 (95% CI: 0.58–1.67) among clopidogrel non-users (interaction effect 1.64, 95% CI: 0.87–3.11). Patients with a longer-term PPI use had a 25% increased rate of MACE compared to PPI non-users, independent of whether or not they were using clopidogrel (adjusted HR 1.24, 95% CI: 0.97–1.58 for clopidogrel users and 1.26, 95% CI: 0.97–1.63 for clopidogrel non-users).

DISCUSSION

In this population-based cohort study of 13 001 patients undergoing PCI, clopidogrel use was associated with a markedly reduced rate of MACE within 12 months after coronary stent implantation, independent of PPI use. Use of PPIs individually or as a class did not modify the protective effect of clopidogrel substantially. However,

Table 4 | Hazard ratio for major adverse cardiovascular events,* comparing use of proton pump inhibitors (PPIs)† with non-use, with or without concomitant use of clopidogrel

	Unadjusted hazard ratio (95% CI)	Interaction effect‡ (95% CI)	*P*§	Adjusted hazard ratio¶ (95% CI)	Interaction effect‡ (95% CI)	*P*§
PPI use overall						
– Clopidogrel	1.18 (0.96–1.44)	1.28 (0.97–1.69)	0.08	1.16 (0.95–1.43)	1.20 (0.91–1.58)	0.19
+ Clopidogrel	1.51 (1.26–1.81)			1.40 (1.17–1.68)		
Longer-term use**						
– Clopidogrel	1.25 (0.97–1.62)	1.02 (0.71–1.45)	0.92	1.26 (0.97–1.63)	0.98 (0.69–1.40)	0.93
+ Clopidogrel	1.28 (1.00–1.63)			1.24 (0.97–1.58)		
New use††						
– Clopidogrel	1.01 (0.60–1.72)	1.69 (0.89–3.20)	0.11	0.98 (0.58–1.67)	1.64 (0.87–3.11)	0.13
+ Clopidogrel	1.71 (1.20–2.44)			1.61 (1.13–2.29)		

* Composite of myocardial infarction, ischaemic stroke, stent thrombosis, target lesion revascularization and cardiac death within 12 months after coronary stent implantation.

† Any use of esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole.

‡ The ratio of the stratum-specific hazard ratios, which estimates the relative hazard rate increase associated with concomitant use of clopidogrel and a proton pump inhibitor, beyond that expected from the independent effects of these drugs alone.

§ Wald χ^2 test for no interaction in the model.

¶ Adjusted for age, gender, diabetes, hypertension, obesity and time-varying use of aspirin, proton pump inhibitors and statins.

** Patients with one or more filled PPI prescriptions before index PCI.

†† Patients with no filled PPI prescriptions before index PCI.

PPIs use was associated with an increased rate of MACE itself, particularly among longer-term users.

Several studies have reported on the effect of coadministering PPIs to clopidogrel.[3, 4, 17, 18] Gilard *et al*[19] first drew attention to this potential drug-drug interaction in a placebo-controlled trial of 124 patients receiving coronary stents. They found a reduced *ex vivo* antiplatelet effect of clopidogrel when combined with omeprazole.[19] Several other *ex vivo* studies supported such an effect for concomitant use of omeprazole,[20–22] but not lansoprazole, pantoprazole, or esomeprazole.[21–25] Recently, however, a *post hoc* analysis of the PRINCIPLE-TIMI 44 trial demonstrated a decreased inhibition of platelet aggregation of a 600 mg clopidogrel loading dose associated with concomitant use of all these four PPIs individually.[26]

Observational studies have showed similar inconsistency regarding whether concomitant clopidogrel and PPI use is[27–31] or is not [26, 32–37] associated with adverse clinical outcomes. The only study that randomly allocated PPI treatment to clopidogrel users was the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT).[38] This study concluded that there was no apparent increased cardiovascular risk by using clopidogrel and omeprazole concomitantly compared with clopidogrel alone,[38] although the confidence limits allowed for a 44% relative increase in cardiovascular risk.[3] Similarly, a *post hoc* analysis of the TRITON-TIMI 38 trial found no clinically relevant cardiovascular risk associated with concomitant clopidogrel and PPI use.[26]

Our finding that PPI use was associated with an increased rate of MACE among clopidogrel users is in line with three meta-analyses estimating that concomitant clopidogrel and PPI use is associated with a 30–40% increased risk for MACE compared with clopidogrel use alone.[4, 17, 18] Importantly, the cardiovascular risk associated with PPI use in our study seemed independent of clopidogrel use. This finding is consistent with previous reports.[32, 35, 39] The apparent increase in risk associated with PPI use may be due to the characteristics of the patients who use them.[32, 35, 39] In Denmark PPIs are prescribed mainly for clear indication such as peptic ulcer disease or gastroesophageal reflux disease, and not routinely in combination with dual antiplatelet therapy. Our nonrandomized design is vulnerable to confounding by unmeasured variables (e.g. cardiovascular risk factors not routinely recorded in registry data such as smoking, alcohol use, lipid levels, and body mass index) and residual confounding from imperfect measured variables (in our study, e.g. diabetes, hypertension, or obesity) might also play a role.[32, 39] Thus, it is important to note that the cardiovascular risks associated with PPI use may not necessarily reflect a direct drug effect.

One major limitation of most previous studies was an inability to quantify the isolated interaction effect on clinical endpoints.[26, 27, 29–31, 33–35, 37] Initiating clopidogrel therapy may not be a valid proxy for exposure status throughout follow-up, because patients may stop and restart treatment or may discontinue completely before the end of the recommended treatment period, for example due to intolerable side effects, as it was seen for more than half of our patients. To quantify the actual interaction effect, it is therefore necessary to examine and compare the rate of MACE associated with use of clopidogrel alone, clopidogrel plus a PPI, a PPI alone, or neither. Through our time-varying clopidogrel and PPI ascertainment, we avoided the assumption that once a patient initiated a medication it was continued for the remainder of the recommended treatment period.

Strength and limitations

A number of issues should be considered when interpreting our study's results. Its population-based design within the setting of a tax-supported universal healthcare system largely eliminated selection biases. Data in the prescription database are virtually complete.[8] Although we had to use prescription data as a proxy for drug use, we based drug exposure information on actual dispensing at pharmacies.[8] Copayment requirements increased the likelihood of compliance. We were able to calculate the number of days exposed from the number of days of medication supplied, increasing the accuracy of exposure information. We also accounted for patient adherence behaviour by allowing up to 7-day gaps between prescription refills.[40] These advanced methods of defining exposure reduced the likelihood of nondifferential misclassification,[41] despite reliance on assumptions regarding consumption of dispensed medications. Discontinuation of PPIs could be associated with poor health.[42] If so, the high rate of PPI discontinuation throughout follow-up would draw the effect estimates towards unity and thus cannot explain the findings of an increased risk associated with PPI use. The results for individual PPIs and individual outcomes were limited by wide confidence intervals, making it difficult to rule out small, but potentially clinically relevant, risks. Also, we cannot not rule out that the cardiovascular risk associated with PPI use is independent of clopidogrel use[32] only among longer-term PPI users and not among patients initiating PPI treatment after PCI. Use of WDHR and DNRP data to

ascertain study outcomes has previously been validated,[7, 43] and the DNPD has been shown to be accurate and complete.[8]

Information on drug use and hospitalizations were collected independently from medical databases, avoiding reliance upon self-report and thus reducing the potential for differential misclassification.[44]

In conclusion, use of PPIs as a class did not modify the protective effect of clopidogrel after coronary stent implantation. PPI use was, however, associated with MACE itself, particularly among patients having used PPIs before PCI.

ACKNOWLEDGEMENTS

Declaration of personal interests: JAB has served as a consultant to Bayer. *Declaration of funding interests:* This study was supported by the Clinical Epidemiology Research Foundation, Denmark. DJR was supported by a VA HSR&D Career Development Award. The funding sources had no role in the design, conduct, analysis or reporting of this study. The contents of this work do not necessarily represent the views of affiliated medical departments or the Danish and US governments.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. ICD and ATC codes.

Table S1. Adjusted hazard ratio for individual outcomes within 12 months after coronary stent implantation, comparing clopidogrel use with non-use, with or without concomitant use of proton pump inhibitors.

Table S2. Hazard ratio for major adverse cardiovascular events, comparing use of individual proton pump inhibitors with non-use, with or without concomitant use of clopidogrel.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

REFERENCES

1. McFadden EP, Stabile E, Regar E, *et al.* Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364**: 1519–21.
2. Geisler T, Langer H, Wydymus M, *et al.* Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27**: 2420–5.
3. Abraham N, Hlatky M, Antman EM, *et al.* ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 Expert Consensus Document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Circulation* 2010; **122**: 2619–33.
4. Hulot J, Collet J, Silvain J, *et al.* Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration. *JACC* 2010; **56**: 134–143.
5. Greenland S, Lash TL, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 71–86.
6. Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011; **39**(7 suppl): 22–5.
7. Schmidt M, Maeng M, Jakobsen CJ, *et al.* Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. *Clinical Epidemiology* 2010; **2**: 137–44.
8. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–8.
9. Available drugs and package sizes on the Danish drug market. Available at: http://www.lmk.dk. Accessed November 1, 2010.
10. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors – emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999; **13**(Suppl 3): 27–36.
11. Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–8.
12. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011; **39**(7 Suppl): 26–29.
13. Cutlip DE, Windecker S, Mehran R, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**: 2344–51.
14. Ellis SG, Vandormael MG, Cowley MJ, *et al.* Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation* 1990; **82**: 1193–202.
15. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. *J Am Coll Cardiol* 2011; **57**: 1251–63.
16. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; **158**: 915–20.
17. Kwok C, Loke Y. Meta-analysis: effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; **31**: 810–23.
18. Siller-Matula JM, Jilma B, Schrör K, Christ G, Huber K. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost* 2010; **8**: 2624–41.
19. Gilard M, Arnaud B, Cornily JC, *et al.* Influence of omeprazole on the antiplatelet

action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; **51**: 256–60.
20. Zuern CS, Geisler T, Lutilsky N, Winter S, Schwab M, Gawaz M. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res* 2010; **125**: e51–e54.
21. Sibbing D, Morath T, Stegherr J, *et al.* Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009; **101**: 714–9.
22. Cuisset T, Frere C, Quilici J, *et al.* Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose. *J Am Coll Cardiol* 2009; **54**: 1149–1153.
23. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. The influence of proton pump inhibitors on the antiplatelet potency of clopidogrel evaluated by 5 different platelet function tests. *J Cardiovasc Pharmacol* 2010; **56**: 532–9.
24. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009; **157**: 148.e1–5.
25. Small DS, Farid NA, Payne CD, *et al.* Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *K Clin Pharmacol* 2008; **48**: 475–484.
26. O'Donoghue ML, Braunwald E, Antman EM, *et al.* Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009; **374**: 989–997.
27. Juurlink DN, Gomes T, Ko DT, *et al.* A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009; **180**: 713–8.
28. Ho PM, Maddox TM, Wang L, *et al.* Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; **301**: 937–44.
29. Rassen J, Choudhry N, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009; **120**: 2322–9.
30. Stockl KM, Le L, Zakharyan A, *et al.* Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med* 2010; **170**: 704–10.
31. van Boxel OS, van Oijen MG, Hagenaars MP, Smout AJ, Siersema PD. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol* 2010; **105**: 2430–6. quiz 2437.
32. Charlot M, Ahlehoff O, Norgaard ML, *et al.* Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010; **153**: 378–86.
33. Ray WA, Murray KT, Griffin MR, *et al.* Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010; **152**: 337–45.
34. Simon T, Verstuyft C, Mary-Krause M, *et al.* Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; **360**: 363–75.
35. Valkhoff VE, t Jong GW, Van Soest EM, Kuipers EJ, Sturkenboom MC. Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors. *Aliment Pharmacol Ther* 2011; **33**: 77–88.
36. Disney BR, Watson RD, Blann AD, Lip GY, Anderson MR. Review article: proton pump inhibitors with clopidogrel–evidence for and against a clinically-important interaction. *Aliment Pharmacol Ther* 2011; **33**: 758–67.
37. Banerjee S, Weideman RA, Weideman MW, *et al.* Effect of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. *Am J Cardiol* 2011; **107**: 871–8.
38. Bhatt DL, Cryer BL, Contant CF, *et al.* Clopidogrel with or without omeprazole in coronary artery disease. *N Eng J Med* 2010; **363**: 1909–17.
39. Dunn SP, Macaulay TE, Brennan DM. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial (abstr). *Circulation* 2009; **118**: S815.
40. Schneeweiss S, Patrick AR, Stürmer T, *et al.* Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care* 2007; **45**(10 Suppl. 2): S131–42.
41. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005; **162**: 1016–23.
42. Stürmer T, Jonsson Funk M, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. *Epidemiology* 2011; **22**: 298–301.
43. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* 2003; **56**: 124–30.
44. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 137–9.

Paper IX

Diclofenac use and cardiovascular risks: series of nationwide cohort studies

Morten Schmidt,[1,2] Henrik Toft Sørensen,[1,3] Lars Pedersen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200, Aarhus, Denmark
[2]Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark
[3]Department of Health Research & Policy (Epidemiology), Stanford University, Stanford, CA, USA

Correspondence to: M Schmidt
morten.schmidt@clin.au.dk
(ORCID 0000-0001-5646-1314)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2018;362:k3426
http://dx.doi.org/10.1136/bmj.k3426

Accepted: 19 July 2018

ABSTRACT

OBJECTIVE

To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of paracetamol, and no initiation.

DESIGN

Series of 252 nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design).

SETTING

Danish, nationwide, population based health registries (1996-2016).

PARTICIPANTS

Individuals eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1 370 832 diclofenac initiators, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 healthcare seeking paracetamol initiators matched by propensity score, and 1 303 209 healthcare seeking non-initiators also matched by propensity score.

MAIN OUTCOME MEASURES

Cox proportional hazards regression was used to compute the intention to treat hazard ratio (as a measure of the incidence rate ratio) of major adverse cardiovascular events within 30 days of initiation.

RESULTS

The adverse event rate among diclofenac initiators increased by 50% compared with non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7), 20% compared with paracetamol or ibuprofen initiators (both 1.2, 1.1 to 1.3), and 30% compared with naproxen initiators (1.3, 1.1 to 1.5). The event rate for diclofenac initiators increased for each component of the combined endpoint (1.2 (1.1 to 1.4) for atrial fibrillation/flutter, 1.6 (1.3 to 2.0) for ischaemic stroke, 1.7 (1.4 to 2.0) for heart failure, 1.9 (1.6 to 2.2) for myocardial infarction, and 1.7 (1.4 to 2.1) for cardiac death) as well as for low doses of diclofenac, compared with non-initiators. Although the relative risk of major adverse cardiovascular events was highest in individuals with low or moderate baseline risk (that is, diabetes mellitus), the absolute risk was highest in individuals with high baseline risk (that is, previous myocardial infarction or heart failure). Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation.

CONCLUSIONS

Diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Diclofenac is the most commonly used non-steroidal anti-inflammatory drug (NSAID) in low, middle, and high income countries

Its cardiovascular risks compared with other traditional NSAIDs have never been examined in a randomised controlled trial, and current concerns about these risks make such a trial unethical to conduct

A series of Danish nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design), included 1 370 832 initiators of diclofenac, 3 878 454 initiators of ibuprofen, 291 490 initiators of naproxen, 764 781 healthcare seeking initiators of paracetamol (matched by propensity score), and 1 303 209 healthcare seeking NSAID non-initiators (matched by propensity score)

WHAT THIS STUDY ADDS

The incidence rate ratio of major adverse cardiovascular events at 30 days among diclofenac initiators increased by 50% versus non-initiators, by 20% versus ibuprofen or paracetamol initiators, and by 30% versus naproxen initiators

The increased risk was observed for atrial fibrillation or flutter, ischaemic stroke, heart failure, myocardial infarction, and cardiac death; both sexes of all ages; and even at low doses of diclofenac.

Risk of upper gastrointestinal bleeding at 30 days with diclofenac was similar to that of naproxen, but considerably higher than for no NSAID initiation, paracetamol, and ibuprofen

Introduction

The cardiovascular risks of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) remain a major safety concern after rofecoxib's thromboembolic properties were revealed.[1] Diclofenac is a traditional non-steroidal anti-inflammatory drug (NSAID) with cyclo-oxygenase-2 (COX 2) selectivity similar to COX 2 inhibitors,[2] but its cardiovascular risks compared with those of other traditional NSAIDs have never been examined in a randomised controlled trial.[3] Current concerns about these risks, as stated by the European Society of Cardiology,[4] now make such a trial unethical to conduct.

Diclofenac is the most frequently used NSAID in low, middle, and high income countries, and is available over the counter in most countries;[5] therefore, its cardiovascular risk profile is of major clinical and public health importance. As a consequence, the European Medicines Agency has again called for a safety assessment of diclofenac.[6] In response, we conducted a series of cohort studies, each mimicking the strict design criteria of a clinical trial (a so-called emulated trial design), to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs.

Methods

Setting

The Danish national health service provides universal tax supported healthcare, guaranteeing unfettered access to general practitioners and hospitals, and part reimbursement for prescribed drug treatments, including diclofenac.[7] Individual level linkage of all Danish registries is possible by use of a unique personal identifier assigned to each Danish citizen at birth and to residents on immigration.[8]

Apart from low dose ibuprofen (200 mg) and diclofenac (from 16 July 2007 to 14 December 2008), all non-aspirin NSAIDs require a prescription in Denmark.[9] Regular users of over-the-counter NSAIDs have an incentive to obtain a prescription because prescription costs are partially reimbursed through the Danish national health service's insurance programme.[9]

Data sources

We used the Danish National Patient Registry covering all Danish hospitals to identify the study population, their comorbidities, and non-fatal endpoints.[10] Each hospital discharge or outpatient visit (since 1977 and 1995, respectively) is recorded in the registry with one primary diagnosis and potentially several secondary diagnoses classified according to the ICD-8 (international classification of diseases, 8th revision) and ICD-10 thereafter.[10] Data on general practice contacts were obtained from the Danish National Health Insurance Service Registry.[11]

We used the Danish National Prescription Registry to identify drug use.[7] Since 1995, this registry has maintained detailed records of all prescriptions dispensed from all Danish pharmacies.[7] We obtained mortality and migration data from the Danish Civil Registration System,[8] which has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[8] Cause of death data were obtained from the Danish Register of Causes of Death.[12]

Design

We used population based registries to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical controlled trial (eTable 1).[13 14] Eligible individuals were those aged at least 18 years with at least one year of continuous prescription records before date of study entry, who did not meet the exclusion criteria (listed below), and who did not redeem NSAID prescriptions in the 12 month washout period before enrolment. Among all eligible individuals in January 1996 (the first trial month), we identified all diclofenac initiators and the following three comparator groups:

- Active NSAID comparators: we identified initiators of ibuprofen or naproxen to enable comparison with other traditional NSAIDs. Initiation was defined as filling a first prescription within the trial month. Any person who fulfilled criteria for both the diclofenac group and an active comparator group was categorised according to the first drug redeemed. If the two drugs were redeemed on the same day, the person was excluded.
- Non-user comparators: we identified non-initiators of NSAIDs from the general population, who were alive and fulfilled the eligibility criteria in January 1996. To account for healthcare seeking behaviour, further restriction was made to individuals with a general practice contact within the trial month. We calculated the propensity score for all eligible individuals initiating diclofenac at enrolment by fitting a logistic regression model including covariates on sex, age, year, comorbidity, and drug treatment use.[15] We then matched non-initiators to diclofenac initiators (1:1) by propensity score within a maximum matching range of 0.025 and without replacement.
- Active non-NSAID comparator: we matched paracetamol initiators from the general population to diclofenac initiators by propensity score. We used a similar matching approach as above, except for adding to the general practice contact criteria that comparators should also redeem a prescription for paracetamol within the trial month. As an analogue to the washout period in the active NSAID comparisons, we also required that paracetamol initiators and NSAID non-initiators had not been enrolled in trials in the previous 12 months.

In all models, enrolled individuals in the January trial were followed from baseline (that is, date of prescription redemption for NSAID/paracetamol initiators and general practice contact for non-initiators) until the first occurrence of a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up, whichever occurred first.

To increase the number of initiators and events, we subsequently applied the approach described above to every month between January 1996 and December 2016, thereby creating a series of emulated trials (n=252), each with a one month enrolment period (fig 1). Fulfilling the eligible criteria at any given baseline, participants could potentially take part in several trials. Thus, NSAID non-initiators in the January 1996 "trial" could still be included in the January 1997 "trial." By contrast, all enrolled individuals in the January 1996 "trial" were ineligible for inclusion in the subsequent 12 months.

Exclusion criteria

Exclusion criteria were based on all information recorded in the Danish National Patient Registry (within five years) and Danish National Prescription Registry (within one year). Exclusion criteria were previous cardiovascular disease (angina pectoris, myocardial infarction, coronary intervention (percutaneous coronary intervention or coronary artery bypass grafting), heart failure, stroke, peripheral vascular disease, venous thromboembolism, atrial fibrillation or flutter, or use of digoxin, nitrates, antiplatelet drugs, or anticoagulant drugs within one year), chronic kidney

doi: 10.1136/bmj.k3426 | *BMJ* 2018;362:k3426 | the bmj

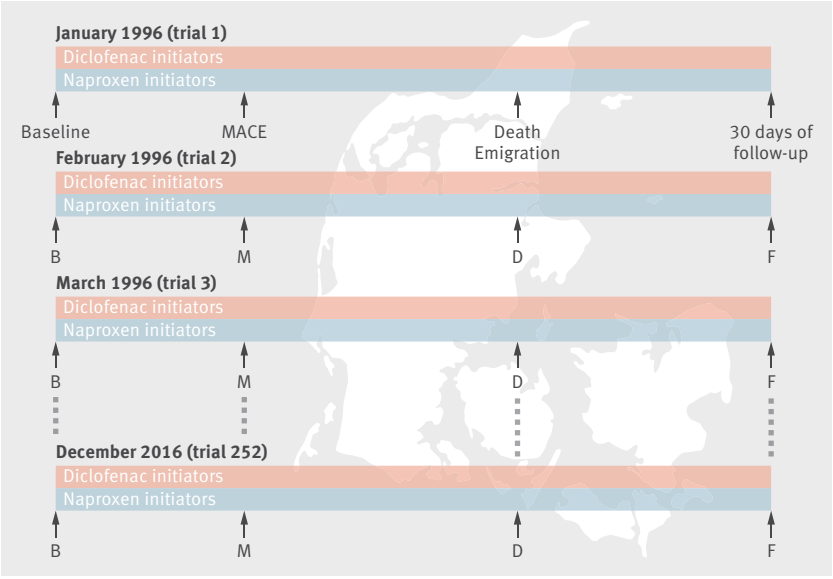


Fig 1 | Emulated trial design, to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs in Denmark. Individual level linkage of nationwide population based registries was used to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical controlled trial. Eligible individuals were aged at least 18 years who had at least one year of prescription history and none of the exclusion criteria. All initiators of diclofenac and naproxen were identified during the month of January 1996. Each person was followed up to a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up. Enrolment was repeated in the months of February and March, and subsequently for every month up to December 2016. The series of 252 emulated trials were then statistically pooled into one model, generating a sample size of 1 370 832 diclofenac initiators and 291 490 naproxen initiators. A similar approach was used to identify ibuprofen initiators (n=3 878 454) and propensity score matched initiators of paracetamol (n=764 781) and NSAID non-initiators (n=1 303 209). B=baseline; MACE=major adverse cardiovascular events; D=death or emigration; F=30 days of follow-up

disease, chronic liver disease, other alcoholism related diseases, ulcer disease, malignancy, schizophrenia (or use of antipsychotic drugs), or dementia.

Endpoints

The primary endpoint—major adverse cardiovascular events—was a composite of non-fatal events[10] and cardiac death.[8] Non-fatal events were defined as first time inpatient diagnoses of atrial fibrillation or flutter, ischaemic stroke, heart failure, and myocardial infarction.[10] For atrial fibrillation or flutter, we also included first time outpatient diagnoses. Cardiac death was defined as death from any cardiac cause. Secondary endpoints included all the individual components of major adverse cardiovascular events. Finally, we stratified cardiac death according to underlying causes.

Participant characteristics

We characterised the study population by age, sex, comorbidity, and drug treatment use at baseline. We compared the distribution of baseline covariates in the propensity score matched samples using the standardised difference[16] and illustrated graphically the propensity score distribution before and after matching. Comorbidity was based on the complete five year inpatient and outpatient medical history in the Danish National Patient Registry (both primary and secondary diagnoses). Drug treatment use was defined as a redeemed prescription within 90 days before enrolment. To increase the completeness of diabetes, chronic obstructive pulmonary disease, and hypertension ascertainment, we also searched the Danish National Prescription Registry for any previous prescription redemption of diabetic, respiratory, or antihypertensive drugs. We defined hypertension as a hospital diagnosis or redemption of at least two prescriptions for antihypertensive drug classes within 90 days before enrolment.[17] All registry codes are provided in eTable 2.

Intention to treat analysis

We estimated an observational analogue of the intention to treat hazard ratio, as a measure of the incidence rate ratio, by fitting a Cox proportional hazards model, using time since start of follow-up as the time scale and a time independent covariate for treatment assignment. We pooled data from all trials into one model and included each trial as a stratum in the regression (using values from 1 to 252). The covariate values for each "trial" were based on the data most recently recorded at the start of the respective trial. Because individuals could participate in more than one of these trials, we used a robust variance estimator to estimate conservative 95% confidence intervals.[18] In the active NSAID comparator models, we adjusted for the baseline covariates on sex, age, year, comorbidity, and drug treatment use. Adjustment was used rather than propensity score matching to approximate a trial setting.

Participant subgroups

In addition to our primary low risk population (defined by eligibility criteria), we repeated the sampling and analyses for patients with diabetes mellitus (that is, at moderate cardiovascular risk at baseline) and for patients with previous myocardial infarction or heart failure (that is, at high cardiovascular risk at baseline). In the high risk group, cardiovascular drug use within one year was omitted as an exclusion criterion. To facilitate the interpretation of the relative effect estimates, we also calculated adjusted incidence rate differences according to baseline cardiovascular risk. Finally, we stratified the study population by age (<65, 65-79, or ≥80 years), sex, calendar period (1996-2002, 2003-09, and 2010-16), and diclofenac dose (low dose (<100 mg) *v* high dose (100 mg) tablets).

Sensitivity analyses

We performed the following sensitivity analyses, in order to:

1. Omit the restriction among NSAID non-initiators to healthcare seekers, to examine the confounding-reducing effect of this inclusion criterion
2. Examine upper gastrointestinal bleeding as a control outcome in the model validation

3. Exclude trial sampling from July 2007 to December 2008, to quantify potential non-differential misclassification due to use of diclofenac obtained over the counter
4. Censor patients on redemption of a prescription for an NSAID other than the active comparator drug received at baseline, to examine the potential impact of crossover
5. Allow only one trial entry per person
6. Change the cutoff limit for low dose diclofenac (from <100 mg to <75 mg and <50 mg tablets), to examine the effect of dose definitions, as high dose diclofenac (150 mg/day) has accounted for almost all outcomes in previous trials[3]
7. Examine subtypes of myocardial infarction separately (ST segment elevation, non-ST segment elevation, and unspecified) to investigate differential effects on severity
8. Use a rule-out approach[19] to estimate how strongly a single unmeasured binary confounder would need to be associated with use of diclofenac and major adverse cardiovascular events to fully explain our findings.

As a worst case scenario, we assumed a confounder prevalence of 25% and use of diclofenac by 4% of the population.[9]

Patient involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Participant characteristics

We identified 1 370 832 diclofenac initiators who met the inclusion criteria, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 matched paracetamol initiators, and 1 303 209 matched non-initiators (67 623 initiators could not be matched, mainly due to advanced age; table 1). Men accounted for about 45% of diclofenac and ibuprofen initiators, 35% of paracetamol initiators, and 40% of naproxen initiators. The median age was 46-49 years among NSAID initiators and 56 years among paracetamol initiators. The proportion of individuals contributing to more than one trial was 31% for diclofenac (1.6% contributed to ≥5 trials), 49.6% for paracetamol (12.3%), 47% for ibuprofen (4.6%), 23% for naproxen (2.2%), and 19% for NSAID non-initiators (0.04%). Diclofenac was initiated primarily for short term treatment. Thus, 44% of patients redeemed one prescription, 19% redeemed two, and 10% redeemed three; only 9% redeemed 10 or more prescriptions. Most diclofenac initiators (75%) redeemed only one prescription within six months of initiation. The design yielded fairly equal distributions of comorbidities and drug treatment use across exposure groups (standardised differences <10%), indicating that diclofenac and ibuprofen/naproxen initiators had similar characteristics and that the propensity score matching was successful (table 1 and eFigure 1).

Event rates

Within 30 days, major adverse cardiovascular events occurred among 1465 (0.10%) diclofenac initiators, 2912 (0.07%) ibuprofen initiators, 205 (0.07%) naproxen initiators, 967 (0.13%) paracetamol initiators, and 898 (0.07%) NSAID non-initiators (eTables 3-4). Corresponding rates of these events per 100 person years were 1.29 (95% confidence interval 1.23 to 1.36) for diclofenac initiators, 0.91 (0.88 to 0.94) for ibuprofen initiators, 0.85 (0.74 to 0.98) for naproxen initiators, 1.53 (1.44 to 1.63) for paracetamol initiators, and 0.83 (0.78 to 0.89) for NSAID non-initiators (eTables 3-4).

Diclofenac *v* non-use

Diclofenac initiators had a 50% increased rate of major adverse cardiovascular events compared with NSAID non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7). Supporting use of a combined endpoint, event rates consistently increased for all individual outcomes: 1.2-fold for atrial fibrillation or flutter, 1.6-fold for ischaemic stroke, 1.7-fold for heart failure, 1.9-fold for myocardial infarction, and 1.7-fold for cardiac death (fig 2 and eTable 5). Cardiac death was driven by death from heart failure (incidence rate ratio 2.3, 1.3 to 4.2), cardiac arrhythmia (1.9, 1.1 to 3.3), and myocardial infarction (1.7, 1.2 to 2.4).

Diclofenac *v* paracetamol

Compared with paracetamol initiators, diclofenac initiators had a 20% increased rate of major adverse cardiovascular events (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3), reflecting a 1.2-fold increased rate of ischaemic stroke and heart failure and a 1.4-fold increased rate of atrial fibrillation or flutter and myocardial infarction (fig 2 and eTable 5). Although overall there was no association with cardiac death (incidence rate ratio 1.0, 0.8 to 1.2), stratification on underlying causes of death revealed a substantial elevated risk of fatal myocardial infarction (1.8, 1.2 to 2.6).

Diclofenac *v* ibuprofen or naproxen

Diclofenac initiators had a 20% increased rate of major adverse cardiovascular events compared with ibuprofen initiators (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3) and a 30% increased rate compared with naproxen initiators (1.3, 1.1 to 1.5; fig 2 and eTable 5). With ibuprofen as reference, the incidence rate ratio increased 1.1-fold for atrial fibrillation or flutter and heart failure, 1.2-fold for myocardial infarction, 1.3-fold for ischaemic stroke, and 1.5-fold for cardiac death. Cardiac death was driven by death due to heart failure (incidence rate ratio 1.9, 1.2 to 3.0), cardiac arrhythmias (1.7, 1.1 to 2.7), and myocardial infarction (1.4, 1.1 to 1.8).

Table 1 | Baseline characteristics of NSAID initiators, paracetamol initiators, and NSAID non-initiators in Denmark (1996-2016)

	Active NSAID comparison					Active non-NSAID comparison			Non-user comparison		
	Diclofenac initiators (No (%))	Ibuprofen initiators		Naproxen Initiators		Diclofenac initiators (No (%))	Paracetamol initiators*		Diclofenac initiators (No (%))	NSAID non-initiators*	
Total		No (%)	SD (%)†	No (%)	SD (%)†		No (%)	SD (%)†		No (%)	SD (%)†
No (%)	1 370 832 (100)	3 878 454 (100)	—	291 490 (100)	—	764 781 (100)	764 781 (100)	—	1 303 209 (100)	1 303 209 (100)	—
Sex											
Male	620 687 (45.3)	1 794 969 (46.3)	−2.0	118 378 (40.6)	9.4	283 531 (37.1)	279 948 (36.6)	1.0	593 396 (45.5)	598 222 (45.9)	−0.7
Age											
Median (IQR)	48 (37.1-59.2)	48 (36.5-58.6)	—	46 (33.9-57.5)	—	56 (45.4-65.6)	56 (45.0-65.5)	—	49 (37.1-59.2)	49 (37.0-59.6)	—
18-49 years	748 873 (54.6)	2 171 622 (56.0)	−2.7	175 777 (60.3)	−11.5	281 997 (36.9)	281 997 (36.9)	−3.1	713 017 (54.7)	711 147 (54.6)	0.3
50-69 years	484 815 (35.4)	1 366 910 (35.2)	0.3	89 280 (30.6)	10.1	348 728 (45.6)	348 728 (45.6)	4.3	460 664 (35.3)	450 367 (34.6)	1.7
≥70 years	137 144 (10.0)	339 922 (8.8)	4.3	26 433 (9.1)	3.2	134 056 (17.5)	134 056 (17.5)	−1.8	129 528 (9.9)	141 695 (10.9)	−3.1
Calendar year											
1996-2000	433 181 (31.6)	730 107 (18.8)	29.7	116 749 (40.1)	−17.7	185 323 (24.2)	185 323 (24.2)	0.0	414 328 (31.8)	414 328 (31.8)	0.0
2001-05	435 908 (31.8)	858 260 (22.1)	21.9	62 814 (21.5)	23.3	217 096 (28.4)	217 096 (28.4)	0.0	412 369 (31.6)	412 369 (31.6)	0.0
2006-10	341 030 (24.9)	967 276 (24.9)	−0.1	46 329 (15.9)	22.4	217 334 (28.4)	217 334 (28.4)	0.0	322 405 (24.7)	322 405 (24.7)	0.0
2011-16	160 713 (11.7)	1 322 811 (34.1)	−55.3	65 598 (22.5)	−28.9	145 028 (19.0)	145 028 (19.0)	0.0	154 107 (11.8)	154 107 (11.8)	0.0
Comorbidities											
Diabetes	32 491 (2.4)	101 116 (2.6)	−1.5	6950 (2.4)	−0.1	28 137 (3.7)	28 137 (3.7)	−0.4	30 408 (2.3)	29 773 (2.3)	0.3
COPD	70 718 (5.2)	199 052 (5.1)	0.1	14 662 (5.0)	0.6	57 414 (7.5)	57 414 (7.5)	−0.4	66 088 (5.1)	64 279 (4.9)	0.6
Hypertension	86 466 (6.3)	268 827 (6.9)	−2.5	17 568 (6.0)	1.2	75 555 (9.9)	75 555 (9.9)	−0.1	80 941 (6.2)	79 631 (6.1)	0.4
Obesity	20 349 (1.5)	77 502 (2.0)	−3.9	4598 (1.6)	−0.8	16 565 (2.2)	16 565 (2.2)	−0.1	18 981 (1.5)	17 010 (1.3)	1.3
Hyperthyroidism	7347 (0.5)	20 583 (0.5)	0.1	1399 (0.5)	0.8	5786 (0.8)	5786 (0.8)	−0.1	6852 (0.5)	6592 (0.5)	0.3
Osteoporosis	8724 (0.6)	31 122 (0.8)	−2.0	1702 (0.6)	0.7	8587 (1.1)	8587 (1.1)	−0.7	8144 (0.6)	8420 (0.6)	−0.3
Rheumatoid arthritis	5993 (0.4)	20 249 (0.5)	−1.2	1396 (0.5)	−0.6	6242 (0.8)	6242 (0.8)	−0.9	5656 (0.4)	6048 (0.5)	−0.4
Osteoarthritis	8131 (0.6)	25 864 (0.7)	−0.9	1734 (0.6)	−0.0	7756 (1.0)	7756 (1.0)	−0.3	7622 (0.6)	7155 (0.5)	0.5
Systemic connective tissue disease	6857 (0.5)	19 826 (0.5)	−0.2	1538 (0.5)	−0.4	6794 (0.9)	6794 (0.9)	−1.0	6431 (0.5)	6259 (0.5)	0.2
Drug treatment use‡											
ACE inhibitors	34 837 (2.5)	110 253 (2.8)	−1.9	7412 (2.5)	−0.0	30 114 (3.9)	30 114 (3.9)	−0.0	32 675 (2.5)	32 760 (2.5)	0.0
ARBs	21 247 (1.5)	65 558 (1.7)	−1.1	4122 (1.4)	1.1	18 312 (2.4)	18 312 (2.4)	−0.3	19 872 (1.5)	19 031 (1.5)	0.5
β blockers	42 819 (3.1)	108 779 (2.8)	1.9	9026 (3.1)	0.2	36 369 (4.8)	36 369 (4.8)	−0.3	40 114 (3.1)	39 197 (3.0)	0.4
Calcium channel blockers	42 165 (3.1)	132 894 (3.4)	−2.0	9045 (3.1)	−0.2	37 134 (4.9)	37 134 (4.9)	0.1	39 486 (3.0)	39 470 (3.0)	0.0
Diuretics	78 849 (5.8)	200 278 (5.2)	2.6	15 408 (5.3)	2.0	70 794 (9.3)	70 794 (9.3)	0.5	73 614 (5.6)	73 970 (5.7)	−0.1
Statins	37 775 (2.8)	148 030 (3.8)	−6.0	8057 (2.8)	−0.1	33 701 (4.4)	33 701 (4.4)	0.0	35 265 (2.7)	33 943 (2.6)	0.6
SSRIs	39 459 (2.9)	117 429 (3.0)	−0.9	7809 (2.7)	1.2	34 870 (4.6)	34 870 (4.6)	−0.6	36 537 (2.8)	37 442 (2.9)	−0.4
Anti-ulcer drugs	78 697 (5.7)	215 882 (5.6)	0.8	14 543 (5.0)	3.3	70 411 (9.2)	70 411 (9.2)	−1.0	73 038 (5.6)	68 299 (5.2)	1.6
Systemic glucocorticoids	33 736 (2.5)	74 017 (1.9)	3.8	5556 (1.9)	3.8	24 268 (3.2)	24 268 (3.2)	−0.5	31 349 (2.4)	29 629 (2.3)	0.9

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; IQR=interquartile range; NSAID=non-steroidal anti-inflammatory drug; SD=standardised difference; SSRI=selective serotonin reuptake inhibitor.

*Matched to diclofenac initiators by propensity score.

†Standardised difference compared with diclofenac initiators. Ibuprofen/naproxen initiators were compared with all 1 370 832 diclofenac initiators, whereas the propensity score matched cohorts were compared only with the diclofenac initiators to whom they were matched to (that is, 764 781 and 1 303 209 diclofenac initiators for paracetamol and NSAID non-initiators, respectively).

‡Filled prescription within 90 days.

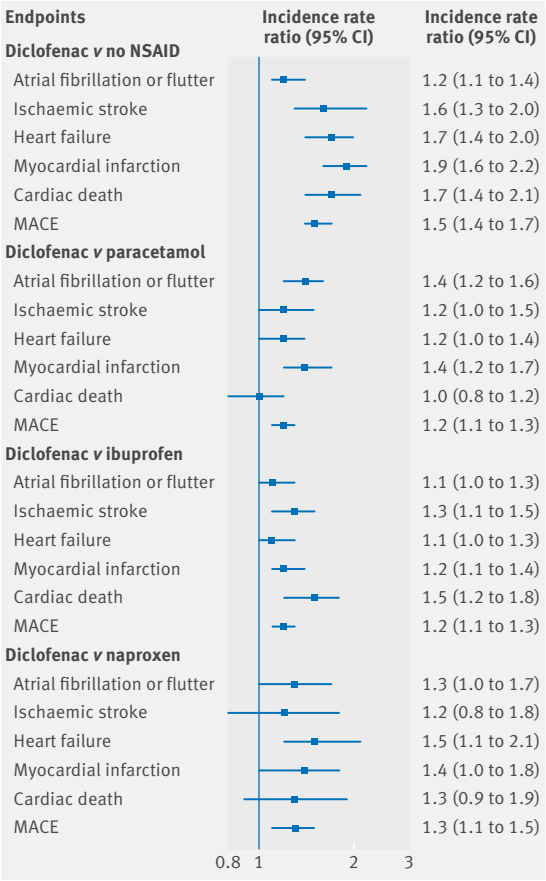


Fig 2 | Cardiovascular risks at 30 days associated with diclofenac initiation compared with no NSAID initiation and initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug; MACE=major adverse cardiovascular event

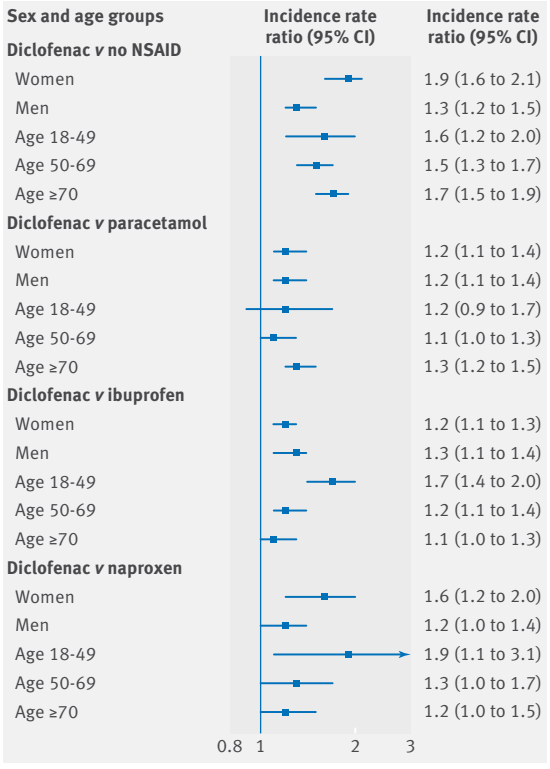


Fig 3 | Risk of major adverse cardiovascular events after diclofenac initiation according to sex and age. NSAID=non-steroidal anti-inflammatory drug

Compared with naproxen initiators, the incidence rate ratio increased 1.2-fold for ischaemic stroke, 1.3-fold for atrial fibrillation or flutter and cardiac death, 1.4-fold for myocardial infarction, and 1.5-fold for heart failure. Consistently, cardiac death was driven by death due to heart failure (incidence rate ratio 1.7, 0.6 to 5.0) and myocardial infarction (1.5, 0.8 to 2.9).

Patient subgroups

The risk of major adverse cardiovascular events remained elevated in sex and age groups (fig 3 and eTables 6-7), and across calendar periods (data not shown). While sex did not modify substantially the effect of diclofenac compared with paracetamol and ibuprofen initiation, diclofenac initiation conferred a higher risk in women than men when compared with NSAID non-initiation (incidence rate ratio 1.9 *v* 1.3) and naproxen initiation (1.6 *v* 1.2).

Stratifying on baseline cardiovascular risk (fig 4 and eTables 8-9), the point estimates for patients with moderate baseline cardiovascular risk were close to those in the overall analyses. For patients with high baseline risk, the incidence rate ratio remained marginally elevated compared with NSAID non-initiation (1.1, 1.0 to 1.3), but levelled out for the active comparator groups. By contrast, the additional absolute number of major adverse cardiovascular events per 1000 diclofenac initiators per year (adjusted incidence rate difference) increased with baseline risk (eTable 10). Thus, among patients at low baseline risk, diclofenac initiators had one additional event versus ibuprofen initiators, one additional event versus naproxen initiators, three additional events versus paracetamol initiators, and four additional events versus NSAID non-initiators. Among patients at moderate baseline risk, corresponding figures were seven, seven, eight, and 14 additional events, respectively; for those at high baseline risk, corresponding numbers were 16, 10, one, and 39 additional events, respectively.

Stratification on dose (fig 5 and eFigure 2) revealed that the increased risk related both to low and high dose diclofenac. There was a non-significant tendency towards increased effect estimates for high doses (fig 5).

Sensitivity analyses

In sensitivity analyses, restriction to healthcare seeking behaviour among NSAID non-initiators was shown to infer important confounder control, because omission of this criterion increased the incidence rate ratio for major adverse cardiovascular events considerably (2.0, 95% confidence interval 1.8 to 2.2). Diclofenac initiation increased upper gastrointestinal bleeding risk at 30 days by approximately 2.5-fold compared with ibuprofen (incidence rate ratio 2.5,

doi: 10.1136/bmj.k3426 | *BMJ* 2018;362:k3426 | the bmj

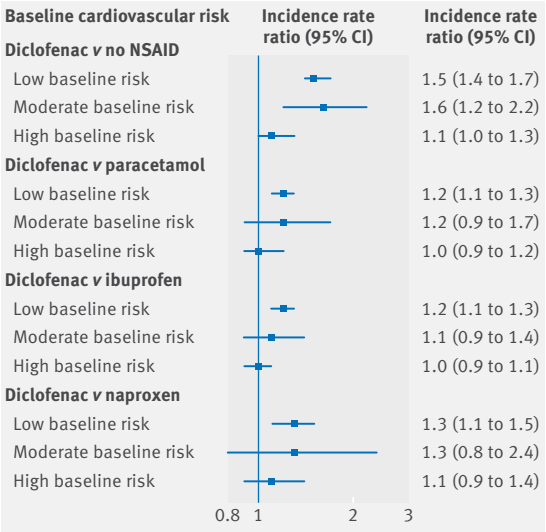


Fig 4 | Risk of major adverse cardiovascular events after diclofenac initiation according to baseline cardiovascular risk. NSAID=non-steroidal anti-inflammatory drug

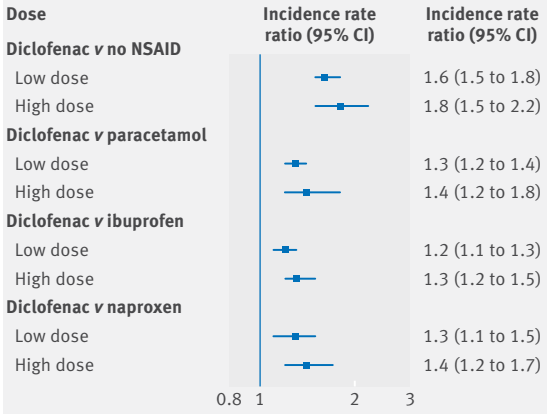


Fig 5 | Risk of major adverse cardiovascular events comparing initiation of low and high dose diclofenac with no NSAID initiation or initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug

2.1 to 3.1) or paracetamol (2.4, 2.0 to 2.9), 4.5-fold compared with no initiation (4.4, 3.5 to 5.5), and to a similar extent as naproxen (0.9, 0.7 to 1.1; eTables 11-13). The results were not influenced by potential over-the-counter use of diclofenac in part of 2007-08 (data not shown), potential crossover between exposure groups (eTable 14), restriction to only one trial entry per person (eTable 15), changes to the low dose cutoff limit (data not shown), and myocardial infarction subtype (data not shown). Finally, an unmeasured confounder that was twice as frequent among diclofenac initiators versus among non-initiators would still need to increase the risk of major adverse cardiovascular events by a factor of nine or more to fully explain the results, if no increased risk actually existed (eFigure 3).

Discussion

In our study, we found that diclofenac initiators were at increased risk of major adverse cardiovascular events—both compared with no NSAID initiation, initiation of paracetamol as an analgesic alternative to NSAIDs, as well as initiation of other traditional NSAIDs. Risk estimates compared with no initiation, paracetamol initiation, and ibuprofen or naproxen initiation increased for almost all individual components of major adverse cardiovascular events (that is, atrial fibrillation or flutter, ischaemic stroke, heart failure, acute myocardial infarction, and cardiac death). The risk increase applied to men and women of all ages. Although the absolute risks were highest in individuals with high baseline cardiovascular risk, the relative risks were highest in those with the lowest baseline risk. While NSAID use previously was considered risk-neutral in short treatment periods and low doses,[20] the risks were apparent even within 30 days and also for low doses of diclofenac. Finally, the upper gastrointestinal bleeding risk of diclofenac was comparable to that for naproxen, but considerably higher than for paracetamol use, ibuprofen use, and no use.

Strengths and limitations

The Danish registry infrastructure made the emulated trial design possible. To our knowledge, the sample size of more than 6.3 million initiators of diclofenac, paracetamol, ibuprofen, or naproxen is larger than all previous meta-analyses of observational and randomised studies taken together.[3 21-23] The largest meta-analysis of randomised trials (Coxib and traditional NSAID Trialists' Collaboration) included only 70 major vascular events in 158 trials comparing traditional NSAIDs with placebo (38 081 participants; 16 217 person years) and 24 major vascular events in 335 trials comparing different traditional NSAIDs (68 507; 22 418).[3] By comparison, our study included over 4500 adverse events among NSAID initiators, close to 1000 adverse events among paracetamol initiators, and a similar number among non-initiators. The tendency we observed for reduced relative risk estimates as baseline risk increased and in comparisons with active comparator drugs is consistent with the principle that effect estimates are highest among individuals at lowest baseline risk.

The population based design in the setting of a tax supported, universal healthcare system largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. The study had no missing data on exposure, confounders, or events. The prescription registry permitted identification of diclofenac use and is virtually complete.[7 9] Our new user design resembled drug allocation in randomised controlled trials.[24] Although we had to use prescription data as a proxy for actual NSAID use, we did not base drug exposure information on written prescriptions, but on actual dispensing at pharmacies.[7] Required copayments increased the likelihood of compliance,[25] although non-compliance in taking the prescribed tablet dose could

have masked a dose-response effect. Over-the-counter use of low dose ibuprofen accounted for 30-35% of total ibuprofen sales and 15-25% of total NSAID sales during the study period.[7] As shown, misclassification of diclofenac use did not affect the results substantially. Non-differential misclassification by over-the-counter ibuprofen use would bias the effect estimates towards unity, if it occurred, and cannot explain the results. The cardiovascular registry diagnoses used in the study have been validated[26] and the mortality and migration data were accurate and complete.[8]

Although the models of healthcare seeking non-initiators and paracetamol initiators varied by design compared with the active NSAID comparators (propensity score matching *v* adjustment), both were based on and controlled for the same measured covariates. The fairly equal distribution of measured covariates among the NSAID groups increased the likelihood that unmeasured variables were also equally distributed. Moreover, confounding by indication was not a concern in the active drug comparisons owing to the shared indications for use of traditional NSAIDs. Still, the emulated trial design lacked baseline randomisation, and therefore, unmeasured confounding cannot be excluded.

Mechanisms

Owing to its short half life of 1-2 hours, diclofenac is prescribed at doses high enough for effective analgesia throughout the dosing interval. The plasma concentration of diclofenac therefore greatly exceeds that necessary to inhibit COX-2 early in the dosing interval, and coincidently inhibits COX-1 (attained selectivity).[27] As plasma concentration falls, diclofenac continues to inhibit COX-2 completely, while its effect on COX-1 subsides gradually, generating a window of pure COX-2 inhibition.[28] Neither ibuprofen nor naproxen show such a window, because their inhibition of COX-1 exceeds that of COX-2 throughout the dosing interval.[27] Selective COX-2 inhibition favours thrombosis by inhibiting generation of COX-2 derived vascular prostacyclin while not affecting COX-1 mediated thromboxane A_2.[29]

Other factors contributing to the cardiovascular toxicity of COX-2 inhibitors include acceleration of atherogenesis,[30] elevation or destabilisation of blood pressure,[31] and risk of heart failure decompensation.[32 33] COX-2 derived prostacyclin also acts as an endogenous anti-arrhythmic agent through inhibition of epicardial sympathetic nerve activity.[34-36] COX-2 inhibition could therefore render patients more susceptible to arrhythmias such as atrial fibrillation.[27] The inhibition of COX-2 up regulation might be particularly harmful during myocardial ischaemia, because thromboxane and prostacyclin are released from the acutely ischaemic myocardium and their balance is related to arrhythmia risk[37] and infarct size.[38]

Previous literature

This large study directly compares the risks of diclofenac initiation with those of paracetamol, ibuprofen, and naproxen for various cardiovascular outcomes. Comparing diclofenac initiation with no NSAID initiation, the consistency between our results and those of previous meta-analyses of both trial and observational data provides strong evidence to guide clinical decision making. The Coxib and traditional NSAID Trialists' Collaboration meta-analysis found a 40% increased risk of vascular events associated with diclofenac use versus placebo or no use (incidence rate ratio 1.41, 95% confidence interval 1.12 to 1.78), driven by an increased rate of myocardial infarction (1.70, 1.19 to 2.41).[3] Also in line with our results, the meta-analysis showed that diclofenac users had an increased risk of heart failure (1.85, 1.17 to 2.94) and vascular death (1.65, 0.95 to 2.85).[3]

The discrepancy between our estimated 60% increased risk and the meta-analysis' estimate for any stroke (1.18, 0.79 to 1.78) could be explained by our focus on ischaemic stroke.[3] The incidence rate ratio for atrial fibrillation or flutter found in our study was lower than previously reported (1.73, 1.53-1.97),[39] in part owing to our ability to control for healthcare seeking behaviour. Finally, the meta-analysis estimated the excess absolute rate of major adverse cardiovascular events per 1000 diclofenac initiators per year as three events among low risk individuals (of which one was fatal) and seven to eight events among high risk individuals (of which two were fatal).[3] Compared with non-initiators, we found a similar excess rate among low risk individuals (about four major adverse cardiovascular events, including one fatal cardiac event), but an even greater rate in high risk individuals (about 40 events, of which about half were fatal).

Conclusions and implications

Our study provides an overview of the spectrum and magnitude of cardiovascular risks related to initiation of diclofenac. We also showed that diclofenac initiators had an upper gastrointestinal bleeding risk similar to that of naproxen initiators and more than twice the risk of ibuprofen initiators. Treatment of pain and inflammation with NSAIDs may be worthwhile for some patients to improve quality of life despite potential side effects. Considering its cardiovascular and gastrointestinal risks, however, there is little justification to initiate diclofenac treatment before other traditional NSAIDs.[40]

It is time to acknowledge the potential health risk of diclofenac and to reduce its use. Diclofenac should not be available over the counter, and when prescribed, should be accompanied by an appropriate front package warning about its potential risks. Moreover, the choice to use diclofenac as the reference group to provide evidence of safety of selective COX-2 inhibitors represents a potential flaw in safety trials.[41-43] Future trials should instead use low dose ibuprofen (≤1200 mg/day) or naproxen (≤500 mg/day) as comparators.[4] In conclusion, our data support that initiation of diclofenac poses a cardiovascular health risk, both compared with no use, paracetamol use, and use of other traditional NSAIDs.

doi: 10.1136/bmj.k3426 | *BMJ* 2018;362:k3426 | the bmj

Contributors: MS and LP conceived the study idea and designed the study. LP collected the data and carried out the analyses. MS organised the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MS and LP are the guarantors.

Funding: The study was supported by the Department of Clinical Epidemiology's Research Foundation at Aarhus Universityand the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation, Novo Nordisk Foundation, and Danish Research Council (grants 11-108354 and 11-115818). The funding sources had no role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Department of Clinical Epidemiology's Research Foundation at Aarhus University and PROCRIN for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data permission: The study was approved by the Danish Data Protection Agency (record No FSEID-00002467).

Data sharing: Not permitted.

1 Bresalier RS, Sandler RS, Quan H, et al, Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102. doi:10.1056/NEJMoa050493
2 Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat* 2007;82:85-94. doi:10.1016/j.prostaglandins.2006.05.019
3 Bhala N, Emberson J, Merhi A, et al, Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-79. doi:10.1016/S0140-6736(13)60900-9
4 Schmidt M, Lamberts M, Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J* 2016;37:1015-23. doi:10.1093/eurheartj/ehv505
5 McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med* 2013;10:e1001388. doi:10.1371/journal.pmed.1001388
6 European Medicines Agency (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). Call for information on effectiveness of risk minimisation on diclofenac (Referral EMEA/H/A-31/1344). February 2017.
7 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol* 2017;46:798-798f.
8 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541-9. doi:10.1007/s10654-014-9930-3
9 Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012. *Clin Epidemiol* 2014;6:155-68. doi:10.2147/CLEP.S59156
10 Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90. doi:10.2147/CLEP.S91125
11 Andersen JS, Olivarius NdeF, Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011;39(Suppl):34-7. doi:10.1177/1403494810394718
12 Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011;39(Suppl):26-9. doi:10.1177/1403494811399958
13 Danaei G, Rodríguez LAG, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res* 2013;22:70-96. doi:10.1177/0962280211403603
14 Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016;183:758-64. doi:10.1093/aje/kwv254
15 D'Agostino RBJr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81. doi:10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
16 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107. doi:10.1002/sim.3697
17 Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124. doi:10.1136/bmj.d124
18 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30. doi:10.2307/2531248
19 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303. doi:10.1002/pds.1200
20 European Medicines Agency. Public CHMP assessment report for medicinal products containing non-selective non-steroidal anti-inflammatory drugs (NSAIDs). 2006. www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054344.pdf. Accessed on April 1, 2015. 2006
21 Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 2017;357:j1909. doi:10.1136/bmj.j1909
22 McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011;8:e1001098. doi:10.1371/journal.pmed.1001098
23 Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086. doi:10.1136/bmj.c7086
24 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20. doi:10.1093/aje/kwg231
25 Danish Medicines Agency. Over-the-counter medicines and reimbursement of medicines in Denmark. www.laegemiddelstyrelsen.dk. Accessed 1 December 2013.
26 Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;6:e012832. doi:10.1136/bmjopen-2016-012832
27 Grosser T, Yu Y, Fitzgerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu Rev Med* 2010;61:17-33. doi:10.1146/annurev-med-011209-153129
28 Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 2006;116:4-15. doi:10.1172/JCI27291
29 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42. doi:10.1056/NEJM200108093450607
30 Egan KM, Lawson JA, Fries S, et al. COX-2-derived prostacyclin confers atheroprotection on female mice. *Science* 2004;306:1954-7. doi:10.1126/science.1103333
31 Aw T-J, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005;165:490-6. doi:10.1001/archinte.165.5.ioi50013
32 Wang D, Patel VV, Ricciotti E, et al. Cardiomyocyte cyclooxygenase-2 influences cardiac rhythm and function. *Proc Natl Acad Sci U S A* 2009;106:7548-52. doi:10.1073/pnas.0805806106
33 Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008;10:1102-7. doi:10.1016/j.ejheart.2008.07.013

34 Miyazaki T, Pride HP, Zipes DP. Prostaglandins in the pericardial fluid modulate neural regulation of cardiac electrophysiological properties. *Circ Res* 1990;66:163-75. doi:10.1161/01.RES.66.1.163
35 Miyazaki T, Zipes DP. Pericardial prostaglandin biosynthesis prevents the increased incidence of reperfusion-induced ventricular fibrillation produced by efferent sympathetic stimulation in dogs. *Circulation* 1990;82:1008-19. doi:10.1161/01.CIR.82.3.1008
36 Coker SJ, Parratt JR. The effects of prostaglandins E2, F2 alpha, prostacyclin, flurbiprofen and aspirin on arrhythmias resulting from coronary artery ligation in anaesthetized rats. *Br J Pharmacol* 1981;74:155-9. doi:10.1111/j.1476-5381.1981.tb09968.x
37 Coker SJ, Parratt JR, Ledingham IM, Zeitlin IJ. Thromboxane and prostacyclin release from ischaemic myocardium in relation to arrhythmias. *Nature* 1981;291:323-4. doi:10.1038/291323a0
38 Timmers L, Sluijter JP, Verlaan CW, et al. Cyclooxygenase-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. *Circulation* 2007;115:326-32. doi:10.1161/CIRCULATIONAHA.106.647230
39 Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. *BMJ* 2011;343:d3450. doi:10.1136/bmj.d3450
40 Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015;162:46-54. doi:10.7326/M14-1231
41 Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-55. doi:10.1001/jama.284.10.1247
42 MacDonald TM, Hawkey CJ, Ford I, et al. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). *Eur Heart J* 2017;38:1843-50.
43 Cannon CP, Curtis SP, FitzGerald GA, et al, MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;368:1771-81. doi:10.1016/S0140-6736(06)69666-9

Web appendix: Supplemental data

Paper X

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvaa073

ORIGINAL ARTICLE
Prevention and epidemiology

Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study

Morten Schmidt [1,2,3] **and Anton Pottegård**[4]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark; [2]Department of Cardiology, Regional Hospital West Jutland, Gl. Landevej 61, 7400 Herning, Denmark; [3]Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark; and [4]Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløws Vej 19, 2nd floor, 5000 Odense C, Denmark

Received 20 May 2020; editorial decision 16 June 2020; accepted 16 June 2020

Aims To examine whether prescription patterns complied with recommendations not to use non-steroidal anti-inflammatory drugs (NSAIDs) in patients with cardiovascular contraindications. Moreover, we examined predictors for initiation and prescriber responsibility.

Methods and results We used Danish medical databases to identify all patients with first-time cardiovascular disease during 1996–2017 (n = 628 834). We assessed standardized prevalence proportions, predictors from logistic regression, and prescriber identifiers. One-year prevalence of NSAID initiation increased 3.4% from 1996 (19.4%) to 2001 (22.7%) and declined by 2.7% thereafter until 2017 (13.5%). Trends were independent of age, sex, and disease subtype, although larger annual declines occurred for heart failure (3.9%) and ischaemic heart disease (3.5%) since 2002. One-year prevalence remained highest among patients with venous thromboembolism (16.6%) and angina (13.8%), and lowest for ST-segment elevation myocardial infarction (7.0%) and heart failure (8.8%). Initiators were predominantly prescribed ibuprofen (59%), diclofenac (23%), and etodolac (6%). Diclofenac and coxib use declined, while ibuprofen and naproxen use increased. Median prescribed pill dose of ibuprofen declined after 2008 from moderate/high (600 mg) to low (400 mg). Treatment duration declined for all NSAIDs, except celecoxib. Rheumatic, obesity, and pain-related conditions predicted NSAID initiation. General practitioners issued 86–91% of all NSAID prescriptions, followed by hospital prescribers (7.3–12%).

Conclusions Initiation of NSAIDs in patients with cardiovascular disease declined since 2002. Shorter treatment duration, declining COX-2 inhibition, and increasing use of naproxen and low-dose ibuprofen suggest adherence to guidelines when NSAIDs cannot be avoided. Still, NSAID use remained prevalent despite cardiovascular contraindications, warranting awareness of appropriateness of use among general practitioners in particular.

Keywords Cardiovascular diseases • Epidemiology • NSAIDs • Trends

Introduction

Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide for the treatment of pain, fever, and inflammation. All NSAIDs increase the risk of elevated blood pressure and congestive heart failure.[1] The risk of thromboembolic events varies with the type of drug but has been shown increased for several newer COX-2 inhibitors (coxibs), older

* Corresponding author. Tel: +45 87167212, Fax: +45 87167215, Email: morten.schmidt@clin.au.dk

COX-2 inhibitors (in particular diclofenac), and non-selective NSAID (in particular high-dose ibuprofen).[1]

Following several risk assessments by the Food and Drug Administration (FDA)[2,3] and the European Medicines Agency (EMA),[4–7] international risk minimization measures have been implemented including box warning labelling on the potential cardiovascular risks and general recommendations to avoid use of NSAIDs in patients with cardiovascular disease. These recommendations also reflect the position from the European Society of Cardiology.[1]

While general population trends show declining use of diclofenac and coxibs in Denmark, their use is persistently high in other Nordic countries such as Norway, Iceland, and Sweden.[8] These trends highlight a varying impact of international recommendations between countries, and likely also patient groups. Patients with existing cardiovascular disease are of key importance because NSAID use in this group is both common (due to age-related musculoskeletal comorbidity) and associated with higher absolute thromboembolic risk increase (due to higher baseline risk). Recent data indicate a persistent high prevalence of diclofenac use in patients with cardiovascular disease.[9] It remains unknown to what extent guidelines and regulatory actions have influenced use of NSAIDs in different cardiovascular subgroups.

We therefore studied temporal trends in NSAID use after first-time diagnosed cardiovascular diseases, and identified predictors for initiation as well as prescriber responsibility.

Methods

Setting

The Danish National Health Service (NHS) provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including NSAIDs.[10] Accurate linkage of all registries at the individual level is possible in Denmark using the unique Central Personal Register number assigned to each Danish citizen at birth and to residents upon immigration.[11]

Over-the-counter (OTC) use of NSAIDs in Denmark is far less common than in many other countries.[12] Thus, all NSAIDs are available by prescription only, except for low-dose ibuprofen (200 mg pills) and diclofenac (between 16 July 2007 and 14 December 2008).[12]Over-the-counter sales of ibuprofen have moreover been restricted to age groups ≥18 years and one package per person per day since 2011, and pack sizes containing a maximum of 20 tablets since 2013.[12] Finally, regular users of NSAIDs that are available OTC have an economic incentive to obtain the drugs by prescription to receive reimbursement.[10] The potential for identifying NSAID use from Danish prescription registries is therefore high with proportions of total sales captured of 66–70% during 2000–2013, increasing to 85% in 2018, for ibuprofen and virtually complete capture for all other non-aspirin NSAIDs.[12]

Data sources

We used the Danish National Patient Registry to identify the study cohorts, non-fatal outcomes, and comorbidities.[13] We used the Danish National Prescription Registry to identify all prescription fillings since 1995.[14] We obtained information on all-cause mortality and migration status from the Danish Civil Registration System.[11]

Cardiovascular disease cohorts

The study cohorts were identified from the Patient Registry between 1 January 1996 and 31 December 2017, with follow-up data through 2018. Applying validated algorithms,[13,15] we used inpatient diagnoses to identify stable angina pectoris, myocardial infarction [MI, including ST-segment elevation (STEMI) and non(N)STEMI], and ischaemic stroke; and in- and outpatient diagnoses to identify atrial fibrillation/flutter, heart failure, venous thromboembolism, valvular heart disease, and infective endocarditis. Both primary and secondary diagnoses were used.[15] For infective endocarditis, we further restricted to patients with admission length ≥2 weeks.[16]

Each of the cohorts was sampled separately (i.e. a patient may be included in more than one cohort). We restricted to first-time (incident) cardiovascular disease cohorts by excluding patients with inpatient or outpatient diagnoses of the index disease prior to our study period (i.e. from 1977 through 1995). Follow-up started at the date of the first-time diagnosis (index date).

Non-steroidal anti-inflammatory drug use

Information on usage of NSAID in the study period was obtained by identifying all filled prescriptions for NSAIDs (excluding glucosamine). The most frequently used individual NSAIDs were examined according to COX-selectivity as non-selective NSAIDs (ibuprofen and naproxen), older COX-2 inhibitors (diclofenac, meloxicam, and etodolac), and coxibs (celecoxib, etoricoxib, and rofecoxib).

Statistical analyses

First, we examined NSAID use after first-time cardiovascular diagnosis. We computed the 1- and 5-year prevalence of NSAID use. We standardized to the age distribution of the index cohort in 2000. We stratified by sex, age (at diagnosis), MI subtype, comorbidity burden (Charlson Comorbidity Index), and NSAID subtypes. We further described the prescribing characteristics of individual NSAIDs, including the proportion of NSAIDs prescribed, the median prescribed pill strength, 1-year accumulated dose distribution [light <15 daily defined dose (DDD), medium 15–50 DDD, and heavy >50 DDD], and number of prescription redemptions among initiators (within 1 year from initiation).

Second, we characterized NSAID initiators and non-initiators (within 1 year after index date) according to demographics, comorbidity, and comedication use, both overall and according to accumulated dose. Comorbidity was based on the complete inpatient and outpatient medical history available in the Patient Registry (both primary or secondary diagnoses) of the comorbidities listed in *Table 1*.[13] To increase the completeness of diagnoses of diabetes and chronic obstructive pulmonary disease, we also identified any previous dispensing of antidiabetic and respiratory medication.[14] We also used the Prescription Registry to obtain information on comedication use defined by prescription fills within 90 days before enrolment (as chronic medication use is usually prescribed for 3 months at a time).[14]

Third, we determined the degree to which age, calendar period, comorbidities, and comedication use predicted NSAID initiation in patients with cardiovascular disease. As prior NSAID use is likely a strong predictor for future use, we restricted these analyses to patients without NSAID redemptions within 90 days before their cardiovascular diagnosis. We used multivariate logistic regression analysis to identify patient covariates predicting NSAID use within 1 year. The model included all covariates in *Table 1*.

Fourth and last, we assessed the proportion of NSAID prescriptions issued by general practitioners, private practicing specialists, hospital prescribers and other prescribers (e.g. dentists).[17] All registry codes are

Table 1 Mean annual change in 1-year prevalence of NSAID use after first-time cardiovascular disease

	1-year prevalence						5-year prevalence					
	Prevalence (%)			Mean annual change (%)			Prevalence (%)			Mean annual change (%)		
	1996	2002	2017	1996–2001	2002–2017	1996–2017	1996	2002	2013	1996–2001	2002–2013	1996–2013
Overall	19.4	22.7	13.5	3.4%	-2.7%	-1.5%	39.9	44.0	34.4	2.1%	-2.0%	-0.8%
Ischaemic heart disease	17.4	20.9	9.9	4.1%	-3.5%	-2.0%	36.4	40.9	31.7	2.4%	-2.0%	-0.8%
Angina pectoris	22.1	24.7	13.8	2.3%	-2.9%	-1.8%	44.6	47.6	36.6	1.3%	-2.1%	-1.1%
Myocardial infarction	14.8	18.0	8.7	4.3%	-3.5%	-2.0%	33.4	38.0	30.5	2.8%	-1.8%	-0.5%
NSTEMI	18.1	20.3	9.6	2.4%	-3.5%	-2.2%	41.9	41.5	33.0	-0.2%	-1.9%	-1.2%
STEMI	12.7	16.3	7.0	5.6%	-3.8%	-2.1%	27.4	36.6	28.8	6.7%	-1.9%	0.3%
Atrial fibrillation/flutter	18.2	20.4	10.9	2.5%	-3.1%	-1.9%	37.5	39.3	28.8	0.9%	-2.4%	-1.4%
Heart failure	17.3	21.0	8.8	4.2%	-3.9%	-2.4%	32.4	37.6	25.5	3.2%	-2.9%	-1.3%
Venous thromboembolism	20.8	24.1	16.6	3.2%	-2.1%	-1.0%	43.1	46.6	37.9	1.6%	-1.7%	-0.7%
Ischaemic stroke	16.9	20.6	10.4	4.4%	-3.3%	-1.8%	34.6	38.8	29.4	2.5%	-2.2%	-0.9%
Valvular heart disease	18.9	22.5	15.3	3.8%	-2.1%	-0.9%	37.8	43.2	34.9	2.9%	-1.8%	-0.5%
Infective endocarditis	13.8	18.6	11.8	7.0%	-2.5%	-0.7%	30.2	33.6	28.2	2.2%	-1.4%	-0.4%

NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

provided in Supplementary material online, *eTable 1*. All analyses were conducted in STATA software V.16.1 (STATA, College Station, TX, USA).

Results

Trends in overall non-steroidal anti-inflammatory drug use

Overall, the use of NSAIDs in patients with cardiovascular disease showed a slight decline throughout the study period (*Figure 1* and *Table 1*). The overall 1-year prevalence initially increased from 1996 (19.4%) to 2002 (22.7%) after which it declined by an average of 2.9% annually to reach 13.5% in 2017 (mean annual decline 1996–2017 was 1.5%). Although higher, the 5-year prevalence followed a similar trajectory, from 40% in 1996, over 44% in 2002 (average annual increase of 2.1%) to 34% in 2013 (average annual decline of 2.0%). Temporal trends in prevalence of use was not influenced substantially by age-standardization and was independent of sex, age, and comorbidity burden (Supplementary material online, *eFigures 1* and *2*).

Similar patterns in trends for 1- and 5-year prevalence were also observed for all individual cardiovascular diseases (*Figure 2*), including MI subtypes (Supplementary material online, *eFigure 3*). However, although similar relative trends were observed, the absolute changes in NSAID initiation differed substantially according to the underlying cardiovascular disease. The mean annual decrease in 1-year prevalence since 2002 was highest for patients with heart failure (3.9%), ischaemic heart disease overall (3.5%), ischaemic stroke (3.3%), atrial fibrillation/flutter (3.1%), infective endocarditis (2.5%), valvular heart disease (2.1%), and venous thromboembolism (2.1%). Accordingly, contraindicated NSAID initiation within 1 year following diagnosis remained in 2017 highest for patients with venous thromboembolism (16.6%), valvular heart disease (15.3%), and angina pectoris (13.8%) and lowest for STEMI (7.0%) and heart failure (8.8%). Similarly, the 5-year prevalence of NSAID use for patients diagnosed in 2013 remained highest for patients with venous thromboembolism (37.9%), angina pectoris (36.6%), and valvular heart disease (34.9%) and lowest for heart failure (25.5%) and infective endocarditis (28.2%).

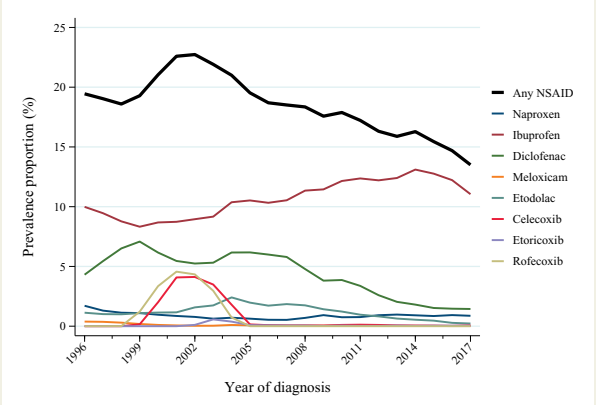


Figure 1 Temporal trends in 1-year prevalence of non-aspirin non-steroidal anti-inflammatory drug use after first-time cardiovascular disease in Denmark (1996–2017).

Trends in individual non-steroidal anti-inflammatory drug use

The majority of NSAID initiators were prescribed ibuprofen (59%), followed by diclofenac (23%) and etodolac (6.3%) (*Table 2*). Correspondingly, the proportion of filled prescriptions was highest for ibuprofen (48%), followed by diclofenac (21%) and etodolac (7.4%). Over time, the use of ibuprofen and naproxen increased alongside a

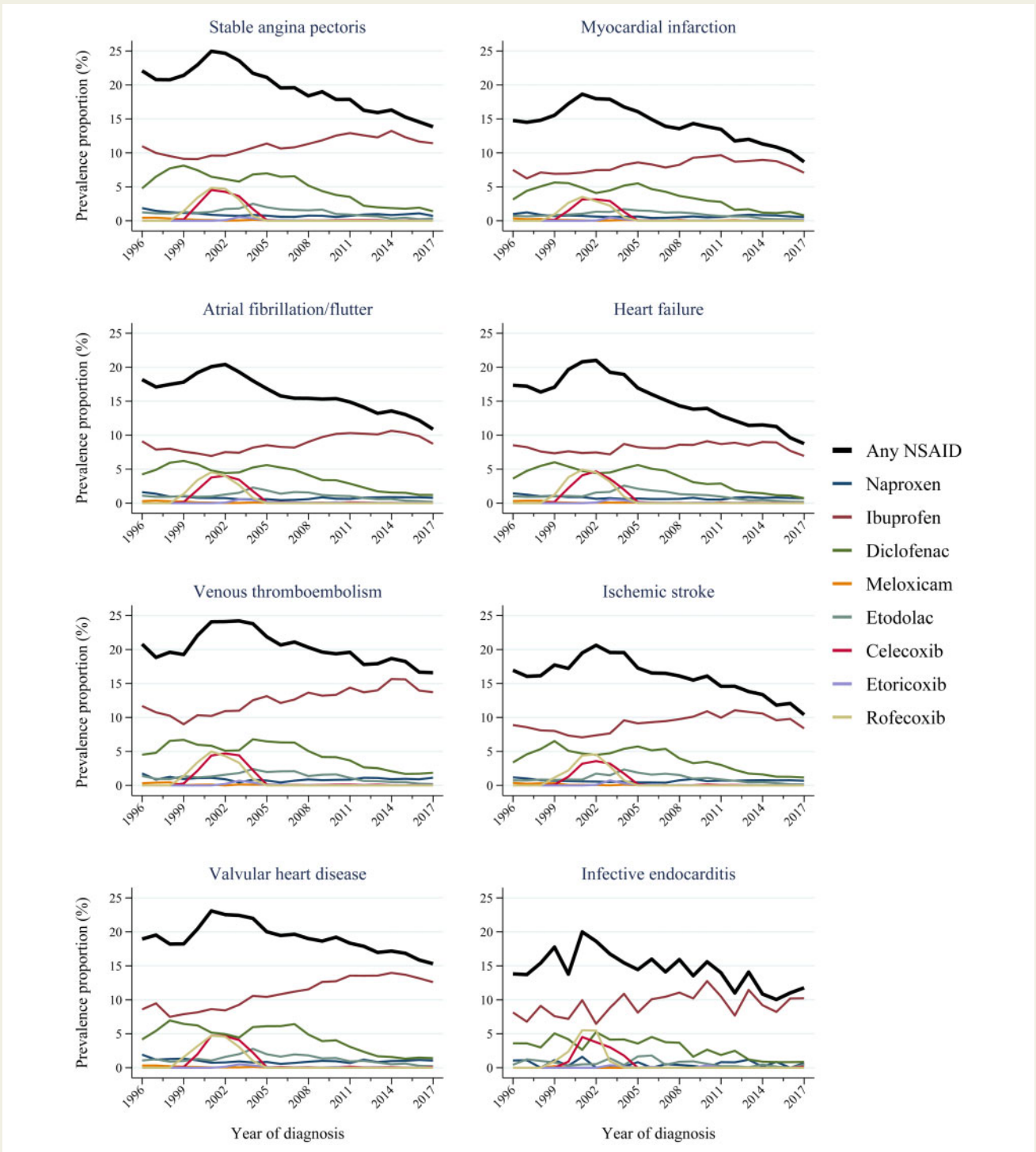


Figure 2 Temporal trends in 1-year prevalence of non-aspirin non-steroidal anti-inflammatory drug use after first-time diagnosis of individual cardiovascular diseases in Denmark (1996–2017).

decline in the use of diclofenac, meloxicam, etodolac, and a marked drop in use of coxibs (*Figure 1* and Supplementary material online, *eTable 2*).

These trends were generally found to be consistent when assessing individual cardiovascular diseases (*Table 1* and *Figure 2*). As exceptions, the prevalence of ibuprofen initiation 1 year after first-time heart failure diagnosis remained stable with a recent tendency to decline. A similar tendency for declining prevalence in ibuprofen initiation since 2014 was also apparent for the other cardiovascular diseases.

Table 2 Trends in prescribing characteristics of individual NSAIDs after first-time cardiovascular disease in Denmark according to dose and treatment duration

NSAID type	People treated, *n* (%)	Filled prescriptions, *n* (%)	Prescribed pill dose (mg), median (IQR)				Number of prescription redemptions among initiators within 1 year, median (IQR)			
			1996	2002	2017	1996–2017	1996	2002	2017	1996–2017
Any NSAID	116 167 (100)	303 759 (100)	—	—	—	—	5 (2–8)	5 (2–8)	3 (1–5)	4 (2–7)
Naproxen	5541 (4.8)	11 499 (3.8)	500 (250–500)	500 (250–500)	500 (500–500)	500 (250–500)	4 (2–7)	3 (2–7)	3 (1–6)	4 (2–7)
Ibuprofen	68 117 (59)	146 987 (48)	400 (400–600)	600 (400–600)	400 (400–600)	400 (400–600)	4 (2–7)	4 (2–7)	2 (1–5)	3 (2–7)
Diclofenac	27 215 (23)	63 180 (21)	50 (50–75)	50 (50–75)	50 (50–75)	50 (50–75)	4 (2–8)	5 (2–8)	3 (2–6)	4 (2–7)
Meloxicam	542 (0.47)	1395 (0.46)	7.5 (7.5–15)	7.5 (7.5–15)	15 (7.5–15)	7.5 (7.5–15)	5 (2–7)	5 (2–7)	4 (4–9)	5 (3–8)
Etodolac	7335 (6.3)	22 508 (7.4)	300 (200–300)	300 (200–300)	300 (200–300)	300 (200–300)	6 (3–9)	7 (3–10)	5 (2–8)	6 (3–10)
Celecoxib	4887 (4.2)	13 607 (4.5)	—	200 (200–200)	200 (100–200)	200 (200–200)	—	6 (3–8)	6 (3–13)	6 (3–9)
Etoricoxib	488 (0.42)	1041 (0.34)	—	120 (90–120)	120 (120–120)	90 (90–120)	—	6 (2–11)	4 (1.5–10)	5 (2–8)
Rofecoxib	4963 (4.3)	14 985 (4.9)	—	25 (12.5–25)	—	25 (12.5–25)	—	6 (3–9)	—	6 (3–9)

IQR, interquartile range.

Trends in dose and treatment duration

Temporal prescribing characteristics of individual NSAIDs (*Table 2* and Supplementary material online, *eTables 3 and 4*) revealed that the median prescribed pill dose (mg) was stable over time at 500 [interquartile range (IQR) 250–500] for naproxen, 50 (50–75) for diclofenac, 300 (200–300) for etodolac, 200 (200–200) for celecoxib, 90 (90–120) for etoricoxib, and 25 (12.5–25) for rofecoxib. There was a tendency for an increase in the median prescribed pill dose of meloxicam over time [overall median 7.5 (IQR 7.5–15) and in 2017 median 15 (IQR 7.5–15)]. The median prescribed pill dose for ibuprofen increased from 400 mg during 1996–2001 to predominantly 600 mg between 2002 and 2008, but then dropped again to 400 mg during 2009–2017.

Among those initiating NSAIDs, the median number (IQR) of prescription redemptions per patient within 1 year was overall 4 (2–7), which reflected a reduction from 5 (2–8) in 1996 to 3 (1–5) in 2017. The median number of prescription redemptions per patient overall varied according to NSAID type, from 3 for ibuprofen to 6 for etodolac, celecoxib, and rofecoxib. However, the number of consecutive prescriptions per patient declined over time for naproxen (from 4 to 3), ibuprofen (from 4 to 2), diclofenac (from 4 to 3), meloxicam (from 5 to 4), etodolac (from 6 to 5), and etoricoxib (from 6 to 4), but not celecoxib (6) (*Table 2*).

Patient characteristics

Overall, the prevalence of NSAID use increased with age up to 80 years after which it decreased for most NSAIDs except celecoxib and rofecoxib (Supplementary material online, *eTables 2 and 5*). Naproxen, ibuprofen, and diclofenac were used in all age groups, whereas meloxicam, etodolac, and coxibs were rarely prescribed in individuals below 50 years of age. The prevalence of individual comorbidities was generally similar across initiators of individual NSAIDs. However, meloxicam, etodolac, and coxibs were more frequently prescribed to individuals with rheumatic diseases or drug use suggestive of rheumatic disease (glucocorticoids and methotrexate) or pain syndromes (paracetamol and opioids). Coxibs were more often prescribed to individuals prescribed anti-ulcer drugs.

Predictors for non-steroidal anti-inflammatory drug initiation

Whereas use of non-selective NSAIDs was independent of sex, female gender was associated with use of both older and newer COX-2 inhibitors (*Table 3*). Age below 50 years predicted initiation of naproxen, ibuprofen, and diclofenac. There was no strong association between age and meloxicam and etodolac. Older age strongly predicted initiation of coxibs. Calendar periods after 2006 predicted ibuprofen initiation. In contrast, recent calendar periods were increasingly inversely associated with initiation of diclofenac, meloxicam, etodolac, celecoxib, etoricoxib, and rofecoxib.

Comorbidity burden was overall also inversely related to NSAID initiation. Among individual comorbidities, the strongest predictors for NSAID initiation were osteoarthritis [odds ratio = 1.53, 95% confidence interval (CI) 1.49–1.56], rheumatoid arthritis (1.48, 95% CI 1.40–1.56), sleep apnoea (1.37, 95% CI 1.29–1.46), obesity (1.32, 95% CI 1.27–1.37), and chronic obstructive pulmonary disease (1.24, 95% CI 1.22–1.26).

Table 3 Associations between patient characteristics and NSAID initiation within 1 year after first-time cardiovascular disease[a]

	Adjusted odds ratio (95% confidence interval)[b]								
	Overall	Non-selective NSAIDs		Older COX-2 inhibitors			Newer COX-2 inhibitors (coxibs)		
		Naproxen	Ibuprofen	Diclofenac	Meloxicam	Etodolac	Celecoxib	Etoricoxib	Rofecoxib
Sex									
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Female	1.07 (1.05–1.08)	0.92 (0.86–0.99)	1.02 (1.00–1.04)	1.07 (1.04–1.11)	1.42 (1.12–1.81)	1.30 (1.22–1.39)	1.49 (1.37–1.61)	1.30 (1.22–1.39)	1.07 (1.04–1.11)
Age									
<50 years	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
50–59 years	0.89 (0.86–0.91)	0.88 (0.78–0.98)	0.85 (0.82–0.88)	0.91 (0.86–0.96)	1.29 (0.80–2.07)	1.15 (1.01–1.32)	1.23 (1.03–1.47)	1.15 (1.01–1.32)	0.91 (0.86–0.96)
60–69 years	0.73 (0.71–0.75)	0.70 (0.63–0.78)	0.67 (0.65–0.69)	0.80 (0.76–0.84)	0.93 (0.58–1.49)	1.14 (1.01–1.29)	1.26 (1.07–1.49)	1.14 (1.01–1.29)	0.80 (0.76–0.84)
70–79 years	0.61 (0.59–0.62)	0.61 (0.55–0.69)	0.53 (0.51–0.54)	0.65 (0.61–0.68)	1.24 (0.80–1.93)	1.07 (0.95–1.21)	1.50 (1.28–1.77)	1.07 (0.95–1.21)	0.65 (0.61–0.68)
80 years or more	0.47 (0.45–0.48)	0.47 (0.42–0.54)	0.37 (0.36–0.39)	0.52 (0.49–0.55)	1.03 (0.65–1.63)	1.00 (0.88–1.13)	1.39 (1.18–1.64)	1.00 (0.88–1.13)	0.52 (0.49–0.55)
Calendar year									
1996–2000	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2001–2005	1.07 (1.05–1.10)	0.62 (0.56–0.68)	1.12 (1.09–1.16)	0.87 (0.83–0.90)	0.19 (0.14–0.27)	1.52 (1.40–1.66)	4.69 (4.23–5.21)	1.52 (1.40–1.66)	0.87 (0.83–0.90)
2006–2010	0.85 (0.84–0.88)	0.56 (0.50–0.62)	1.31 (1.27–1.35)	0.69 (0.66–0.72)	0.11 (0.07–0.17)	1.09 (0.99–1.19)	0.11 (0.08–0.15)	1.09 (0.99–1.19)	0.69 (0.66–0.72)
2011–2015	0.73 (0.71–0.75)	0.67 (0.61–0.74)	1.43 (1.39–1.47)	0.30 (0.28–0.31)	0.08 (0.05–0.12)	0.39 (0.35–0.44)	0.11 (0.08–0.14)	0.39 (0.35–0.44)	0.30 (0.28–0.31)
2016–2017	0.61 (0.59–0.63)	0.67 (0.59–0.76)	1.29 (1.24–1.34)	0.18 (0.17–0.20)	0.03 (0.01–0.09)	0.16 (0.13–0.20)	0.07 (0.04–0.11)	0.16 (0.13–0.20)	0.18 (0.17–0.20)
Comorbidities									
Diabetes	1.06 (1.03–1.09)	1.12 (1.00–1.26)	1.06 (1.02–1.09)	1.07 (1.01–1.13)	1.24 (0.82–1.88)	1.15 (1.03–1.28)	1.08 (0.94–1.24)	1.15 (1.03–1.28)	1.07 (1.01–1.13)
Hypertension	1.03 (1.00–1.05)	1.16 (1.06–1.28)	1.04 (1.01–1.07)	1.01 (0.96–1.06)	0.74 (0.50–1.11)	1.04 (0.95–1.14)	0.98 (0.88–1.10)	1.04 (0.95–1.14)	1.01 (0.96–1.06)
Obesity	1.32 (1.27–1.37)	1.14 (0.97–1.34)	1.29 (1.23–1.35)	1.36 (1.26–1.46)	1.14 (0.59–2.20)	1.30 (1.12–1.51)	1.25 (1.02–1.54)	1.30 (1.12–1.51)	1.36 (1.26–1.46)
COPD	1.24 (1.22–1.26)	1.25 (1.16–1.35)	1.22 (1.19–1.24)	1.26 (1.22–1.31)	1.11 (0.85–1.45)	1.26 (1.17–1.35)	1.21 (1.11–1.32)	1.26 (1.17–1.35)	1.26 (1.22–1.31)
Sleep apnoea	1.37 (1.29–1.46)	1.35 (1.05–1.72)	1.37 (1.28–1.46)	1.20 (1.04–1.38)	0.74 (0.10–5.32)	1.14 (0.83–1.55)	1.14 (0.67–1.95)	1.14 (0.83–1.55)	1.20 (1.04–1.38)
Hyperthyroidism	0.97 (0.92–1.02)	0.88 (0.69–1.12)	0.98 (0.92–1.05)	0.99 (0.89–1.09)	0.85 (0.38–1.92)	0.89 (0.72–1.10)	0.95 (0.75–1.20)	0.89 (0.72–1.10)	0.99 (0.89–1.09)
Osteoporosis	0.90 (0.87–0.94)	0.89 (0.75–1.06)	0.93 (0.89–0.97)	0.89 (0.82–0.97)	1.59 (0.97–2.62)	0.97 (0.84–1.12)	0.86 (0.72–1.04)	0.97 (0.84–1.12)	0.89 (0.82–0.97)
Rheumatoid arthritis	1.48 (1.40–1.56)	1.74 (1.41–2.15)	1.28 (1.19–1.37)	1.27 (1.13–1.42)	1.76 (0.93–3.33)	1.47 (1.21–1.78)	1.59 (1.27–1.99)	1.47 (1.21–1.78)	1.27 (1.13–1.42)
SCTD	1.08 (1.03–1.13)	1.18 (0.97–1.43)	1.08 (1.01–1.14)	1.08 (0.98–1.18)	1.12 (0.61–2.05)	0.92 (0.77–1.11)	1.14 (0.93–1.40)	0.92 (0.77–1.11)	1.08 (0.98–1.18)
Osteoarthritis	1.53 (1.49–1.56)	1.33 (1.21–1.46)	1.46 (1.42–1.50)	1.41 (1.36–1.47)	1.85 (1.38–2.48)	1.73 (1.60–1.87)	1.59 (1.44–1.75)	1.73 (1.60–1.87)	1.41 (1.36–1.47)
Comorbidity burden[c]									
None	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low	0.96 (0.94–0.98)	0.95 (0.87–1.04)	0.97 (0.94–0.99)	0.96 (0.92–1.00)	0.89 (0.65–1.21)	0.94 (0.87–1.02)	1.03 (0.94–1.14)	0.94 (0.87–1.02)	0.96 (0.92–1.00)
Moderate	0.83 (0.80–0.86)	0.81 (0.69–0.96)	0.82 (0.78–0.86)	0.85 (0.79–0.92)	1.02 (0.61–1.72)	0.89 (0.78–1.03)	0.92 (0.78–1.09)	0.89 (0.78–1.03)	0.85 (0.79–0.92)
Severe	0.73 (0.70–0.76)	0.70 (0.58–0.83)	0.78 (0.75–0.82)	0.76 (0.70–0.82)	0.71 (0.36–1.42)	0.62 (0.52–0.74)	0.81 (0.67–0.99)	0.62 (0.52–0.74)	0.76 (0.70–0.82)
Medication use[d]									
Antiplatelet drugs	1.03 (1.01–1.05)	0.96 (0.87–1.05)	1.01 (0.98–1.04)	1.06 (1.01–1.10)	0.95 (0.68–1.32)	1.11 (1.02–1.21)	1.03 (0.94–1.14)	1.11 (1.02–1.21)	1.06 (1.01–1.10)
Anticoagulent drugs	0.77 (0.74–0.80)	0.84 (0.71–0.99)	0.75 (0.71–0.78)	0.77 (0.71–0.84)	0.90 (0.46–1.77)	0.80 (0.68–0.95)	0.97 (0.79–1.18)	0.80 (0.68–0.95)	0.77 (0.71–0.84)

Continued

Table 3 *Continued*

	Adjusted odds ratio (95% confidence interval)[b]								
	Overall	Non-selective NSAIDs		Older COX-2 inhibitors			Newer COX-2 inhibitors (coxibs)		
		Naproxen	Ibuprofen	Diclofenac	Meloxicam	Etodolac	Celecoxib	Etoricoxib	Rofecoxib
Statins	1.08 (1.05–1.11)	1.15 (1.02–1.29)	1.11 (1.08–1.15)	1.06 (1.00–1.12)	0.85 (0.46–1.57)	0.97 (0.86–1.09)	0.85 (0.71–1.01)	0.97 (0.86–1.09)	1.06 (1.00–1.12)
ACE inhibitors	1.01 (0.98–1.03)	1.04 (0.93–1.17)	1.01 (0.98–1.04)	0.98 (0.93–1.04)	1.01 (0.65–1.55)	0.95 (0.85–1.06)	0.93 (0.81–1.07)	0.95 (0.85–1.06)	0.98 (0.93–1.04)
ARBs	1.04 (1.00–1.07)	0.95 (0.81–1.11)	1.01 (0.97–1.06)	1.06 (0.99–1.14)	1.27 (0.70–2.31)	1.06 (0.92–1.22)	1.10 (0.92–1.31)	1.06 (0.92–1.22)	1.06 (0.99–1.14)
Beta-blockers	1.01 (0.99–1.03)	1.03 (0.93–1.14)	0.97 (0.94–1.00)	1.10 (1.05–1.15)	0.94 (0.64–1.38)	1.00 (0.91–1.10)	1.12 (1.00–1.25)	1.00 (0.91–1.10)	1.10 (1.05–1.15)
CCBs	1.01 (0.99–1.04)	0.96 (0.86–1.06)	1.01 (0.98–1.04)	0.96 (0.91–1.01)	1.22 (0.88–1.71)	1.13 (1.03–1.24)	1.04 (0.93–1.17)	1.13 (1.03–1.24)	0.96 (0.91–1.01)
Diuretics	0.99 (0.97–1.01)	1.01 (0.92–1.10)	0.97 (0.94–0.99)	0.97 (0.93–1.01)	0.91 (0.69–1.19)	1.04 (0.96–1.12)	1.06 (0.97–1.16)	1.04 (0.96–1.12)	0.97 (0.93–1.01)
SSRI	1.03 (1.00–1.06)	0.76 (0.64–0.89)	1.04 (1.00–1.08)	1.09 (1.02–1.16)	1.24 (0.79–1.94)	1.09 (0.96–1.23)	1.14 (0.99–1.30)	1.09 (0.96–1.23)	1.09 (1.02–1.16)
Antipsychotic drugs	0.94 (0.90–0.98)	0.84 (0.68–1.03)	0.99 (0.93–1.04)	0.92 (0.85–1.00)	1.12 (0.65–1.93)	0.82 (0.69–0.98)	0.91 (0.76–1.11)	0.82 (0.69–0.98)	0.92 (0.85–1.00)
Anti-ulcer drugs	0.98 (0.96–1.01)	0.99 (0.89–1.10)	0.88 (0.86–0.91)	1.10 (1.05–1.16)	1.28 (0.91–1.81)	1.19 (1.08–1.30)	1.35 (1.21–1.50)	1.19 (1.08–1.30)	1.10 (1.05–1.16)
Gout agents	1.38 (1.30–1.46)	1.84 (1.51–2.25)	1.30 (1.21–1.39)	1.40 (1.26–1.56)	0.83 (0.31–2.23)	1.08 (0.86–1.36)	0.94 (0.70–1.27)	1.08 (0.86–1.36)	1.40 (1.26–1.56)
Systemic glucocorticoids	1.01 (0.97–1.04)	0.98 (0.85–1.13)	0.95 (0.91–0.99)	0.99 (0.93–1.06)	1.49 (1.00–2.23)	1.17 (1.04–1.32)	1.23 (1.07–1.41)	1.17 (1.04–1.32)	0.99 (0.93–1.06)
Methotrexate	1.04 (0.92–1.17)	1.12 (0.71–1.77)	0.95 (0.82–1.11)	1.16 (0.92–1.47)	3.31 (1.21–9.05)	1.32 (0.89–1.96)	1.50 (0.95–2.37)	1.32 (0.89–1.96)	1.16 (0.92–1.47)
Paracetamol	1.11 (1.08–1.14)	1.14 (1.02–1.27)	1.12 (1.08–1.16)	1.01 (0.96–1.06)	0.92 (0.64–1.31)	1.21 (1.10–1.33)	1.29 (1.16–1.44)	1.21 (1.10–1.33)	1.01 (0.96–1.06)
Opiods	1.05 (1.02–1.07)	0.93 (0.83–1.05)	0.93 (0.90–0.97)	1.13 (1.07–1.19)	1.00 (0.69–1.45)	1.12 (1.02–1.24)	1.45 (1.31–1.62)	1.12 (1.02–1.24)	1.13 (1.07–1.19)

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor antagonists; CCBs, calcium channel blockers; DDD, daily defined dose; Glucocorticoids, systemic glucocorticoids; SCTD, systemic connective tissue disease; SSRI, selective serotonin reuptake inhibitors.

[a]Restriction to those patients without ongoing NSAID treatment at time of their cardiovascular diagnosis.

[b]Adjusted for all the other variables.

[c]Four categories of comorbidity burden were defined based on Charlson Comorbidity Index scores of 0 (none), 1 (low), 2 (moderate), and 3 or more (severe).

[d]Prescription filling within 90 days before index disease.

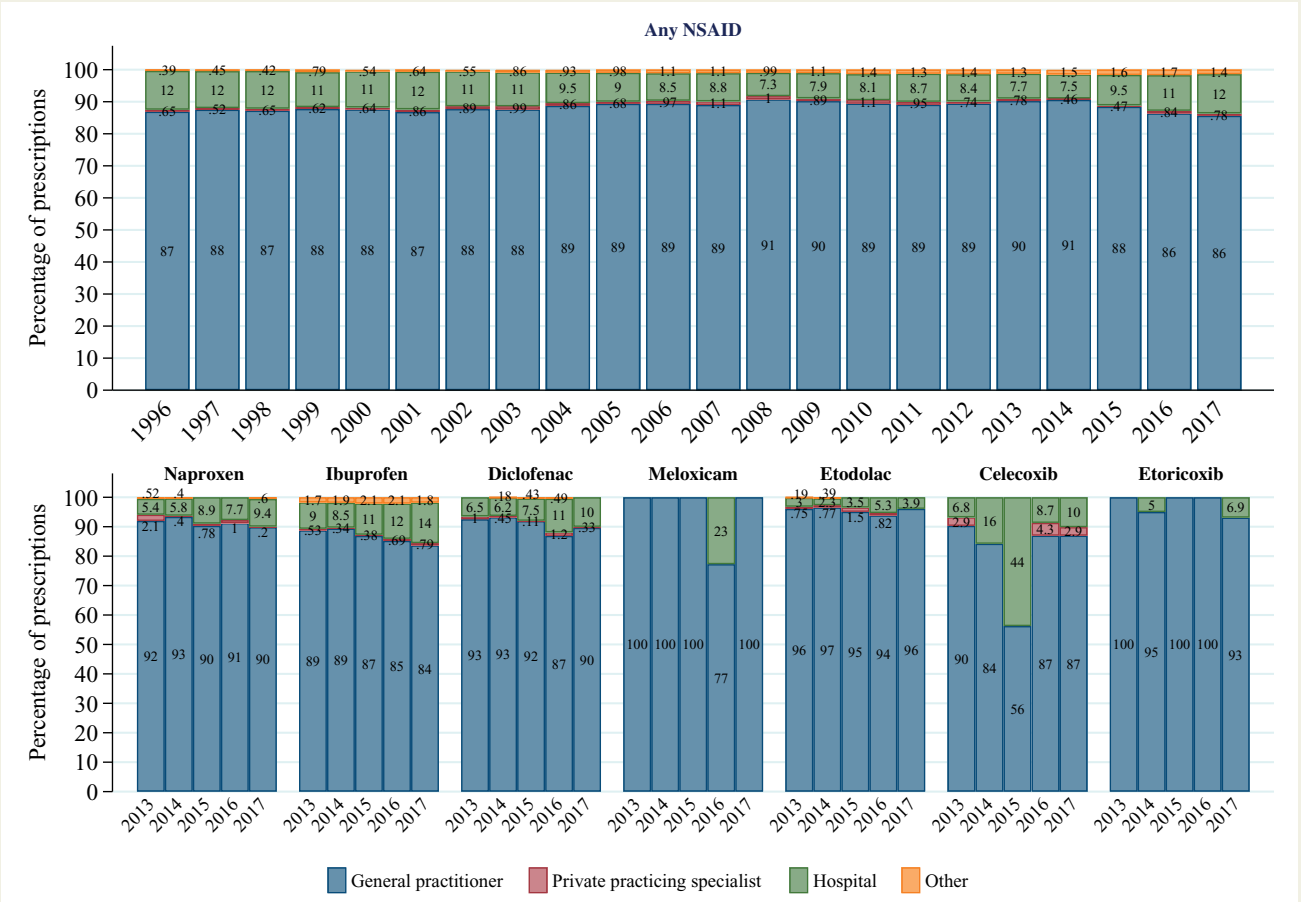


Figure 3 Prescriber responsibility for initiating non-aspirin non-steroidal anti-inflammatory drugs within 1 year after first-time cardiovascular disease (1996–2017).

Among individual drugs, gout agents most strongly predicted overall NSAID initiation (odds ratio = 1.38, 95% CI 1.30–1.46), primarily driven by use of naproxen (1.84, 95% CI 1.51–2.25), ibuprofen (1.30, 95% CI 1.21–1.39), and diclofenac (1.40, 95% CI 1.26–1.56). In contrast, paracetamol, opioids, antiulcer drugs, and systemic glucocorticoids were strongly associated with coxib initiation.

Prescriber responsibility

General practitioners issued 86–91% of the NSAID prescriptions to patients with first-time cardiovascular disease between 1996 and 2017, while hospital prescribers were responsible for 7.3–12% and private practicing specialists ≤1.1% of NSAID prescribing (*Figure 3*). The figures for general practice were driven by ibuprofen (84–89%), naproxen (90–93%), and diclofenac (87–93%), but even higher for meloxicam (77–100%), etodolac (94–97%), and etoricoxib (93–100%). An exception was celecoxib with a lower proportion prescribed in general practice (56–90%) and a higher proportion of hospital prescribers (6.8–44%).

Discussion

The prevalence of NSAID initiation after first-time cardiovascular disease has declined in Denmark by close to 3% annually since 2002. This trend was observed for all major cardiovascular diseases, but strongest for patients with heart failure and ischaemic heart disease. The overall trends, however, reflected large differences in the temporal use of individual NSAIDs. As recommended by clinical guidelines when NSAID use cannot be avoided, treatment duration was shortened, initiation of older and newer COX-2 inhibitors declined, and naproxen and low-dose ibuprofen use increased. Rheumatic, obesity, and pain-related comorbidity predicted NSAID initiation in general, whereas factors associated with gastrointestinal bleeding risk (older age, antiulcer drugs, systemic glucocorticoids, and severe comorbidity burden) predicted use of coxibs specifically. Despite declining overall trends, the prevalence of contraindicated NSAID initiation after newly diagnosed cardiovascular disease remained high, with general practice being the health care sector responsible for the vast majority of all NSAID prescriptions.

Previous literature

Drug utilization studies are fundamental to identify and improve potential irrational drug prescribing habits. Few studies have examined nationwide trends and predictors of NSAID use in patients with cardiovascular disease. The available evidence, as summarized below, all indicate high-prevalent use of NSAID in cardiovascular patients across Europe, USA, and Canada, with a concerning higher proportion of older and newer COX-2 inhibitors used in these countries compared with Denmark.

Following a 2005 FDA warning,[2] initial studies of the rate of potentially inappropriate medication prescriptions in the USA decreased from 46% in 2006–2007 to 41% in 2009–2010,[18] among which the prevalence of NSAID prescriptions showed the largest decline compared with other drug categories.[18] However, subsequent data from the US National Health and Nutrition Examination Survey 2009–2010 on self-reported NSAID use in patients with pre-existing cardiovascular disease showed higher prevalence of NSAID use among patients with vs. without cardiovascular disease (43% vs. 24%), consistent for both prescription (10% vs. 4%) and OTC use (38% vs. 22%). Fifty-four percent of cardiovascular patients reported prescribed NSAID use for 1 year or longer compared with 46% among those without cardiovascular disease.[19] When adjusting for age, sex, race, and education, the odds for NSAID use was overall 2.1-fold increased among individuals with vs. without cardiovascular disease, but with substantial variation within cardiovascular disease subtypes (1.6-fold for ischaemic heart disease and 0.8-fold for congestive heart failure).[19] Another US study showed that prescribed NSAID for musculoskeletal pain management in subsequent years (2010–2013) increased from 14% to 16% in patients with hypertension, heart failure, or chronic kidney disease.[20]

A Canadian cohort study during 2012–2016 of 814 049 elderly patients ≥65 years with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease showed an overall declining trend in prescription NSAID use over time, with an absolute reduction of 2.1% from 2012 (10%) to 2016 (8.1%).[21] The prescribing rate decreased relatively by 2.0% per quarter during the period.[21] Almost one-fifth of all prescribed NSAID was coxibs (18%).[21]

An Italian study during 2008–2011 of 511 989 elderly patients ≥65 years with cerebro-cardiovascular disease showed a 21–48% prevalence of NSAID use across five different regions.[22] The prevalence of NSAID use decreased from 31% in 2008 to 23% in 2011 and was highest for nimesulide (9.6%) and diclofenac (7.5%), followed by ketoprofen (5.4%), ibuprofen (5.3%), coxibs (3.8%), ketorolac (2.4), piroxicam (1.9%), aceclofenac (1.3%), meloxicam (0.9%), and naproxen (0.7%). The highest proportion of new NSAID use was nimesulide (22% in 2011), diclofenac (21% in 2011), and coxibs (9% in 2011), which sum COX-2 selective agents to at least 30% of all NSAIDs in 2011.[22]

Most recent, a German study compared diclofenac use before and after implementation of European risk minimization measures in 2013.[9] The study focused on the prevalence of congestive heart failure, ischaemic heart disease, peripheral arterial disease, and cerebrovascular disease among diclofenac initiators and found, similar to our study, that although use of diclofenac declined, the prevalence of NSAID initiators with cardiovascular contraindications remained high (12% in 2014).[9] The study also reported on the diclofenac prescribers in general (not only for cardiovascular patients) and found 61% prescribed by general practitioners, 22% by orthopaedists, 6.8% by surgeons, and 9.1% by others.[9]

Interpretation of trends

While NSAIDs are generally now considered contraindicated in patients with cardiovascular disease (except pericarditis),[1] it was not the case through the entire study period. The declining trends in prevalence since 2002 therefore likely in part reflect temporal changes in clinical guidelines and regulatory actions.

The FDA requested in 2005 revised NSAID labelling to include a boxed warning about the potential increased risk of cardiovascular disease.[2] FDA warnings were further strengthened in 2015.[3] The EMA raised first concerns about the cardiovascular risks of coxibs as a class in 2005, and in 2006 also diclofenac (particularly at a high dose of 150 mg daily) and high-dose ibuprofen (2400 mg daily).[4] As smaller risks with use of other NSAIDs could not be excluded, the EMA recommended use of NSAIDs at the lowest effective dose for the shortest possible duration.[4] Updated risk assessments were carried out by the EMA in the following years: in 2012, previous conclusions were confirmed but also added that naproxen may be associated with lower thromboembolic risk than other NSAIDs although small risks cannot be excluded[5]; in 2013, a firm conclusion was drawn that diclofenac use was associated with an elevated risk of acute cardiovascular events[6]; and in 2015 that ibuprofen in high dose (≥2400 mg/day) increased cardiovascular risks to a degree similar to coxibs and diclofenac, that moderate dose (1200–2400 mg/day) likely increased risk in a dose-dependent manner, and that low dose (≤1200 mg/day) did not increase risk.[7] Dexibuprofen was expected to have similar cardiovascular risk as high-dose of ibuprofen when used at equipotent doses. The clinical impact of a potential reduced antiplatelet drug effect of acetylsalicylic acid when administered concomitantly with ibuprofen/dexibuprofen remains debated.[7] Latest the EMA called in 2017 again for another safety assessment of diclofenac.[23] As a result, data accumulate on the cardiotoxicity of diclofenac,[8,24] prompting recent withdrawal of OTC diclofenac also in Norway and Sweden,[25] although the final EMA report is yet to be made public.

The Danish Medicines Agency issued the first national warning about diclofenac in 2008 after which OTC diclofenac was prohibited.[12] Latest, the European Society of Cardiology stated in 2016 their position that NSAIDs should in general not be used in patients with established or at high risk of cardiovascular disease and when prescribing traditional NSAIDs, older selective COX-2 inhibitors such as diclofenac, should be avoided.[1] The Danish Society for Cardiology has adapted this position.[26]

The overall trends in NSAID use paralleled widely with trends for the whole Danish population[8,12] and were thus not specific or markedly better for patients with cardiovascular disease. Nonetheless, considering the changes to national and international recommendations above, our results are encouraging in showing a substantial and ongoing decline in NSAID use since 2002, with a particular decline in use of coxibs after 2004 and diclofenac after 2008, but also a beginning decline in ibuprofen use after 2014. Moreover, the general shift away from selective COX-2 inhibitors towards ibuprofen/naproxen supports adherence to guideline recommendations when NSAID cannot be avoided. Finally, the general reduction in treatment

duration and shift from predominantly moderate/high to low-dose ibuprofen supports the EMA recommendation of lowest effective dose for the shortest possible duration.[4,5]

The relatively short delay from guideline changes to clinical implications in Denmark, likely reflected a combination of supportive digital health solutions and a long tradition for and adherence to national guidelines.[10] Still, it should be noted that adherence to guidelines does not alone explain the trend in use as the decline started in 2002, that is, before the first FDA/EMA (2005)[2,4] and Danish (2008)[12] recommendations. The establishment of the Institute for Rational Pharmacotherapy in Denmark in 1999 with its impact on general practitioners' prescribing habits and enforcement of paracetamol as the first-line drug for pain management likely contributed to reduce NSAID use in the early period of the decline.[27]

Despite these positive trends, the recommendation from the European Society of Cardiology to consider NSAIDs contraindicated in patients with cardiovascular disease is clear.[1] A continuous 1-year prevalence of NSAID use in 2017 close to 15%, increasing to above 30% within 5 years, is therefore too high. Part of the explanation for this apparent high-prevalent contraindicated use is likely that NSAIDs previously was thought to be risk-neutral in low doses and short treatment periods. Both assumptions are incorrect as general rules. While ibuprofen in low doses (≤1200 mg/day) according to EMA recommendations are considered safe for low-risk populations,[7] it is not the case in the presence of cardiovascular disease.[1] The cardiovascular risks of older COX-2 inhibitors as diclofenac are clinical relevant even at low doses and also short treatment durations.[24] The adverse event rate thus increases at time of initiation and accumulate thereafter.

Strengths and limitations

The 22-year nationwide inclusion period provided high statistical precision and enabled subgroup analyses of individual cardiovascular diseases and NSAIDs. The population-based design in the setting of a tax supported, universal healthcare system largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups.[10] The prescription data, including prescriber information, are considered valid.[14,17] Moreover, NSAID use was not based on written prescriptions, but on actual dispensing at pharmacies.[14] Required copayments increased the likelihood of compliance, although any non-compliance would not influence the estimated proportion of patients prescribed NSAIDs. Any OTC use of ibuprofen or diclofenac would only underestimate results.[12]

The algorithms identifying the individual cardiovascular diseases have all been validated and found adequate with positive predictive values around 93% for angina pectoris,[15] 97% for MI (96% for STEMI and 92% for NSTEMI),[15] 95% for atrial fibrillation/flutter,[15] 76%–84% for heart failure,[15,28] 88% for venous thromboembolism,[15] 97% for ischaemic stroke,[13] 96% for valvular heart disease,[15] and 90% infective endocarditis.[16] The mortality and migration data were accurate and complete.[11]

Implications

The persistent high-prevalent contraindicated NSAID use in patients with newly diagnosed cardiovascular disease is a major public health concern that needs attention from health care authorities and relevant medical societies. A novel finding in our study was the assessment of prescriber responsibility, which documents the central role of general practice. Although general practitioners should be acknowledged for their contributions to overall declining and more differentiated NSAID use in patients with cardiovascular disease as described above, the burden of minimizing the remaining contraindicated NSAID use, however, also lies in general practice given that 9 out 10 such prescriptions are issued here.

Conclusions

Following regulatory actions and changes in clinical guidelines, initiation of NSAIDs after newly diagnosed cardiovascular disease has declined consistently in Denmark since 2002, and most for patients with heart failure or ischaemic heart disease. Temporal changes in prescribing behaviour towards shorter treatment periods, less use of COX-2 inhibitors—in particular diclofenac and coxibs—and more naproxen and low-dose ibuprofen, indicate adherence to clinical guidelines when NSAIDs cannot be avoided. Despite these overall encouraging utilization trends, contraindicated NSAID use remain too common, being initiated in more than one in 10 cardiac patients within a year after diagnosis, increasing to above three in 10 patients within 5 years. Safer alternatives to pain relief should always be sought out before initiating NSAIDs in the presence of cardiovascular disease. Interventions to promote appropriateness of use, in particular targeted at general practitioners, are warranted.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

Acknowledgements

Martin Thomsen Ernst is acknowledged for assisting with data management and analysis.

Data permission

The study was approved by the Danish Data Protection Agency.

Funding

M.S. is supported by the Novo Nordisk Foundation (NNF19OC0054908).

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval

No ethical committee approval was needed.

Data sharing

Data cannot be shared according to Danish law. Data can be obtained upon application to the Danish Health Data Authority. Cohort definition as well as statistical codes may be shared upon reasonable request.

Patient and public involvement

No patient involvement.

Conflict of interest: none declared.

References

1. Schmidt M, Lamberts M, Olsen AM, Fosbøll EL, Niessner A, Tamargo J, Rosano G, Agewall S, Kaski JC, Kjeldsen K, Lewis BS, Torp-Pedersen C. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J* 2016;**37**:1015–1023.
2. U.S. Food & Drug Administration. COX-2 Selective (Includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). 2005.
3. U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA Strengthens Warning that Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can Cause Heart Attacks or Strokes. 2015.
4. European Medicines Agency. Public CHMP Assessment Report for Medicinal Products Containing Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). EMEA/H/A-5.3/800. 2006.
5. European Medicines Agency. Assessment Report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Cardiovascular Risk. EMA/696137/2012. 2012.
6. European Medicines Agency. Assessment Report for Diclofenac Containing Medicinal Products (Systemic Formulations). EMA/544760/2013. 2013.
7. European Medicines Agency. Assessment Report. Ibuprofen and Dexibuprofen Containing Medicinal Products (Systemic Formulations). EMA/348171/2015. 2015.
8. Kristensen KB, Karlstad Ø, Martikainen JE, Pottegård A, Wastesson JW, Zoega H, Schmidt M. Nonaspirin nonsteroidal antiinflammatory drug use in the Nordic countries from a cardiovascular risk perspective, 2000-2016: a drug utilization study. *Pharmacotherapy* 2019;**39**:e1001388–11.
9. Scholle O, Kollhorst B, Haug U. Are prescribers not aware of cardiovascular contraindications for diclofenac? A claims data analysis. *J Intern Med* 2020;**287**:171–179.
10. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, Sørensen HT. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;**11**:563–591.
11. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–549.
12. Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other non-steroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012. *Clin Epidemiol* 2014;**6**:155–168.
13. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen H. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.
14. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: the Danish National Prescription Registry. *Int J Epidemiol* 2017;**46**:798–798.
15. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832.
16. Østergaard L, Adelborg K, Sundbøll J, Pedersen L, Loldrup Fosbøl E, Schmidt M. Positive predictive value of infective endocarditis in the Danish National Patient Registry: a validation study. *Epidemiol Infect* 2018;**146**:1965–1967.
17. Rasmussen L, Valentin J, Gesser KM, Hallas J, Pottegård A. Validity of the prescriber information in the Danish National Prescription Registry. *Basic Clin Pharmacol Toxicol* 2016;**119**:376–380.
18. Davidoff AJ, Miller GE, Sarpong EM, Yang E, Brandt N, Fick DM. Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria. *J Am Geriatr Soc* 2015;**63**:486–500.
19. Castelli G, Petrone A, Xiang J, Shrader C, King D. Rates of nonsteroidal anti-inflammatory drug use in patients with established cardiovascular disease: a retrospective, cross-sectional study from NHANES 2009-2010. *Am J Cardiovasc Drugs* 2017;**17**:243–249.
20. Rosenberg A, Agiro A, Gottlieb M, Barron J, Brady P, Liu Y, Li C, DeVries A. Early trends among seven recommendations from the choosing wisely campaign. *JAMA Intern Med* 2015;**175**:1913–1920.
21. Bouck Z, Mecredy GC, Ivers NM, Barua M, Martin D, Austin PC, Tepper J, Bhatia RS. Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease. *JAMA Intern Med* 2018;**178**:1516–1510.
22. Roberto G, Bartolini C, Rea F, Onder G, Vitale C, Trifirò G, Kirchmayer U, Chinellato A, Lucenteforte E, Corrao G, Mugelli A, Lapi F, Gini R; on behalf of the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE). NSAIDs utilization for musculoskeletal indications in elderly patients with cerebro/cardiovascular disease. *Eur J Clin Pharmacol* 2018;**74**:637–637.
23. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Call for Information on Effectiveness of Risk Minimisation on Diclofenac (Referral EMEA/H/A-31/1344). 2017.
24. Schmidt M, Sørensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ* 2018;**362**:k3426.
25. Swedish Medical Products Agency. Diclofenac tablets become prescription only drugs. https://www.lakemedelsverket.se/sv/nyheter/tabletter-och-kapslar-med-diklofenak-blir-receptbelagda (15 July 2020).
26. Schmidt M, Olsen AM, Fosbøl EL, Schou M, Søndergaard HM, Soja AMB, Jacobsen S, Poulsen HE, Gislason GH. [NSAID use in patients with cardiovascular disease—a position paper from the Danish Society of Cardiology]. *Cardiologisk Forum* 2016;**1**:1–6.
27. Gudex C, Hoffmann M, Brørs O, Dahlqvist R. [GPs' perceptions of the Institute for Rational Pharmacotherapy]. *Ugeskr Laeger* 2009;**171**:522–526.
28. Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0-I50.9) in the Danish National Patient Register. *Dan Med J* 2018;**65**:A5470.

Paper XI

BMJ

BMJ 2011;343:d3450 doi: 10.1136/bmj.d3450

RESEARCH

Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study

Morten Schmidt *junior research fellow*[1], Christian F Christiansen *senior registrar*[1], Frank Mehnert *biostatistician*[1], Kenneth J Rothman *professor*[2 3], Henrik Toft Sørensen *professor*[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, 8200 Aarhus N, Denmark; [2]RTI Health Solutions, Research Triangle Institute, Research Triangle Park, NC, USA; [3]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Objectives To examine the risk of atrial fibrillation or flutter associated with use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclo-oxygenase (COX) 2 inhibitors.

Design Population based case-control study using data from medical databases.

Setting Northern Denmark (population 1.7 million).

Participants 32 602 patients with a first inpatient or outpatient hospital diagnosis of atrial fibrillation or flutter between 1999 and 2008; 325 918 age matched and sex matched controls based on risk-set sampling.

Main outcome measures Exposure to NSAID use at the time of admission (current use) or before (recent use). Current use was further classified as new use (first ever prescription redemption within 60 days before diagnosis date) or long term use. We used conditional logistic regression to compute odds ratios as unbiased estimates of the incidence rate ratios.

Results 2925 cases (9%) and 21 871 controls (7%) were current users of either non-selective NSAIDs or COX 2 inhibitors. Compared with no use, the incidence rate ratio associating current drug use with atrial fibrillation or flutter was 1.33 (95% confidence interval 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for COX 2 inhibitors. Adjustments for age, sex, and risk factors for atrial fibrillation or flutter reduced the incidence rate ratio to 1.17 (1.10 to 1.24) for non-selective NSAIDs and 1.27 (1.20 to 1.34) for COX 2 inhibitors. Among new users, the adjusted incidence rate ratio was 1.46 (1.33 to 1.62) for non-selective NSAIDs and 1.71 (1.56 to 1.88) for COX 2 inhibitors. Results for individual NSAIDs were similar.

Conclusions Use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation or flutter. Compared with non-users, the association was strongest for new users, with a 40-70% increase in relative risk (lowest for non-selective NSAIDs and highest for COX 2 inhibitors). Our study thus adds evidence that atrial fibrillation or flutter needs to be added to the cardiovascular risks to be considered when prescribing NSAIDs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammatory conditions and pain.[1] By inhibiting cyclo-oxygenase (COX)-1 mediated production of prostaglandins,[1] non-selective NSAIDs are known to cause gastrointestinal toxicity[1] and a variety of nephrotoxic syndromes.[2] An alternative is selective COX 2 inhibitors, available in the form of older or newer agents.[3] The newer COX 2 inhibitors, introduced into clinical practice in 1998, were developed as NSAIDs with an improved gastrointestinal side effect profile.[1] The cardiovascular safety of all marketed newer COX 2 inhibitors requires thorough evaluation in view of the increased cardiovascular[4-6] and renal risk[2] reported for several of these drugs.

Atrial fibrillation is the most common rhythm disorder observed in clinical practice. It more than doubles in prevalence during each advancing decade of life, from 0.5% at age 50-59 years to

Correspondence to: M Schmidt msc@dce.au.dk

Extra material supplied by the author (see http://www.bmj.com/content/343/bmj.d3450/suppl/DC1)

Webappendix: Registry codes
Webfigure: Required strength of an unmeasured confounder
Webtable 1: Characteristics of cases with atrial fibrillation or flutter and controls from northern Denmark, 1999-2008, according to their NSAID use
Webtable 2: Adjusted incidence rate ratios with 95% confidence intervals associating NSAID use and atrial fibrillation or flutter, stratified by age group, cardiovascular disease, chronic kidney disease, and rheumatoid arthritis
Webtable 3: Adjusted incidence rate ratios for atrial fibrillation or flutter comparing use of individual NSAIDs with ibuprofen as referent exposure
Webtable 4: Association between NSAID use and atrial fibrillation or flutter, overall and restricted to patients without systemic inflammatory conditions
Webtable 5: Association between NSAID use by type of medication and atrial fibrillation or flutter, overall and restricted to patients without systemic inflammatory conditions

above 10% at age 80-89 years.[7] It is associated with increased mortality and morbidity, mainly due to haemodynamic impairments that exacerbate or even cause heart failure,[8] and a threefold to fourfold increased risk of thromboembolic stroke.[9]

Use of NSAIDs may increase the risk of atrial fibrillation through its adverse renal effects—for example, fluid retention, electrolyte disturbances, and blood pressure destabilisation [2 6]—but the evidence for such effects is limited.[10 11] Although no original research has been published on COX 2 inhibitors and atrial fibrillation, a meta-analysis summarised data from 114 clinical trials and found that rofecoxib was associated with an increased risk of cardiac arrhythmias (relative risk 2.90, 95% confidence interval 1.07 to 7.88).[10] Because the meta-analysis included only 286 incident arrhythmias, precision was low and risk of arrhythmia subtypes such as atrial fibrillation could not be examined.[10] Recently, traditional NSAIDs (that is, non-selective NSAIDs and older COX 2 inhibitors) have been associated with increased risk of chronic atrial fibrillation (incidence rate ratio 1.44, 1.08 to 1.91).[11]

Any confirmed association between use of NSAIDs and atrial fibrillation would have major clinical and public health implications. Older people are of special concern because the prevalence of use of NSAIDs and the incidence of atrial fibrillation increase with age. To address the limitations of the existing literature, we conducted a large population based case-control study examining whether and to what extent use of NSAIDs increases the risk of atrial fibrillation or flutter.

Methods

Setting

We conducted this population based case-control study in northern Denmark, which has 1.7 million inhabitants (30% of the Danish population). Since 1998 complete computerised prescription records have been available for this population.[12] Our study period encompassed 1 January 1999 to 31 December 2008, which yielded at least one year of prescription history for all study participants.

The Danish National Health Service provides universal tax supported healthcare, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications, including NSAIDs.[13] Most patients with atrial fibrillation or flutter are diagnosed during a hospital admission or at a hospital outpatient clinic.[14] Very few cardiologists work outside the public hospital system in Denmark. Linkage among national registries is possible using the unique central personal registry number assigned to each Danish citizen at birth and to residents on immigration.[15]

Patients with atrial fibrillation or flutter

We used the Danish National Registry of Patients,[16] covering all non-psychiatric hospitals since 1977 and emergency room and outpatient clinic visits since 1995, to identify all patients with a first time inpatient or outpatient diagnosis of atrial fibrillation or flutter during the study period. Because atrial fibrillation and flutter share risk factors and to some degree pathophysiology,[17 18] we collapsed them into one disease entity.[17 18] More than 90% of patients registered with these codes had atrial fibrillation.[19] We considered the date of the first diagnosis of atrial fibrillation or flutter to be the index date for cases.

Population controls

We used the Danish Civil Registration System to select 10 population controls for each case, matched for age and sex.[15] This registry has recorded vital statistics for the Danish population since 1968 with daily updates.[15] We selected controls using risk set sampling.[20] Controls were assigned an index date identical to that of corresponding cases.

Non-steroidal anti-inflammatory drug use

We used the prescription database in the region[12] to identify prospectively all prescriptions of NSAIDs redeemed by cases and controls before their index date. Except for ibuprofen in the 200 mg tablet dose, all non-aspirin NSAIDs are available by prescription only.[13] Regular users of ibuprofen typically are registered in the database because the cost automatically is partly refunded when the drug is prescribed by a doctor.[13]

We identified prescriptions for non-aspirin non-selective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid), older COX 2 inhibitors (diclofenac, etodolac, nabumeton, and meloxicam), and newer COX 2 inhibitors (celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib).[3 21] Because of overlapping COX 2 selectivity, we collapsed the groups of older and newer COX 2 inhibitors into one group.[3] Associated ATC (Anatomical Therapeutic Chemical Classification System) codes are provided in the web appendix.

We defined current users of NSAIDs as people who redeemed their most recent prescription within 60 days before their index date. We chose an exposure window of 60 days to capture most current users, as prescriptions of NSAIDs are seldom provided for more than 60 days at a time in Denmark.[22] Some side effects may arise shortly after starting treatment[2 6] and inclusion of long term users, who are more likely to tolerate the drug, could lead to underestimation of the association with atrial fibrillation or flutter.[23] We therefore categorised current users into two groups: new users, defined by having redeemed their first ever prescription within 60 days before the index date, and long term users, defined by having redeemed their first prescription more than 60 days before the index date. We defined people who had redeemed their most recent prescription 61-365 days before the index date as recent users. We defined people with no redeemed prescriptions 365 days before their index date as non-users (reference group).

Patient characteristics

Because a number of risk factors for atrial fibrillation or flutter can also be associated with use of NSAIDs,[24 25] we obtained data from the Danish National Registry of Patients on any previous hospital diagnosis since 1977 of diseases that may increase the risk of atrial fibrillation or flutter (listed in table 1).[24 25] To increase the sensitivity of the diagnoses, we used the prescription database[12] to obtain data on any use since 1998 of relevant drugs. Furthermore, we identified current use of oral glucocorticoids, because these are associated with increased risk of atrial fibrillation or flutter.[26] Associated ICD (International Classification of Diseases) and ATC codes are provided in the web appendix.

Statistical analysis

Initially, we created contingency tables for the main study variables from which we calculated the frequency of cases and controls in categories of exposure and other variables. We then stratified the contingency tables according to each of the

potential confounding factors listed in table 1.[27] Next we used conditional logistic regression to compute odds ratios for atrial fibrillation or flutter among current, new, long term, and recent users of non-selective NSAIDs or COX 2 inhibitors.[28] Current users of both subclasses of the drugs were treated as a separate group. Because we used risk set sampling of controls, the odds ratios estimated the incidence rate ratios.[28] We fitted models controlling for the potential confounding factors listed in table 1. We repeated the analyses in predefined subgroups of sex, age, and presence or absence of cardiovascular disease, chronic kidney disease, osteoarthritis, rheumatoid arthritis, or systemic connective tissue disease. In the stratified analysis, we disregarded the matching and performed unconditional logistic regression with additional adjustments for the matching factors. We repeated the overall analysis for the six most frequently prescribed NSAIDs. To evaluate clinically relevant heterogeneity across drugs, we then compared individual NSAIDs directly using ibuprofen as the referent exposure. Because all patients needed pain relief, this comparison was likely to reduce confounding by indication. We used the tablet dose from the last redeemed prescription as a proxy for the total daily dose and examined the effect associated with low and high tablet dose.

In four secondary analyses we restricted cases to patients with atrial fibrillation or flutter: who had their diagnosis listed as the first diagnosis in the discharge summary, thereby detecting the potential effect of diagnostic surveillance bias among NSAID users;[28] who had never redeemed a prescription for digoxin or a vitamin K antagonist before their index date, thereby excluding patients with atrial fibrillation or flutter treated by their general practitioner with no previous hospitalisation; who underwent cardioversion within one year after the index date, thereby relating use of NSAIDs to disease severity; or who had no cancer, chronic obstructive pulmonary disease or asthma, inflammatory bowel disease, rheumatoid or psoriatic arthritis, or systemic connective tissue disease, thereby reducing confounding from systemic inflammation. Finally, using a rule-out approach,[29] we estimated how strongly a single unmeasured binary confounder would need to be associated with use of NSAIDs and atrial fibrillation or flutter to fully explain our findings.[29]

Results

Patient characteristics

Descriptive data are presented in table 1 for the 32 602 cases and 325 918 population controls (web table 1 divides cases and controls according to their use of NSAIDs). Among the cases, 27 984 (85.8%) were diagnosed with atrial fibrillation or flutter during hospital admission, 4220 (12.9%) at an outpatient clinic, and 398 (1.2%) at an emergency department. The median age was 75 years, and 54% were male. Among cases, 80.1% had been diagnosed previously with cardiovascular disease compared with 58.7% of controls. Cancer, chronic obstructive pulmonary disease or asthma, diabetes mellitus, glucocorticoid use, hyperthyroidism, and osteoarthritis were also more common among cases than controls.

Risk of atrial fibrillation or flutter

As table 2 shows, the age and sex matched incidence rate ratio associating current drug use with atrial fibrillation or flutter was 1.33 (95% confidence interval 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for COX 2 inhibitors compared with non-users. The crude incidence rate ratios, dissolving the matched sets, were similar to the matched incidence rate ratios, indicating that the matched factors were on balance not associated with the exposure. Adjustment for confounders reduced the incidence rate ratio to 1.17 (1.10 to 1.24) for non-selective NSAIDs and 1.27 (1.20 to 1.34) for COX 2 inhibitors. Older and newer COX 2 inhibitors had similar estimates of effect. The increased risk was driven by new users with an adjusted incidence rate ratio of 1.46 (1.33 to 1.62) for non-selective NSAIDs and 1.71 (1.56 to 1.88) for COX 2 inhibitors.

The stratified analyses showed no observable sign of modified measure of effect by sex, osteoarthritis, or systemic connective tissue disease (data not shown). The data indicated that the risk of atrial fibrillation or flutter associated with use of NSAIDs was highest in the elderly (web table 2). Among patients with chronic kidney disease, the adjusted incidence rate ratio was 2.87 (1.53 to 5.38) for new users of COX 2 inhibitors and 1.75 (1.11 to 2.77) for long term users of non-selective NSAIDs (fig 1). Among patients with rheumatoid arthritis, the adjusted incidence rate ratio was 2.49 (1.40 to 4.42) for new users of COX 2 inhibitors and 1.44 (1.01 to 2.03) for long term users of non-selective NSAIDs). Similar to the overall results, the adjusted incidence rate ratio in the secondary analysis restricted to patients without systemic inflammatory conditions was 1.45 (1.29 to 1.63) for new users of non-selective NSAIDs and 1.64 (1.46 to 1.84) for new users of COX 2 inhibitors.

The results for the individual NSAIDs are shown in table 3. The adjusted incidence rate ratio for atrial fibrillation or flutter among new drug users was 1.43 (1.28 to 1.59) for ibuprofen, 1.44 (0.97 to 2.12) for naproxen, 1.73 (1.53 to 1.97) for diclofenac, 1.51 (1.17 to 1.95) for etodolac, 1.83 (1.44 to 2.34) for celecoxib, and 1.59 (1.24 to 2.02) for rofecoxib. In the direct drug comparison (web table 3), no NSAIDs were associated with a lower risk than ibuprofen, and diclofenac in particular conferred higher risk (1.19, 1.00 to 1.40 for new use). The increased effect estimates associated with use of the individual NSAIDs remained raised for both high dose and low dose tablets. High dose tablets of ibuprofen, naproxen, and diclofenac, however, were associated with higher risks than low dose tablets (data not shown).

Supporting the robustness of our findings, the results of the remaining three secondary analyses were similar to the overall results (web tables 4 and 5 show the results for patients without systemic inflammatory conditions). Finally, we estimated that an unmeasured confounder that was twice as frequent among users of NSAIDs as non-users would need to increase the risk of atrial fibrillation or flutter by a factor of six or more to fully explain the results, if no increased risk actually existed (web figure).

Discussion

In this large population based case-control study, we found that patients starting treatment with non-aspirin NSAIDs were at increased risk of atrial fibrillation or flutter compared with those not using NSAIDs. The relative risk increase was 40-70%—equivalent to approximately four extra cases per year of atrial fibrillation per 1000 new users of non-selective NSAIDS and seven extra cases per year of atrial fibrillation per 1000 new users of COX 2 inhibitors.[7] The risk appeared highest in older people. Patients with chronic kidney disease or rheumatoid arthritis were at particularly increased risk when starting treatment with COX 2 inhibitors.

Several issues should be considered when interpreting our results. The study's population based design within the setting of a tax supported universal healthcare system largely removed

selection biases. The positive predictive value of a diagnosis of atrial fibrillation or flutter has been reported to be as high as 97% in the Danish National Registry of Patients.[19] Coding errors were thus unlikely to have had any important influence on our results. We considered cases of atrial fibrillation and flutter together, but our results were driven by atrial fibrillation. Although our findings also related to people treated with cardioversion within one year after first diagnosis, our study was limited by its inability to separate paroxysmal, persistent, and permanent atrial fibrillation.

Data in the prescription database are virtually complete.[12] Although we had to use prescription data as a proxy for actual use of NSAIDs, we did not base drug exposure information on written prescriptions,[11] but on actual dispensing at pharmacies.[12] Requirement of co-payment increased the likelihood of compliance.[13] We lacked information on over the counter use of low dose (200 mg/tablet) ibuprofen, which accounted for 30% of total ibuprofen sales and 15% of total NSAID sales during the study period.[13] This misclassification of drug exposure would most likely have been non-differential and thus would have biased the effect estimates towards the null. Therefore, to the extent such misclassification occurred, our effect estimates are underestimates.

Our results may be affected by confounding from unmeasured variables, particularly by underlying inflammatory conditions leading to use of NSAIDs. Although our estimates did not change when patients with systemic inflammatory conditions were excluded in a subanalysis, we cannot rule out that new users may have more severe underlying inflammation, which may increase the risk of atrial fibrillation.[30] Finally, we lacked data on lifestyle factors, including smoking and body size. Nevertheless, we note that we did adjust partly for lifestyle factors by controlling for history of cancer, chronic obstructive pulmonary disease, and ischaemic heart disease, and that our findings could not be explained by even a strong single unmeasured confounder.

Our study is the first on NSAIDs and atrial fibrillation to include both non-selective NSAIDs and COX 2 inhibitors. A case-control study of patients in the United Kingdom diagnosed in 1996 with chronic atrial fibrillation (n=1035) or paroxysmal atrial fibrillation (n=525) found that contemporary use of traditional NSAIDs was associated with an increased risk of chronic atrial fibrillation (incidence rate ratio 1.44, 95% confidence interval 1.08 to 1.91) and modestly associated with paroxysmal atrial fibrillation (1.18, 0.85 to 1.66)—that is, with magnitude of the association similar to our results.[11] By contrast with our findings, however, in the UK study, long term use of NSAIDs was associated with the largest risk increase for atrial fibrillation.

The meta-analysis,[10] involving 116 094 patients using newer COX 2 inhibitors, had 6394 composite renal outcome events but only 286 composite arrhythmia outcome events, of which ventricular fibrillation, cardiac arrest, and sudden cardiac death accounted for most.[10] Although rofecoxib was associated with an increased relative risk for the composite renal outcome of 1.53 (95% confidence interval 1.33 to 1.76) and the composite arrhythmia outcome (2.90, 1.07 to 7.88),[10] the small number and types of arrhythmias available for analysis did not allow for examination of atrial fibrillation as an outcome. In the present study, we found an increased risk of atrial fibrillation or flutter associated with older and newer COX 2 inhibitors. Notably, COX 2 inhibitors, in particular diclofenac, were associated with higher risks than non-selective NSAIDs, indicating the important pharmacological role of COX 2 inhibition.[3 5]

Use of NSAIDs may increase the risk of atrial fibrillation or flutter through renal and cardiovascular related actions. Five per cent of patients treated with NSAIDs experience nephrotoxic syndromes.[2] Both COX enzymes are expressed in distinct anatomic regions of adult kidney tissue.[2] Thus, inhibition of synthesis of COX derived prostaglandin impairs inflammation and a variety of physiological processes.[2] These changes may induce increases in blood pressure due to expansion of plasma volume, increased peripheral resistance, attenuation of diuretic and antihypertensive drug effects,[2 6] and fluctuation of serum potassium as a result of decreased potassium excretion in the distal nephron.[2] Thus, the increased risk among new users may be attributable to short term adverse renal effects of NSAIDs, which subsequently trigger atrial fibrillation.[24] The finding that patients with chronic kidney disease have a markedly higher risk when starting treatment with COX 2 inhibitors supports this hypothesis.[2 6]

In conclusion, we found that use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation or flutter. Compared with non-users, the association was strongest for new users, with a 40-70% relative risk increase (lowest for non-selective NSAIDs and highest for COX 2 inhibitors). Our study thus adds evidence that atrial fibrillation or flutter need to be added to the cardiovascular risks under consideration when prescribing NSAIDs.

Contributors: MS, CFC, and HTS conceived the study idea. All authors designed the study. FM and HTS collected the data. MS, CFC, and HTS reviewed the literature. MS, CFC, FM, and HTS analysed the data. All authors participated in the interpretation of the findings. MS wrote the initial draft. All authors participated in critical revision of the manuscript for important intellectual content and approved the final version. HTS is the guarantor.

Funding: The study was supported by the Danish Medical Research Council (grant 271-05-0511), the Clinical Epidemiological Research Foundation, Denmark, the Danish Heart Association, and an Aarhus University scholarship. Department of Clinical Epidemiology collaborates within the EU Seventh Framework Programme: Arrhythmogenic potential of drugs (ARITMO). None of the funding sources had a role in the study design, conduct, analysis, or reporting.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any company for the submitted work, although the Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, none of which has any relation to the present study; no relation with organisations that might have an interest in the submitted work in the previous three years, except KJR, who received payment from Bayer for a lecture on venous thromboembolism; no non-financial interests that may be relevant to the submitted work.

Ethical approval: This study was approved by the Danish Data Protection Agency (record no 2004-41-4693) and the Aarhus University Hospital registry board. The study does not involve any contact with patients or any intervention, and it is not necessary to procure permission from the Danish Scientific Ethics Committee.

Data sharing: No additional data available.

1 Laine L. The gastrointestinal effects of non-selective NSAIDs and COX-2-selective inhibitors. *Semin Arthritis Rheum* 2002;32:25-32.
2 Whelton A. Renal aspects of treatment with conventional non-steroidal antiinflammatory drugs versus cyclooxygenase-2-specific inhibitors. *Am J Med* 2001;110:33S-42S.
3 Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat* 2007;82:85-94.
4 Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.

What is already known on this topic

Atrial fibrillation is the most commonly sustained rhythm disorder observed in clinical practice, and NSAIDs are among the most widely used drugs worldwide.

No previous study has examined whether use of COX 2 inhibitors increases the risk of atrial fibrillation.

What this study adds

Use of non-selective NSAIDs or selective COX 2 inhibitors was associated with an increased risk of atrial fibrillation or flutter.

Compared with non-users, the association was strongest for new users, with a 40-70% increase in relative risk (lowest for non-selective NSAIDs and highest for COX 2 inhibitors).

5 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
6 Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005;165:490-6.
7 Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-53.
8 Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure—five more years. *N Eng J Med* 2004;351:2437-40.
9 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
10 Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA* 2006;296:1619-32.
11 De Caterina R, Ruigómez A, Rodríguez LA. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. *Arch Intern Med* 2010;170:1450-5.
12 Ehrenstein V. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;2:273-9.
13 Danish Medicines Agency. Reimbursement of medicines. www.dkma.dk.
14 Guidelines for treatment of atrial fibrillation in primary care in Denmark. [In Danish]www.laegehaandbogen.dk/default.aspx?document=1560.
15 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.
16 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
17 Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. *J Am Coll Cardiol* 2008;51:779-86.
18 Badhwar N, Scheinman MM. Atrial fibrillation after atrial flutter ablation: is atrial fibrillation the primary arrhythmia? *J Cardiovasc Electrophysiol* 2008;19:1151-2.
19 Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med* 2004;164:1993-8.
20 Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 1992;135:1019-28.
21 Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:413-21.
22 Thomsen RW, Riis A, Munk EM, Norgaard M, Christensen S, Sorensen HT. 30-day mortality after peptic ulcer perforation among users of newer selective COX-2 inhibitors and traditional NSAIDs: a population-based study. *Am J Gastroenterol* 2006;101:2704-10.
23 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20.
24 Van der Hooft CS, Heeringa J, van Herpen G, Kors JA, Kingma JH, Stricker BH. Drug-induced atrial fibrillation. *J Am Coll Cardiol* 2004;44:2117-24.
25 Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840-4.
26 Christiansen CF, Christensen S, Mehnert F, Cummings SR, Chapurlat RD, Sørensen HT. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. *Arch Intern Med* 2009;169:1677-83.
27 Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. *Am J Epidemiol* 2000;151:531-9.
28 Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology* . 3rd ed. Lippincott Williams and Wilkins, 2008.
29 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303.
30 Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J* 2005;26:2083-92.

Accepted: 4 March 2011

Cite this as: *BMJ* 2011;343:d3450

Tables

Table 1| Characteristics of patients with atrial fibrillation or flutter and controls from northern Denmark, 1999-2008. Data are number (%)

	Cases (n=32 602)	Controls (n=325 918)
Sex, female	14 993 (46.0)	149 878 (46.0)
Age, years		
0-49	1544 (4.7)	15 506 (4.8)
50-59	3358 (10.3)	33 473 (10.3)
60-69	6277 (19.3)	63 242 (19.4)
70-79	10 273 (31.5)	102 303 (31.4)
>80	11 150 (34.2)	111 394 (34.2)
Comorbidity		
Alcoholism related disorder*	901 (2.8)	6171 (1.9)
Cancer†	4089 (12.5)	31 638 (9.7)
Cardiovascular diseases		
Hospital diagnosis†	26 127 (80.1)	191 200 (58.7)
Use of cardiovascular drugs‡	25 657 (78.7)	188 516 (57.8)
ACE or A2R inhibitors	9820 (30.1)	65 598 (20.1)
Aspirin	14 304 (43.9)	96 294 (29.6)
β blockers	11 598 (35.6)	63 144 (19.4)
Calcium channel blockers	9001 (27.6)	58 259 (17.9)
Diuretics	18 316 (56.2)	126 537 (38.8)
Nitrates	6809 (20.9)	41 147 (12.6)
Statins	3913 (12.0)	27 431 (8.4)
Other antihypertensives	887 (2.7)	6259 (1.9)
Chronic kidney disease†	874 (2.7)	3608 (1.1)
COPD or asthma§	7987 (24.5)	53 448 (16.4)
Current use of oral glucocorticoids‖	2246 (6.9)	10 383 (3.2)
Diabetes mellitus§	3192 (9.8)	22 715 (7.0)
Hyperthyroidism§	1614 (5.0)	10 335 (3.2)
Hypothyroidism§	1263 (3.9)	11 827 (3.6)
Liver disease or chronic pancreatitis†	306 (0.9)	2068 (0.6)
Osteoarthritis†	4249 (13.0)	35 458 (10.9)
Rheumatoid arthritis†	592 (1.8)	4112 (1.3)
Systemic connective tissue disease†	791 (2.4)	5811 (1.8)

ACE=angiotensin converting enzyme; A2R=angiotensin-2 receptor; COPD=chronic obstructive pulmonary disease.

*Acute alcohol intoxication or alcoholism related disease other than those affecting the liver or pancreas.

†Any hospital diagnosis recorded in the Danish National Registry of Patients since 1977.

‡Any redeemed prescription recorded in the prescription database since 1998.

§Any hospital diagnosis since 1977 or any redeemed prescription since 1998 of associated drugs.

‖Prescription redemption within 60 days before the index date.

Table 2| **Association between use of NSAIDs and atrial fibrillation or flutter**

		Incidence rate ratio (95% CI)	
	Number of cases/controls	Unadjusted*	Adjusted†
No use‡	24 593/260 139	1.00 (reference)	1.00 (reference)
Non-selective NSAIDs			
Current use§	1 385/10 985	1.33 (1.26 to 1.41)	1.17 (1.10 to 1.24)
New use||	480/3197	1.59 (1.44 to 1.75)	1.46 (1.33 to 1.62)
Long term use¶	905/7788	1.23 (1.14 to 1.32)	1.05 (0.98 to 1.13)
Recent use**	2 315/20 453	1.20 (1.14 to 1.25)	1.09 (1.04 to 1.14)
COX 2 inhibitors			
Current use§	1 540/10 886	1.50 (1.42 to 1.59)	1.27 (1.20 to 1.34)
Older COX 2 inhibitors	977/6 981	1.49 (1.39 to 1.60)	1.31 (1.22 to 1.40)
Newer COX 2 inhibitors	448/3 119	1.51 (1.37 to 1.67)	1.20 (1.09 to 1.33)
New use||	561/3088	1.93 (1.76 to 2.11)	1.71 (1.56 to 1.88)
Long term use¶	979/7798	1.33 (1.24 to 1.43)	1.10 (1.03 to 1.18)
Recent use**	2 078/18 634	1.18 (1.13 to 1.24)	1.04 (0.99 to 1.09)
Older COX 2 inhibitors	1 396/12 892	1.11 (1.05 to 1.17)	1.01 (0.96 to 1.07)
Newer COX 2 inhibitors	596/5 152	1.23 (1.13 to 1.35)	1.02 (0.94 to 1.12)
Combination††	79/468	1.79 (1.41 to 2.27)	1.47 (1.15 to 1.87)

*Age and sex matched.

†Adjusted for all covariates listed in table 1 using conditional logistic regression.

‡No prescription redemption for any NSAID within 365 days before the index date.

§Prescription redemption within 60 days before the index date.

||Current users who redeemed their first ever prescription within 60 days before the index date.

¶Current users who redeemed their first prescription more than 60 days before the index date.

**Most recent prescription redemption within 61-365 days before the index date.

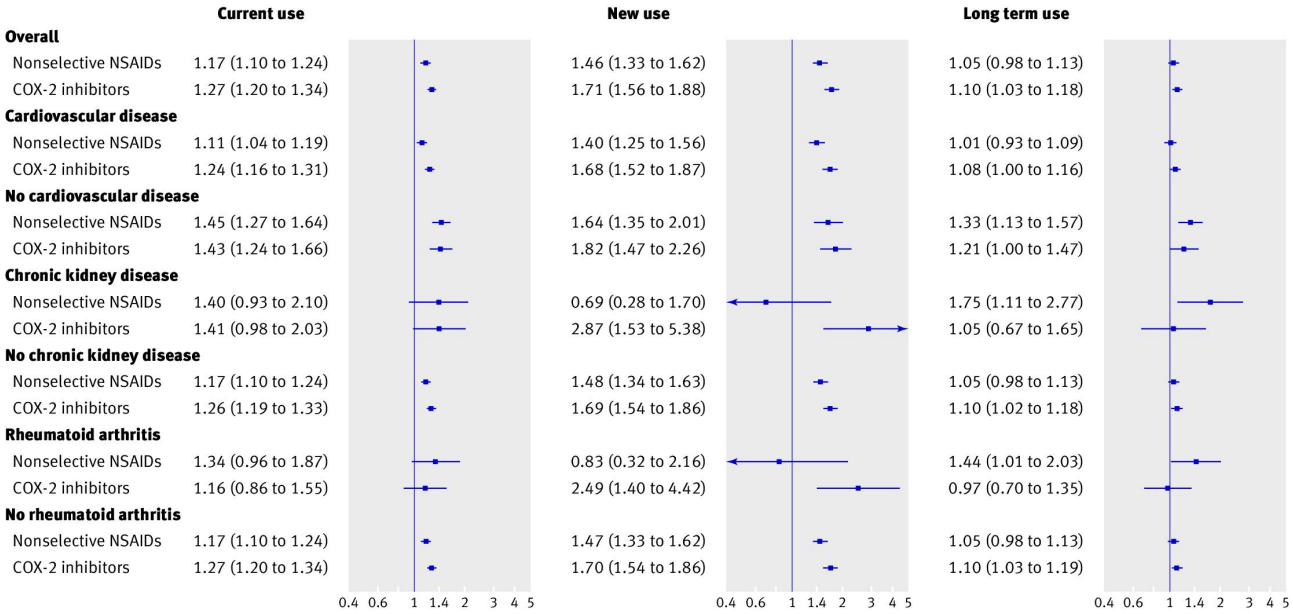
††Current use of both non-selective NSAIDs and COX 2 inhibitors.

Table 3| **Association between use of NSAIDs by type of medication and atrial fibrillation or flutter**

		Incidence rate ratio (95% CI)	
	Number of cases/controls	Unadjusted	Adjusted
No use	24 593/260139	1.00 (reference)	1.00 (reference)
Ibuprofen			
Current use	1044/8484	1.30 (1.22 to 1.39)	1.15 (1.07 to 1.23)
New use	389/2660	1.55 (1.39 to 1.72)	1.43 (1.28 to 1.59)
Long term use	655/5824	1.19 (1.09 to 1.29)	1.02 (0.94 to 1.11)
Recent use	1868/16295	1.21 (1.15 to 1.27)	1.10 (1.05 to 1.16)
Naproxen			
Current use	102/738	1.46 (1.19 to 1.80)	1.28 (1.04 to 1.59)
New use	30/213	1.49 (1.01 to 2.18)	1.44 (0.97 to 2.12)
Long term use	72/525	1.45 (1.13 to 1.85)	1.23 (0.95 to 1.58)
Recent use	171/1390	1.30 (1.11 to 1.53)	1.19 (1.01 to 1.40)
Diclofenac			
Current use	684/4654	1.56 (1.44 to 1.69)	1.38 (1.27 to 1.50)
New use	292/1647	1.88 (1.66 to 2.13)	1.73 (1.53 to 1.97)
Long term use	392/3007	1.38 (1.24 to 1.53)	1.19 (1.07 to 1.33)
Recent use	1021/9527	1.13 (1.06 to 1.21)	1.03 (0.96 to 1.10)
Etodolac			
Current use	223/1730	1.37 (1.19 to 1.57)	1.18 (1.03 to 1.36)
New use	70/451	1.64 (1.28 to 2.11)	1.51 (1.17 to 1.95)
Long term use	153/1279	1.27 (1.07 to 1.50)	1.07 (0.91 to 1.27)
Recent use	285/2605	1.16 (1.03 to 1.31)	1.04 (0.92 to 1.18)
Celecoxib			
Current use	201/1380	1.55 (1.34 to 1.80)	1.22 (1.05 to 1.42)
New use	83/387	2.29 (1.80 to 2.90)	1.83 (1.44 to 2.34)
Long term use	118/993	1.27 (1.05 to 1.53)	0.99 (0.81 to 1.20)
Recent use	287/2487	1.23 (1.09 to 1.40)	1.02 (0.90 to 1.16)
Rofecoxib			
Current use	210/1483	1.51 (1.31 to 1.75)	1.23 (1.06 to 1.43)
New use	80/443	1.93 (1.52 to 2.45)	1.59 (1.24 to 2.02)
Long term use	130/1040	1.33 (1.11 to 1.60)	1.08 (0.89 to 1.30)
Recent use	278/2312	1.29 (1.13 to 1.46)	1.07 (0.94 to 1.22)

See user definitions and description of unadjusted and adjusted model in text and table 2.

Figure



Adjusted incidence rate ratios (95% confidence intervals) for the association between use of NSAIDs and atrial fibrillation or flutter in patients with or without cardiovascular disease, chronic kidney disease, or rheumatoid arthritis

Paper XII

Journal of Thrombosis and Haemostasis, **9**: 1326–1333 DOI: 10.1111/j.1538-7836.2011.04354.x

ORIGINAL ARTICLE

Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism

M. SCHMIDT,*† C. F. CHRISTIANSEN,* E. HORVÁTH-PUHÓ,* R. J. GLYNN,‡ K. J. ROTHMAN§ and H. T. SØRENSEN*

**Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus; †Department of Cardiology, Aarhus University Hospital, Skejby, Denmark; ‡Divisions of Pharmacoepidemiology and Pharmacoeconomics and Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and §RTI Health Solutions, Research Triangle Institute, Research Triangle Park, NC, USA*

To cite this article: Schmidt M, Christiansen CF, Horváth-Puhó E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. *J Thromb Haemost* 2011; **9**: 1326–33.

Summary. *Background:* The association between the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2-selective inhibitors (COX2Is) and the risk of venous thromboembolism (VTE) remains unclear. *Objectives:* To examine this association. *Patients/Methods:* We conducted a population-based case–control study in northern Denmark (population of 1.7 million). Using the National Patient Registry, we identified patients with a first hospital VTE diagnosis during 1999–2006 (n = 8368) and their comorbidities. For each case, we selected 10 controls (n = 82 218) matched by age and sex. From the prescription database, we ascertained the use of NSAIDs at the time of diagnosis (current use) or before (recent use), and comedications. Current use was further classified as new use (first-ever prescription redemption within 60 days before diagnosis date) or long-term use. We used odds ratios from a logistic regression model to estimate incidence rate ratios (IRRs) with 95% confidence intervals (CIs). *Results:* As compared with no use, the adjusted IRR associating current non-selective NSAID use with VTE was 2.51 (95% CI 2.29–2.76), and that for current COX2I use was 2.19 (95% CI 1.99–2.41). Recent users had substantially smaller increases than current users. The adjusted IRRs among long-term users were 2.06 for non-selective NSAIDs (95% CI 1.85–2.29) and 1.92 for COX2Is (95% CI 1.72–2.15). Similarly increased risks were found for unprovoked VTE (occurrence in the absence of pregnancy, cancer, major trauma, fracture or surgery within 3 months preceding the VTE), deep vein thrombosis, pulmonary embolism, and individual NSAIDs. *Conclusions:* The use of non-selective NSAIDs or COX2Is was associated with a two-fold or more increased risk of VTE.

Correspondence: Morten Schmidt, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark.
Tel.: +45 8942 4800; fax: +45 8942 4801.
E-mail: msc@dce.au.dk

Received 21 January 2011, accepted 10 May 2011

Keywords: cardiovascular disease, case–control study, cyclooxygenase-2 inhibitors, epidemiology, non-steroidal anti-inflammatory drugs, venous thromboembolism.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely employed to treat inflammatory conditions and pain [1]. By inhibiting cyclooxygenase (COX)-1-mediated production of prostaglandins [1], non-selective NSAIDs are known to cause gastrointestinal toxicity [1]. An alternative is provided by COX-2-selective inhibitors (COX2Is), which are available in the form of older or newer agents [2]. The newer COX2Is (coxibs), introduced into clinical practice in 1998, were developed as NSAIDs with an improved gastrointestinal side effect profile [1]. The safety of both traditional NSAIDs (i.e. older COX2Is and non-selective NSAIDs) and coxibs is controversial, because several of these drugs increase the risk of arterial thromboembolic events [3]. Whether the use of NSAIDs is related to the risk of venous thrombosis remains unclear [4,5].

Venous thrombosis occurs predominantly in the deep vessels of the lower limbs (deep vein thrombosis [DVT]) and is a common disease process affecting more than one per 1000 persons each year in Western populations [6–8]. It is associated with serious complications such as pulmonary embolism (PE) and post-thrombotic syndrome [6,8]. DVT and PE are collectively referred to as venous thromboembolism (VTE) [6]. VTE incidence increases exponentially with age for both men and women [6], with a recurrence rate as high as 30% within 10 years [6]. The classic risk factors for VTE include immobilization, cancer, fractures, pregnancy, and recent surgery [7,8].

We hypothesized that prothrombotic drugs such as non-aspirin NSAIDs increase the risk of VTE [3]. Whereas conflicting results exist for traditional NSAIDs [4,5], no data exist on the clinical association between coxibs and VTE. Any increased VTE risk associated with NSAID use would have major clinical and public health implications, especially in the elderly, where the prevalence of NSAID use and the

incidence of VTE are high. We conducted a large population-based case–control study examining the association between the use of non-selective NSAIDs or COX2Is and the risk of VTE.

Methods

Setting

We conducted this study in northern Denmark, which has 1.7 million inhabitants (approximately 30% of the Danish population). Since 1998, complete computerized prescription records have been available for this population. Our study period began on 1 January 1999, thus providing at least 1 year of prescription history for all study participants. We included subjects to 31 December 2006.

The Danish National Health Service provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including NSAIDs [9]. Linkage among national registries is possible in Denmark by use of the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration [10].

VTE

We used the Danish National Patient Registry [11], covering all Danish hospitals, to identify all VTE patients defined by an incident inpatient or outpatient diagnosis of lower limb DVT or PE during the study period. This registry contains data on dates of admission and discharge, all discharge diagnoses from non-psychiatric hospitals after 1977, and emergency room and outpatient clinic visits after 1995 [11]. Each discharge is associated with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and the 10th revision (ICD-10) thereafter [11].

We identified both primary and secondary diagnoses of DVT (ICD-8, 451.00; ICD-10, I80.1–3) and PE (ICD-8, 450.99; ICD-10, I26). To reduce potential coding errors, we excluded patients who had an outpatient PE diagnosis with no subsequent inpatient VTE diagnosis. In a secondary analysis, we excluded VTE cases with the following classic risk factors: pregnancy, major trauma, fracture, surgery within 3 months preceding VTE, pre-existing cancer, or a new cancer diagnosis within 3 months after VTE [12]. The date of the first VTE diagnosis was taken as the index date for cases.

Controls

We used the Danish Civil Registration System to select 10 population controls for each case, matched on age and sex [10]. This registry has maintained data on all vital statistics – including date of birth, change of address, date of emigration, and exact date of death – for the Danish population since 1968, with daily updates [10]. We selected controls using risk-set sampling: controls had to be alive and at risk for a first VTE hospitalization on the index date of the case to whom each was matched. Controls were assigned an index date identical to that of corresponding cases.

NSAID use

We used the regional prescription database [13] to identify prospectively all NSAID prescriptions filled by cases and controls before their index date. Pharmacies in Denmark are equipped with electronic accounting systems, which are primarily used to secure reimbursement from the National Health Service. For each filled prescription, the patient's personal registry number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system and the date on which the drug was dispensed are transferred electronically from the pharmacies to the prescription database [13].

Except for ibuprofen in the 200 mg per tablet dose, all non-aspirin NSAIDs are available by prescription only [9]. Regular users of ibuprofen are typically registered in the database, because the cost is partly refunded when the drug is prescribed by a physician.

We identified prescriptions for non-selective non-aspirin NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, tolfenamic acid, and indomethacin), older COX2Is (diclofenac, etodolac, nabumeton, and meloxicam), and newer COX2Is (celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib) [2]. Because of overlapping COX-2 selectivity, we collapsed the groups of older and newer COX2Is into one group named COX2Is [2]. In primary analyses, the exposures consisted of the NSAID subclasses of non-selective NSAIDs and COX2Is. In addition, preplanned analyses were conducted for the six individual NSAIDs most frequently prescribed in the study population. The ATC codes are provided in Data S1.

We defined current NSAID users as persons who filled their most recent NSAID prescription within 60 days before their index date. We chose an exposure window of 60 days to capture most current users, as NSAID prescriptions are seldom provided for more than 60 days at a time in Denmark [14]. Because some side effects may arise shortly after therapy initiation and inclusion of long-term users may lead to underestimation of these complications [15], we further categorized current users into two groups: new users, defined by having filled their first-ever prescription within 60 days before their index date; and long-term users, defined by having filled additional prescriptions 61–365 days before their index date. The long-term user group was of interest because the longer period of use should eliminate any protopathic bias, i.e. the association between new NSAID use and prodromal symptoms related to an incipient occurrence of VTE [16]. We defined persons who had filled their most recent prescription between 61 and 365 days before their index dates as recent users. We defined persons with no filled NSAID prescriptions 365 days before their index date as non-users (reference group).

Other patient characteristics

We obtained information from 1977 from the Danish National Patient Registry [11] on inpatient and outpatient diagnoses of the following conditions that may be associated with NSAID use: cardiovascular disease, chronic obstructive pulmonary disease (COPD) or asthma, diabetes mellitus, liver disease, obesity, osteoarthritis, osteoporosis, renal failure, rheumatoid arthritis, and systemic connective tissue disease. To account further for potential unmeasured confounding from frailty and immobility, we included recent hospital admission as a dichotomous variable defined by any inpatient diagnosis of other diseases within 3 months before the index date. To increase the sensitivity of the diagnoses for diabetes mellitus, pulmonary disease, or cardiovascular disease, we used the prescription database to obtain data on any use since 1998 of the following drugs: antidiabetic drugs (oral antidiabetics and insulin), respiratory drugs, and cardiovascular drugs (angiotensin-converting enzyme inhibitors or angiotensin II receptor inhibitors, aspirin, β-blockers, calcium channel blockers, clopidogrel, diuretics, nitrates, statins, and other antihypertensives). We also obtained data on concurrent use of antipsychotics, hormone replacement therapy, oral glucocorticoids, and vitamin K antagonists, because these drugs affect the VTE risk [5,7,8]. The ICD and ATC codes are provided in Data S1.

Statistical analysis

Initially, we created contingency tables for the main study variables, from which we calculated the frequency of cases and controls in categories of exposures, and medical and demographic variables. We then stratified the contingency tables according to each of the potential confounding factors listed in Table 1.

Next, we used unconditional logistic regression with adjustment for the matching factors of age and sex to estimate odds ratios with 95% confidence intervals (CIs) for VTE among current, new, long-term and recent users of non-selective NSAIDs or COX2Is as compared with non-users. Subjects with current use of both non-selective NSAIDs and COX2Is (51 cases and 86 controls) were included in each subclass analysis. Because we used risk-set sampling of controls, the odds ratios estimate the incidence rate ratios (IRRs) [17]. Afterwards, we fitted models with adjustments for the potential confounding factors listed in Table 1. To examine the effects of different exposure definitions, we repeated the analyses for exposure windows of 15, 30, 90 and 120 days. Stratified analysis was performed on subgroups of sex, age, cancer, cardiovascular disease, diabetes mellitus, musculoskeletal or connective tissue disease (osteoarthritis, rheumatoid arthritis, or systemic connective tissue disease), obesity, trauma or fracture, and recent hospital admission.

To determine whether IRRs differed between all (composite) VTEs and unprovoked VTEs, between VTE subtypes, or between individual NSAIDs, the analyses were repeated for unprovoked VTE, DVT, PE, and the six individual NSAIDs most frequently prescribed. To evaluate clinically relevant heterogeneity across drugs in VTE risk, we added a direct comparison of VTE risk among the individual NSAIDs, using ibuprofen as a referent exposure. Patients with concomitant use of ibuprofen and another NSAID were excluded from this analysis. Because all patients had a need for pain relief, this comparison probably reduced confounding by indication. We identified the tablet dose from the last filled prescription, and examined the impact associated with low and high tablet dose.

We quantified the influence of potential unmeasured confounding on the observed association by means of a rule-out approach [18]. We estimated how strongly a single unmeasured binary confounder would need to be associated with NSAID use and VTE to fully explain our findings. We illustrated this association graphically. We assumed, as a worst case scenario, that the prevalence of such a confounder was 30% in the population and that 10% of the population used NSAIDs. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Characteristics are provided in Table 1 for the 8368 patients with VTE and the 82 218 population controls. Slightly less than half of the cases were male and half were 70 years or older; 48.5% of controls and 61.4% of cases had been diagnosed previously with cardiovascular disease or had used cardiovascular drugs. COPD or asthma, diabetes mellitus, obesity and musculoskeletal and connective tissue diseases were also more common among cases than controls. Among all VTE patients, 4691 had unprovoked VTE. The distribution of characteristics among unprovoked VTE patients was similar to that for the overall group.

Risk of VTE

The age-adjusted and sex-adjusted IRRs for VTE among current users were 3.24 (95% CI 2.98–3.52) for non-selective NSAIDs and 3.10 (95% CI 2.84–3.38) for COX2Is as compared with no use (Table 2). The crude IRRs were similar to the age- and sex-adjusted IRRs. The matching factors were thus not strongly associated with the exposure.

Adjusting for the potential confounders in Table 1 reduced the IRRs to 2.51 (95% CI 2.29–2.76) for non-selective NSAIDs and 2.19 (95% CI 1.99–2.41) for COX2Is. Among new users, confounder adjustment reduced the IRRs for VTE from 5.78 (95% CI 4.97–6.72) to 4.56 for non-selective NSAIDs (95% CI 3.85–5.40) and from 4.40 (95% CI 3.73–5.19) to 3.23 for COX2Is (95% CI 2.69–3.89). Among long-term users, the adjusted IRRs for VTE were 2.06 for non-selective NSAIDs (95% CI 1.85–2.29) and 1.92 for COX2Is (95% CI 1.72–2.15). Although the effect estimates were substantially smaller than for current use, recent use of non-selective NSAIDs (adjusted IRR 1.44, 95% CI 1.33–1.56) and COX2Is (adjusted

Table 1 Characteristics of cases with composite or unprovoked venous thromboembolism (VTE) and population controls from northern Denmark, 1999–2006

	Composite VTE		Unprovoked VTE	
	Cases (%) n = 8368	Controls (%) n = 82 218	Cases (%) n = 4691	Controls (%) n = 40 152
Female sex	4493 (53.7)	44 143 (53.7)	2446 (52.1)	20 627 (51.4)
Age (years)				
< 55	1922 (23.0)	19 115 (23.2)	1227 (26.2)	11 430 (28.5)
55-70	2621 (31.3)	25 889 (31.5)	1423 (30.3)	12 597 (31.4)
≥ 71	3825 (45.7)	37 214 (45.3)	2041 (43.5)	16 125 (40.2)
Median age (IQR)	69 (56-78)	68 (56-78)	67 (54-78)	66 (52-77)
Classic risk factors				
Cancer*	1788 (21.4)	7099 (8.6)	–	–
Pregnancy†	47 (0.6)	151 (0.2)	–	–
Surgery†	2431 (29.1)	4027 (4.9)	–	–
Trauma or fracture†	722 (8.6)	1548 (1.9)	–	–
Other comorbidities‡				
Cardiovascular disease§	5138 (61.4)	39 868 (48.5)	2746 (58.5)	17 765 (44.2)
COPD or asthma§	1994 (23.8)	12 531 (15.2)	1090 (23.2)	5696 (14.2)
Diabetes mellitus§	649 (7.8)	4857 (5.9)	345 (7.4)	2194 (5.5)
Liver disease	103 (1.2)	413 (0.5)	54 (1.2)	180 (0.4)
Obesity	383 (4.6)	1533 (1.9)	196 (4.2)	663 (1.7)
Osteoarthritis	1270 (15.2)	8136 (9.9)	598 (12.7)	3435 (8.6)
Osteoporosis	259 (3.1)	1870 (2.3)	113 (2.4)	800 (2.0)
Renal failure	159 (1.9)	556 (0.7)	64 (1.4)	225 (0.6)
Rheumatoid arthritis	201 (2.4)	1031 (1.3)	106 (2.3)	408 (1.0)
Systemic connective tissue disease	277 (3.3)	1419 (1.7)	139 (3.0)	583 (1.5)
Recent hospital admission¶	2075 (24.8)	3563 (4.3)	582 (12.4)	779 (1.9)
NSAID use**				
Ibuprofen	684 (8.2)	2323 (2.8)	380 (8.1)	1074 (2.7)
Naproxen	37 (0.4)	224 (0.3)	16 (0.3)	116 (0.3)
Diclofenac	385 (4.6)	1413 (1.7)	191 (4.1)	662 (1.6)
Etodolac	105 (1.3)	475 (0.6)	54 (1.2)	210 (0.5)
Celecoxib	115 (1.4)	431 (0.5)	47 (1.0)	183 (0.5)
Rofecoxib	98 (1.2)	352 (0.4)	46 (1.0)	151 (0.4)
Comedication use**				
Antipsychotics	370 (4.4)	1906 (2.3)	216 (4.6)	825 (2.1)
Hormone replacement therapy	488 (5.8)	4213 (5.1)	265 (5.6)	1848 (4.6)
Oral glucocorticoids	832 (9.9)	2092 (2.5)	384 (8.2)	872 (2.2)
Vitamin K antagonists	221 (2.6)	1599 (1.9)	97 (2.1)	676 (1.7)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug. *Pre-existing cancer or a cancer diagnosis within 3 months after the index date. †Any inpatient or outpatient diagnosis within 3 months before the index date. ‡Any inpatient or outpatient diagnosis since 1977. §Any inpatient or outpatient diagnosis since 1977 or any filled prescription since 1998. ¶Any inpatient diagnosis, within 3 months before the index date, other than the diseases listed in Table 1. **Prescription redemption within 60 days before the index date (except for vitamin K antagonists [90 days] and hormone replacement therapy [120 days]).

IRR 1.41, 95% CI 1.30–1.54) was also moderately associated with an increased VTE risk. For all user definitions, the corresponding effect estimates were similarly increased for unprovoked VTE (Table 2) and VTE subtypes (Table 3). The IRRs were higher for DVT than for PE (Table 3).

Current use of individual NSAIDs was associated with composite and unprovoked VTE (Table 4), for both high-dose and low-dose tablets (data not shown), as well as DVT and PE (Table S1), with a magnitude of the association similar to the results for the overall NSAID subclasses. In the direct drug comparison (Table 5), naproxen use was associated with a substantially lower risk of composite VTE (adjusted IRR 0.54, 95% CI 0.36–0.80) and unprovoked VTE (adjusted IRR 0.39, 95% CI 0.23–0.68) than ibuprofen.

From the stratified analysis (Table S2), sex and age seemed to modify the rate ratio estimates for VTE associated with the use of non-selective NSAIDs and COX2Is, with the highest effect among males and persons younger than 55 years. Consistent with the principle that the effect estimates were lower among those at higher baseline risk, the estimates were slightly lower in strata of patients with cardiovascular disease, diabetes mellitus, obesity, osteoarthritis, rheumatoid arthritis, systemic connective tissue disease, and trauma or fracture.

We estimated that an unmeasured confounder that is four times more frequent among NSAID users than non-users would need to increase the risk of VTE by a factor of 17 or more to explain our findings fully, if no increased risk actually existed. Figure 1 illustrates this association for current use of

Table 2 Incidence rate ratios for venous thromboembolism (VTE) associated with non-steroidal anti-inflammatory drug (NSAID) use

	Incidence rate ratio (95% confidence interval)					
	Composite VTE			Unprovoked VTE		
	No. of cases/controls	Unadjusted*	Adjusted†	No. of cases/controls	Unadjusted*	Adjusted†
No use	5483/66 311	1 (reference)	1 (reference)	3202/32 677	1 (reference)	1 (reference)
Non-selective NSAIDs						
Current use‡	794/2971	3.24 (2.98–3.52)	2.51 (2.29–2.76)	438/1365	3.28 (2.92–3.67)	2.71 (2.40–3.05)
New use§	257/543	5.78 (4.97–6.72)	4.56 (3.85–5.40)	152/257	6.19 (5.05–7.59)	5.43 (4.37–6.74)
Long-term use¶	537/2428	2.68 (2.43–2.95)	2.06 (1.85–2.29)	286/1108	2.62 (2.29–3.00)	2.13 (1.84–2.45)
Recent use**	904/6282	1.75 (1.63–1.89)	1.44 (1.33–1.56)	456/3085	1.54 (1.38–1.71)	1.38 (1.24–1.54)
COX2Is						
Current use‡	709/2760	3.10 (2.84–3.38)	2.19 (1.99–2.41)	341/1240	2.76 (2.43–3.13)	2.15 (1.88–2.46)
New use§	198/546	4.40 (3.73–5.19)	3.23 (2.69–3.89)	109/242	4.63 (3.68–5.82)	4.18 (3.29–5.32)
Long-term use¶	511/2214	2.77 (2.50–3.06)	1.92 (1.72–2.15)	232/998	2.31 (1.99–2.67)	1.71 (1.46–2.00)
Recent use**	806/5092	1.91 (1.76–2.07)	1.41 (1.30–1.54)	403/2340	1.75 (1.56–1.95)	1.46 (1.30–1.64)

COX2I, cyclooxygenase-2-selective inhibitor. *Adjusted for the matching factors of age and sex. †Additional adjustments for the potential confounders listed in Table 1 (i.e. cancer, pregnancy, surgery, trauma, fracture, cardiovascular disease, chronic obstructive pulmonary disease, asthma, diabetes mellitus, liver disease, obesity, osteoarthritis, osteoporosis, renal failure, rheumatoid arthritis, systemic connective tissue disease, other inpatient hospital admission within 3 months before VTE, and current use of antipsychotics, hormone replacement therapy, oral glucocorticoids, and vitamin K antagonists). The classic VTE risk factors (cancer, pregnancy, surgery, trauma, and fracture) were not included, per definition, in the model for unprovoked VTE.
‡Prescription redemption within 60 days before the index date.
§Current users who filled their first-ever prescription within 60 days before their index date.
¶Current users who filled their first prescription between 61 and 365 days before their index date.
** Most recent prescription redemption within 61-365 days before the index date.

Table 3 Incidence rate ratios for deep vein thrombosis or pulmonary embolism associated with non-steroidal anti-inflammatory drug (NSAID) use

	Incidence rate ratio (95% confidence interval)					
	Deep vein thrombosis			Pulmonary embolism		
	No. of cases/controls	Unadjusted	Adjusted	No. of cases/controls	Unadjusted	Adjusted
No use	3486/43 304	1 (reference)	1 (reference)	1997/23 007	1 (reference)	1 (reference)
Non-selective NSAIDs						
Current use	568/1907	3.71 (3.36–4.10)	2.98 (2.67–3.32)	226/1064	2.45 (2.11–2.85)	1.74 (1.47–2.06)
New use	194/354	6.87 (5.75–8.22)	5.72 (4.70–6.96)	63/189	3.87 (2.90–5.17)	2.58 (1.85–3.59)
Long-term use	374/1553	2.99 (2.66–3.37)	2.36 (2.07–2.69)	163/875	2.15 (1.81–2.55)	1.55 (1.28–1.88)
Recent use	596/4085	1.83 (1.66–2.00)	1.53 (1.38–1.69)	308/2197	1.63 (1.43–1.85)	1.30 (1.13–1.50)
COX2Is						
Current use	473/1724	3.40 (3.05–3.78)	2.46 (2.19–2.77)	236/1036	2.63 (2.26–3.05)	1.76 (1.48–2.09)
New use	139/340	5.10 (4.17–6.23)	3.93 (3.14–4.90)	59/206	3.32 (2.47–4.44)	2.19 (1.56–3.06)
Long-term use	334/1384	2.97 (2.62–3.37)	2.10 (1.83–2.41)	177/830	2.45 (2.07–2.90)	1.64 (1.35–2.00)
Recent use	539/3214	2.08 (1.88–2.29)	1.55 (1.39–1.73)	267/1878	1.64 (1.43–1.87)	1.20 (1.03–1.40)

COX2I, cyclooxygenase-2-selective inhibitor. See user definitions and description of the unadjusted and adjusted model in the text or in Table 2.

COX2Is. Even stronger confounders would be needed to explain the findings for current use of non-selective NSAIDs or new use of either subclass. The adjusted IRR for current use of non-selective NSAIDs or COX2Is decreased with increasing exposure windows (Table S3).

Discussion

In this population-based case–control study we found that the use of non-selective NSAIDs or COX2Is was associated with an increased risk of VTE. Although new user estimates may, in particular, be influenced by protopathic bias, the association was also observed for long-term users, who would be less susceptible to such bias. The results were consistent, in that similarly increased risks were found for unprovoked VTE, DVT, PE, and individual NSAIDs. Furthermore, as NSAIDs are often prescribed for < 60 days in Denmark, the true VTE risk associated with NSAID use may be even higher, as indicated by the sensitivity analysis.

The present study is the first to examine the association between COX2Is and VTE. Case reports have previously associated celecoxib with DVT [19] and valdecoxib with PE [20], and in a murine model, rofecoxib has also been associated with VTE [21]. Investigating multiple risk factors for VTE, two

Table 4 Incidence rate ratios for composite or unprovoked venous thromboembolism (VTE) associated with individual non-steroidal anti-inflammatory drug use

	Incidence rate ratio (95% confidence interval)			
	Composite VTE		Unprovoked VTE	
	Unadjusted	Adjusted	Unadjusted	Adjusted
No use	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Ibuprofen				
Current use	3.57 (3.26–3.90)	2.79 (2.52–3.08)	3.62 (3.20–4.09)	2.98 (2.62–3.39)
Recent use	1.81 (1.67–1.96)	1.50 (1.37–1.64)	1.59 (1.42–1.79)	1.43 (1.27–1.61)
Naproxen				
Current use	2.01 (1.42–2.86)	1.52 (1.03–2.25)	1.43 (0.85–2.42)	1.23 (0.71–2.13)
Recent use	1.59 (1.24–2.04)	1.28 (0.97–1.68)	1.45 (1.03–2.04)	1.16 (0.81–1.68)
Etodolac				
Current use	2.63 (2.12–3.25)	1.96 (1.55–2.47)	2.52 (1.86–3.40)	1.87 (1.36–2.57)
Recent use	2.35 (1.97–2.80)	1.74 (1.43–2.12)	1.69 (1.29–2.23)	1.38 (1.03–1.84)
Diclofenac				
Current use	3.30 (2.94–3.71)	2.38 (2.09–2.71)	2.95 (2.50–3.48)	2.41 (2.03–2.87)
Recent use	1.93 (1.75–2.13)	1.47 (1.32–1.63)	1.83 (1.59–2.10)	1.58 (1.37–1.82)
Celecoxib				
Current use	3.14 (2.55–3.87)	1.89 (1.49–2.39)	2.44 (1.77–3.38)	1.79 (1.27–2.52)
Recent use	2.21 (1.84–2.65)	1.54 (1.26–1.89)	2.20 (1.69–2.86)	1.58 (1.20–2.08)
Rofecoxib				
Current use	3.27 (2.61–4.10)	2.26 (1.75–2.91)	2.93 (2.10–4.08)	2.12 (1.49–3.04)
Recent use	1.98 (1.63–2.40)	1.32 (1.06–1.64)	1.51 (1.12–2.02)	1.15 (0.84–1.56)

See user definitions and description of the unadjusted and adjusted model in the text or in Table 2.

Table 5 Incidence rate ratios for composite or unprovoked venous thromboembolism (VTE) comparing current use of individual non-steroidal anti-inflammatory drugs with ibuprofen as referent exposure

	Incidence rate ratio (95% confidence interval)			
	Composite VTE		Unprovoked VTE	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Ibuprofen	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Naproxen	0.56 (0.39–0.80)	0.54 (0.36–0.80)	0.39 (0.23–0.66)	0.39 (0.23–0.68)
Etodolac	0.83 (0.66–1.05)	0.84 (0.65–1.08)	0.80 (0.57–1.11)	0.76 (0.54–1.07)
Diclofenac	0.91 (0.79–1.06)	0.86 (0.74–1.01)	0.81 (0.66–0.99)	0.83 (0.67–1.03)
Celecoxib	1.01 (0.80–1.28)	0.84 (0.65–1.09)	0.77 (0.54–1.10)	0.76 (0.53–1.10)
Rofecoxib	1.13 (0.88–1.45)	1.01 (0.77–1.33)	0.95 (0.66–1.36)	0.91 (0.62–1.33)

See current user definition and description of the unadjusted and adjusted model in the text or in Table 2.

previous studies included the use of traditional NSAIDs. In a cohort study from the USA with 148 054 person-years of follow-up, the use of traditional NSAIDs was not associated with VTE after confounder adjustments [4]. A case–control study of 6550 patients, diagnosed with VTE between 1994 and 2000 in the UK, found an elevated VTE risk among current users of traditional NSAIDs (adjusted odds ratio 1.86, 95% CI 1.65–2.10) [5]. Similarly to our findings, the risk increase was related to both DVT and PE [5]. The authors, however, did not find long-term (at least 1 month) NSAID use for an osteoarthritis indication to be associated with VTE, raising the possibility of a protopathic bias [16]. In the present study, we found an association for both new and long-term use of non-selective NSAIDs, older COX2Is, and newer COX2Is. The increased risk was also observed for patients with diseases of the musculoskeletal system or connective tissue, including osteoarthritis. As in previous reports on the arterial thrombotic risk of NSAIDs [3], in our data naproxen had the safest risk profile.

Until recently, atherosclerotic and venous thrombosis have been considered to be two separate disease entities, because arterial thrombi mainly comprise platelets, whereas venous thrombi comprise red blood cells and fibrin [22]. Each of these disorders, however, is a marker of increased risk of the other [22,23]. Consistent with this pattern, we found evidence that all non-aspirin NSAIDs, several of which increase the risk of arterial thrombosis [3], are also associated with an increased risk of venous thrombosis.

In our study, the population-based design in the setting of a tax-supported universal healthcare system largely removed

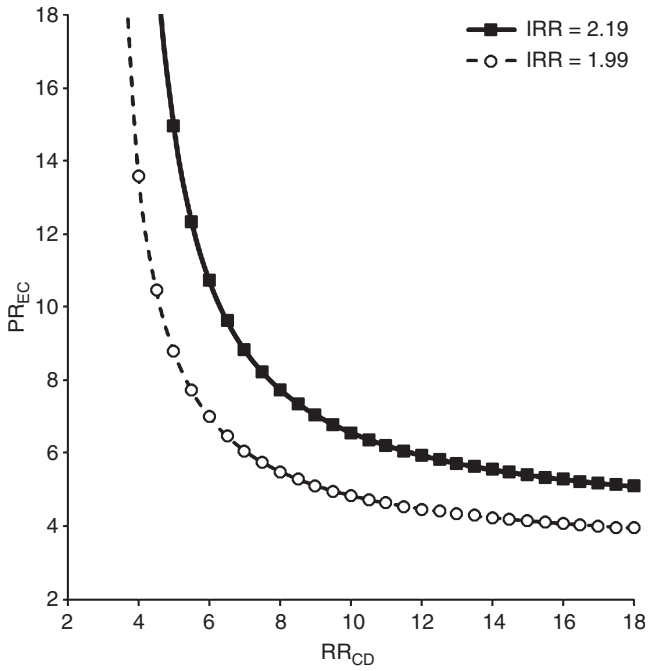


Fig. 1. Required strength of an unmeasured confounder. Sensitivity analysis illustrating how strongly an unmeasured confounder would need to be associated with NSAID use (prevalence ratio for exposure–confounder association [PR_{EC}]) and venous thromboembolism (VTE) (relative risk of the disease in patients with the confounder [RR_{CD}]) to fully explain our estimates. The graphs depict the adjusted incidence rate ratio (IRR) for composite VTE associated with current use of cyclooxygenase-2-selective inhibitors (solid line) along with the lower limit of the 95% confidence interval (dashed line).

selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. The large study population yielded robust and consistent estimates across VTE subtypes and individual NSAIDs. Furthermore, we were able to link different population-based registries with virtually complete data on outpatient visits, hospitalizations, and drug use.

Data in Denmark's regional prescription database are almost complete [13]. Although we had to use prescription data as a proxy for actual NSAID use, we did not base drug exposure information on written prescriptions, but on actual dispensing at pharmacies [13]. Copayment requirements increased the likelihood of compliance. Nevertheless, we lacked information on over-the-counter use of low-dose (200 mg per tablet) ibuprofen, which accounted for 30% of total ibuprofen sales and 15% of total NSAID sales during the study period [14]. Any misclassification of drug exposure, including drugs prescribed for 'as-needed' use, would have biased the effect estimates towards the null, implying that our effect estimates are underestimates. The cancer and procedure data that we used to define provoked VTE have high validity, making the specificity of this classification high [23]. A potential weakness is that our VTE data were derived from discharge diagnoses. Approximately 20% of patients listed as having a VTE inpatient diagnosis in the hospital registry might not fulfill the strict criteria for the disease [24]. Nevertheless, the accuracy of the VTE diagnosis is unlikely to differ by previous medication exposure, so any misclassification would be non-differential and would lead to underestimates. Such misclassification cannot explain our results.

Our study did not have the advantage of random assignment, and therefore our results may be vulnerable to confounding from unmeasured variables, including the underlying condition leading to NSAID use, use of oral contraceptives, limitations in mobility, and body size [6–8]. Recent use is a possible marker of uncontrolled confounding by indication. In our study, recent use was associated with VTE occurrence, but much less than current use. Because NSAID use was associated with VTE among both men and women, oral contraceptives are unlikely to have had a substantial confounding influence. Finally, we note that we did adjust indirectly for unmeasured lifestyle factors by controlling for history of COPD and ischemic heart disease, and that our findings could not easily be explained by even a strong, single, unmeasured confounder.

In conclusion, we found an association between use of all non-aspirin NSAIDs and an increased risk of VTE. The two-fold increased VTE risk associated with long-term use provides the most valid estimate of the association. It will fall to future studies to establish whether this association is causal.

Disclosure of Conflict of Interests

The study was supported by an Aarhus University scholarship and the Clinical Epidemiological Research Foundation, Denmark. R. J. Glynn receives funding for venous thromboembolism research from grant AG031061 from the US National Institute on Aging. These funding sources had no role in the design, conduct, analysis, or reporting of this study. None of the authors received any fees, honoraria, grants or consultancies that would constitute a conflict of interest with the current study. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Incidence rate ratios associating individual NSAID use with deep vein thrombosis and pulmonary embolism.
Table S2. Stratified analyses of the adjusted incidence rate ratios associating NSAID use and venous thromboembolism.
Table S3. Sensitivity analysis examining the impact of different exposure windows on the rate of venous thromboembolism.
Data S1. ATC and ICD codes.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied

by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

References

1 Laine L. The gastrointestinal effects of nonselective NSAIDs and COX-2-selective inhibitors. *Semin Arthritis Rheum* 2002; **32**: 25–32.
2 Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat* 2007; **82**: 85–94.
3 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Metaanalysis of randomised trials. *BMJ* 2006; **332**: 1302–8.
4 Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002; **162**: 1182–9.
5 Huerta C, Johansson S, Wallander MA, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med* 2007; **167**: 935–43.
6 Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Haemost* 2006; **21**: 23–9.
7 Goldhaber SZ. Pulmonary embolism. *Lancet* 2004; **363**: 1295–305.
8 Kyrle PA, Eichinger S. Deep vein thrombosis. *Lancet* 2005; **365**: 1163–74.
9 Danish Medicines Agency. http://www.dkma.dk. Accessed 20 January 2011.
10 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; **53**: 441–9.
11 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–8.
12 Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol* 2005; **162**: 975–82.
13 Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–8.
14 Thomsen RW, Riis A, Munk EM, Norgaard M, Christensen S, Sorensen HT. 30-day mortality after peptic ulcer perforation among users of newer selective COX-2 inhibitors and traditional NSAIDs: a population-based study. *Am J Gastroenterol* 2006; **101**: 2704–10.
15 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; **158**: 915–20.
16 Horwitz RI, Feinstein AR. The problem of 'protopathic bias' in case–control studies. *Am J Med* 1980; **68**: 255–8.
17 Rothman KJ, Greenland S, Lash TL. Case–control studies. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008: 124–5.
18 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006; **15**: 291–303.
19 Chan AL. Celecoxib-induced deep vein thrombosis. *Ann Pharmacother* 2005; **39**: 1138.
20 Westgate EJ, FitzGerald GA. Pulmonary embolism in a woman taking oral contraceptives and valdecoxib. *PLoS Med* 2005; **2**: e197.
21 Nagai N, Hoylaerts MF, Gallacher DJ, Lu HR, Lijnen HR. Prothrombotic effect of Rofecoxib in a murine venous thrombosis model. *Thromb Res* 2008; **122**: 668–73.
22 Prandoni P. Venous and arterial thrombosis: two aspects of the same disease? *Clin Epidemiol* 2009; **1**: 1–6.
23 Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet* 2007; **370**: 1773–9.
24 Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjønneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol* 2010; **63**: 223–8.

Paper XIII

Preadmission use of nonaspirin nonsteroidal anti-inflammatory drugs and 30-day stroke mortality

Morten Schmidt, MD
Erzsébet Hováth-Puhó, PhD
Christian Fynbo Christiansen, PhD
Karin L. Petersen, PhD
Hans Erik Bøtker, DMSci
Henrik Toft Sørensen, DMSci

Correspondence to Dr. Schmidt: morten.schmidt@clin.au.dk

ABSTRACT

Objectives: To examine whether preadmission use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) influenced 30-day stroke mortality.

Methods: We conducted a nationwide population-based cohort study. Using medical databases, we identified all first-time stroke hospitalizations in Denmark between 2004 and 2012 (n = 100,043) and subsequent mortality. We categorized NSAID use as current (prescription redemption within 60 days before hospital admission), former, and nonuse. Current use was further classified as new or long-term use. Cox regression was used to compute hazard ratios (HRs) of death within 30 days, controlling for potential confounding through multivariable adjustment and propensity score matching.

Results: The adjusted HR of death for ischemic stroke was 1.19 (95% confidence interval [CI]: 1.02–1.38) for current users of selective cyclooxygenase (COX)-2 inhibitors compared with nonusers, driven by the effect among new users (1.42, 95% CI: 1.14–1.77). Comparing the different COX-2 inhibitors, the HR was driven by new use of older traditional COX-2 inhibitors (1.42, 95% CI: 1.14–1.78) among which it was 1.53 (95% CI: 1.02–2.28) for etodolac and 1.28 (95% CI: 0.98–1.68) for diclofenac. The propensity score–matched analysis supported the association between older COX-2 inhibitors and ischemic stroke mortality. There was no association for former users. Mortality from intracerebral hemorrhage was not associated with use of nonselective NSAIDs or COX-2 inhibitors.

Conclusions: Preadmission use of COX-2 inhibitors was associated with increased 30-day mortality after ischemic stroke, but not hemorrhagic stroke. Use of nonselective NSAIDs at time of admission was not associated with mortality from ischemic stroke or intracerebral hemorrhage.

Neurology® 2014;83:1–10

GLOSSARY

CI = confidence interval; **COPD** = chronic obstructive pulmonary disease; **COX** = cyclooxygenase; **DNRP** = Danish National Registry of Patients; **HR** = hazard ratio; ***ICD*** = *International Classification of Diseases*; **ICH** = intracerebral hemorrhage; **NSAID** = nonsteroidal anti-inflammatory drug; **PGE_2** = prostaglandin E_2; **SAH** = subarachnoid hemorrhage.

Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely to treat inflammatory conditions and pain. They include nonselective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors.[1] Some COX-2 inhibitors have been associated with increased risk of ischemic stroke,[2,3] but it remains unclear whether preadmission use of COX-2 inhibitors also affects the outcome of an ischemic insult.

The role of COX inhibition in outcome after cerebral ischemia is controversial.[4–7] Experimental animal studies have found that COX-2 inhibition reduces edema, neuroinflammation, and infarct size in rodent stroke models.[4–6] In contrast, other studies have found a neuroprotective role of COX-2–derived prostaglandin E_2 (PGE_2).[7] Moreover, the individual roles of COX-1 and COX-2 in neuroinflammation are debated because COX-1, classically viewed as the homeostatic isoform, also is actively involved in brain injury after stroke, which indicates a therapeutic potential for nonselective NSAIDs.[8]

Supplemental data at Neurology.org

From the Departments of Clinical Epidemiology (M.S., E.H.-P., C.F.C., H.T.S.) and Cardiology (M.S., H.E.B.), Aarhus University Hospital, Denmark; and California Pacific Medical Center Research Institute (M.S., K.L.P.), San Francisco.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Strikingly, the experimental animal research on the role of COX enzymes in cerebral ischemia[4–7] has not yet been examined in the clinical setting. Such data are needed to understand and potentially prevent death from stroke. To clarify these issues, we conducted a nationwide population-based cohort study to examine whether use of nonselective NSAIDs or COX-2 inhibitors at time of hospitalization for stroke influenced 30-day mortality after ischemic stroke, intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH).

METHODS

Setting. Since January 1, 2004, the Danish National Database of Reimbursed Prescriptions has maintained complete computerized prescription records for the entire Danish population.[9] The study period chosen for the current study was July 1, 2004 through December 31, 2012, in order to ensure the availability of at least a 6-month prescription history for all study participants. The Danish population in this study period included 6,379,918 inhabitants.

In Denmark, the National Health Service provides tax-supported health care, including unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications.[9] All Danish registries can be linked at the individual level using the unique Civil Personal Register number assigned to each Danish citizen at birth or upon immigration.[10]

Stroke. Patients with acute stroke are usually hospitalized in Denmark, with an estimated admission rate of 90%.[11] The Danish National Registry of Patients (DNRP)[12] contains data on dates of admission and discharge from all Danish nonpsychiatric hospitals since 1977 and on emergency room and outpatient specialist clinic visits since 1995.[12] Each hospital discharge or outpatient visit is recorded in the DNRP with one primary diagnosis and one or more secondary diagnoses. Diagnoses are classified according to *ICD-8* until the end of 1993 and *ICD-10* thereafter.[12]

We used the DNRP to identify all inpatient primary and secondary diagnoses of ischemic stroke, ICH, SAH, and unspecified stroke during the study period. To include only incident strokes, we did not include patients who had diagnoses of stroke or hemiplegia (a secondary measure of previous stroke) in the DNRP before our study period.[11] Because of their low positive predictive value, we also excluded emergency room diagnoses of stroke in the absence of a subsequent inpatient diagnosis.[13] The DNRP also provided information on CT or MRI performed during hospital admission.

NSAID use. As previously described,[14,15] we used the nationwide prescription database to identify prospectively all NSAID prescriptions filled by stroke patients before their admission date.[9] Danish pharmacies have electronic accounting systems, which are primarily used to secure reimbursement from the National Health Service.[9] For each filled prescription, the patient's Civil Personal Register number, the date of dispensing, and the amount and type of drug prescribed according to the Anatomical Therapeutic Chemical classification system are transferred electronically from the pharmacies to the prescription database.[9] Except for low-dose ibuprofen (200 mg/tablet), all nonaspirin NSAIDs are available only by prescription.[16] Regular ibuprofen users are also often registered in the prescription database, because the cost of the drug is partly refunded when the drug is prescribed by a physician.[16]

We identified prescriptions for nonselective NSAIDs (naproxen, ibuprofen, dexibuprofen, piroxicam, ketoprofen, tolfenamic acid, and indomethacin) and COX-2 inhibitors. COX-2 inhibitors were subcategorized as older COX-2 inhibitors (etodolac, diclofenac, meloxicam, and nabumetone) or coxibs (rofecoxib, celecoxib, and etoricoxib).[1]

We defined current NSAID users as persons who redeemed their most recent NSAID prescription within 60 days before their admission date. We chose a 60-day exposure window to capture most current users, because NSAID prescriptions in Denmark are seldom provided for more than 60 days at a time.[15] We defined former users as persons who had filled their most recent prescription between 60 and 180 days before their admission date. If a true effect of NSAID use exists, we expected the effect to be greater among current users than former users. Nonusers were defined as persons with no filled NSAID prescriptions 180 days before their admission date. Because some side effects may arise shortly after therapy initiation, inclusion of long-term users may lead to underestimation of these complications.[17] We therefore subcategorized current users into new users (who had filled their first-ever prescription within 60 days before their admission date) and long-term users (who had filled additional prescriptions more than 60 days before their admission date).

Mortality. As a measure of short-term mortality, we obtained 30-day all-cause mortality data from the Danish Civil Registration System.[10] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[10]

Comorbidity. The complete inpatient and outpatient medical history available in the DNRP[12] provided information on known prognostic factors (myocardial infarction, atrial fibrillation or flutter, intermittent arterial claudication, diabetes, and dementia)[18] and other potential confounders (angina pectoris, heart valve disease, venous thromboembolism, obesity, chronic kidney disease, hypertension, chronic obstructive pulmonary disease [COPD], alcoholism-related diseases, cancer, rheumatoid arthritis, connective tissue disease, osteoarthritis, and osteoporosis). To increase the completeness of diagnoses of diabetes, COPD, and alcoholism-related diseases, we also searched the prescription database for any previous dispensing of diabetic medication, respiratory medication, and alcohol deterrents.[9] As noninflammatory pain-related indications for NSAID use, we also identified migraine, recent dental procedure, and fracture or trauma. We defined migraine from a previous diagnosis in the DNRP or prescription redemptions for medicines (triptans or ergots) used to treat migraine attacks. As a measure of recent dental procedure, we obtained data from the Danish National Health Service Registry on all dental visits within 15 days before the last NSAID prescription redemption.[19] We defined fractures and traumas from diagnoses in the DNRP within 60 days before the last NSAID prescription.

Comedications. We used the prescription database to ascertain concurrent use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists, β-blockers, calcium channel blockers, diuretics, nitrates (if ≥2 prescriptions), statins, aspirin, clopidogrel, vitamin K antagonists, systemic glucocorticoids, selective serotonin reuptake inhibitors, and bisphosphonates. Because chronic medication use is rarely prescribed for more than 3 months at a time, comedication use was defined as prescription redemption within 90 days before the hospital admission date.

Statistical analysis. We characterized the cohort according to sex, age group, comorbidities, comedication use, and whether CT/MRI was performed during hospital admission. Among current NSAID users, we further estimated the proportion of patients registered with migraine, recent dental procedure, and fracture or trauma.

We followed all patients from admission date until death, emigration, or 30 days of follow-up, whichever came first. We used a Cox proportional hazards regression model to estimate hazard ratios of death within 30 days for current, new, long-term, and former use compared with nonuse. As the primary analysis, we used a multivariable model adjusting for the known prognostic factors, other potential confounders, and comedication use as defined above.

We performed several sensitivity analyses. To increase the precision of the estimates for ischemic stroke, we repeated the analyses including also unspecified stroke diagnoses because at least two-thirds of unspecified strokes are known to be ischemic strokes.[13] To increase the positive predictive value of the stroke diagnosis, we repeated the analysis restricting to patients with primary stroke diagnoses and a CT or MRI scan during hospital admission. To examine the sensitivity of the estimates to differences in exposure definitions, we also repeated the analysis using a 30-day exposure window. We stratified analyses by sex, age group, and presence/absence of rheumatoid arthritis, osteoarthritis, myocardial infarction, atrial fibrillation or flutter, hypertension, diabetes mellitus, and COPD.

Finally, we performed a propensity score–matched analysis by generating a logistic regression model that predicted current NSAID use among stroke patients conditional on the variables included in the multivariable model.[20] We computed the probability of current NSAID use (i.e., the propensity score) for all stroke patients and illustrated the propensity score distribution among current users and nonusers. Using a greedy matching algorithm, we matched each NSAID user with the nonuser with the closest propensity score.[21] The matching was performed without replacement, within a maximum matching range (caliper width) in propensity score of ± 0.025, and separately for each class and individual type of NSAID.[21] Using robust standard errors that account for clustering in matched pairs, we repeated the Cox regression comparing mortality rates between current NSAID users and propensity score–matched nonusers.[21] The proportional hazard assumption was visually assessed and confirmed by log–log plots.

Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All registry codes are provided in table e-1 on the *Neurology*® Web site at Neurology.org.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Danish Data Protection Agency (record number 2011-41-5755). Because this study did not involve contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

RESULTS We identified 100,043 patients with first-time stroke, among which 51,224 (51%) had ischemic stroke (median age: 74 years), 11,779 (12%) had ICH (median age: 72 years), 4,528 (5%) had SAH (median age: 58 years), and 32,512 (32%) had unspecified stroke (median age: 76 years). A total of 10,835 stroke patients (10.8%) were current NSAID users, 8402 (8.4%) were former users, and 80,806 (80.8%) were nonusers. Among the current NSAID users, 51.4% used ibuprofen, 3.2% used naproxen, 27.0% used diclofenac, 10.7% used etodolac, 1.0% used celecoxib, and 0.5% used rofecoxib. The proportion of patients with postdischarge NSAID use during follow-up was 15.5% after ischemic stroke, 6.1% after ICH, and 4.9% after SAH. The proportion of stroke patients with ICH or SAH was 16.5% among current NSAID users and 15.7% among nonusers. Among current NSAID users, 4.1% had migraine, 4.7% a recent dental procedure, and 2.2% a recent trauma or fracture. Migraine was more prevalent among current NSAID users with SAH (9.6%) than ischemic stroke (4.1%) and ICH (3.8%). There was substantial overlap in propensity score distributions among NSAID users and nonusers before matching (figure e-1) and we achieved virtually complete matching of controls to current NSAID users (100% for ischemic stroke, 99.9% for ICH, 99.2% for SAH, and 100% for unspecified stroke). The most notable difference in patient characteristics before matching (tables 1 and e-2) was that a higher proportion of NSAID users had obesity, COPD, rheumatic disease, osteoarthritis, or glucocorticoid use than nonusers. After matching, the characteristics of NSAID users and nonusers were equally distributed (table e-3).

Overall 30-day mortality among NSAID nonusers was 8.7% for ischemic stroke, 35.1% for ICH, 24.5% for SAH, and 14.3% for unspecified stroke. After multivariable adjustment (table 2), current use of nonselective NSAIDs was not associated with mortality from ischemic stroke compared with nonusers (hazard ratio [HR] = 1.00, 95% confidence interval [CI]: 0.87–1.15). However, the HR for ischemic stroke was 1.19 (95% CI: 1.02–1.38) for current users of COX-2 inhibitors, driven by the effect among new users (HR = 1.42, 95% CI: 1.14–1.77). Comparing initiation of different types of COX-2 inhibitors and the statistical precision, the effect was driven by older COX-2 inhibitors (multivariable-adjusted HR = 1.42, 95% CI: 1.14–1.78), among which it was 1.53 (95% CI: 1.02–2.28) for etodolac users and 1.28 (95% CI: 0.98–1.68) for diclofenac users (table 3). The results for individual NSAID types and ICH and SAH are presented in table e-4. The propensity score–matched analysis supported the association between use of older COX-2 inhibitors and ischemic stroke (HR = 1.31, 95% CI: 1.04–1.64 among current users and 1.44, 95% CI: 1.09–1.89 among new users).

We observed no association between former use of COX-2 inhibitors and ischemic stroke mortality (table e-5). Overall use of nonselective NSAIDs and COX-2 inhibitors was not substantially associated with 30-day mortality after ICH and SAH (tables 2 and e-5). New users of nonselective NSAIDs had, however, a reduced HR for SAH-related mortality (0.61, 95% CI: 0.41–0.91). Of note, similar reduced HR for SAH mortality was seen for former users (HR = 0.69, 95% CI: 0.49–0.97) (table e-5). The results were robust when including unspecified strokes

Table 1 Characteristics of stroke patients according to preadmission use of nonaspirin NSAIDs

	Nonaspirin NSAID use											
	Ischemic stroke			Intracerebral hemorrhage			Subarachnoid hemorrhage			Unspecified stroke		
	Current use (n = 5,304)	Former use (n = 4,433)	Nonuse (n = 41,487)	Current use (n = 1,213)	Former use (n = 890)	Nonuse (n = 9,676)	Current use (n = 489)	Former use (n = 345)	Nonuse (n = 3,694)	Current use (n = 3,829)	Former use (n = 2,734)	Nonuse (n = 25,949)
Female sex	52.1	50.3	46.6	53.5	48.9	47.5	62.0	63.5	56.7	55.7	52.0	49.6
Age, y												
<60	18.7	21.9	20.0	19.0	24.6	24.9	52.6	51.0	54.2	15.6	17.6	16.3
60–69	22.3	21.9	22.7	20.1	17.8	21.2	21.5	22.0	21.0	19.5	21.8	19.6
70–79	29.8	28.3	26.3	29.3	27.4	25.4	12.7	16.2	13.8	29.3	27.8	27.2
≥80	29.1	27.9	30.9	31.7	30.2	28.5	13.3	10.7	11.0	35.6	32.8	37.0
Comorbidity level[a]												
Low	44.9	45.0	49.3	43.7	46.0	50.9	62.0	53.9	64.7	39.4	39.8	43.7
Moderate	40.2	38.9	35.9	41.1	38.3	34.0	29.0	37.1	27.3	41.2	40.8	37.8
High	14.9	16.2	14.9	15.2	15.7	15.1	9.0	9.0	8.0	19.3	19.4	18.4
Individual comorbidities												
Myocardial infarction	7.3	7.9	8.5	5.3	7.6	6.1	2.5	4.6	3.2	8.8	9.7	9.9
Angina pectoris	13.9	15.8	14.9	11.0	14.0	11.8	8.0	9.9	6.9	16.6	18.7	16.6
Atrial fibrillation or flutter	10.8	11.8	13.4	11.3	12.4	13.5	5.7	5.8	5.3	12.7	13.9	14.9
Heart valve disease	3.9	4.2	4.4	2.4	5.2	4.2	2.5	2.0	1.9	3.9	4.8	4.9
Intermittent claudication	3.0	3.2	3.1	2.5	1.0	1.8	1.0	0.6	1.3	3.5	2.6	3.0
Venous thromboembolism	3.6	3.8	3.4	4.0	3.1	3.5	2.5	1.7	2.0	4.5	4.8	4.0
Obesity	6.2	5.1	3.5	5.4	4.0	2.9	4.3	4.3	2.8	5.8	5.6	3.7
Diabetes mellitus	13.6	13.6	12.4	9.7	8.9	9.7	7.6	6.7	5.4	15.1	16.0	14.4
Chronic kidney disease	1.8	2.1	2.4	1.6	2.7	2.9	1.4	1.4	1.6	2.4	2.9	3.2
Hypertension	25.7	26.6	24.4	22.3	25.1	23.3	16.6	18.6	13.7	28.2	26.9	26.2
COPD	24.1	24.5	19.2	22.1	21.5	18.3	18.6	25.5	17.3	25.0	24.2	21.0
Alcoholism-related disease	7.1	6.9	6.1	7.3	8.8	8.1	8.6	7.8	7.1	7.6	8.1	6.6
Dementia	2.3	2.6	3.0	4.0	2.5	4.1	1.2	1.2	1.4	3.0	3.4	4.3
Cancer	14.7	14.2	13.5	18.3	18.0	15.0	10.0	9.3	8.6	17.1	17.1	15.4
Rheumatoid arthritis	3.0	2.5	1.6	3.5	2.5	1.5	4.1	2.9	1.1	3.8	2.7	1.7
Connective tissue disease	3.3	3.5	2.6	3.2	3.0	2.2	3.3	2.9	1.6	3.7	3.3	2.8
Osteoarthritis	27.6	25.2	14.9	24.3	23.7	13.3	19.8	17.7	9.4	30.2	26.3	15.1
Osteoporosis	6.2	5.8	4.8	7.0	7.6	5.4	5.9	4.3	2.8	6.1	6.0	5.3

Continued

Table 1 Continued

	Nonaspirin NSAID use											
	Ischemic stroke			Intracerebral hemorrhage			Subarachnoid hemorrhage			Unspecified stroke		
	Current use (n = 5,304)	Former use (n = 4,433)	Nonuse (n = 41,487)	Current use (n = 1,213)	Former use (n = 890)	Nonuse (n = 9,676)	Current use (n = 489)	Former use (n = 345)	Nonuse (n = 3,694)	Current use (n = 3,829)	Former use (n = 2,734)	Nonuse (n = 25,949)
Comedication												
ACE or A2R inhibitors	29.2	27.7	25.6	23.4	22.7	19.8	20.2	18.0	13.8	28.8	26.0	25.4
β-Blockers	20.8	21.2	20.1	14.8	18.2	16.2	9.6	11.0	8.9	21.5	20.3	20.9
Calcium channel blockers	17.7	16.9	15.2	11.0	9.8	9.7	11.2	11.6	7.3	17.1	17.2	15.7
Diuretics	31.1	27.5	24.9	25.6	22.5	20.7	18.6	15.1	12.1	36.1	32.3	30.0
Nitrates	2.0	1.5	1.7	1.3	0.9	1.3	0.8	0.6	0.6	2.8	2.2	2.2
Statins	18.2	17.3	15.9	14.2	15.7	13.8	11.5	14.2	9.6	16.8	17.7	15.9
Acetylsalicylic acid	26.3	23.2	22.7	20.0	24.3	20.8	11.5	13.6	9.6	28.0	26.4	25.6
Clopidogrel	1.6	2.2	1.9	0.7	1.2	1.7	1.0	0.3	1.0	1.8	2.3	2.0
Vitamin K antagonists	3.2	4.2	4.4	8.9	9.4	10.3	2.7	3.2	3.6	4.5	4.8	5.7
Systemic glucocorticoids	7.2	6.0	3.9	4.8	5.2	3.7	3.9	4.6	2.5	8.0	7.6	4.9
SSRIs	10.1	9.0	7.9	11.6	9.2	9.4	7.6	7.2	7.0	12.4	10.7	9.8
Bisphosphonates	4.5	4.2	3.1	5.3	4.3	3.5	4.5	3.2	2.1	4.6	4.2	3.4
CT/MRI scan during admission	92.5	91.8	92.2	91.9	91.5	91.4	90.0	91.3	91.9	80.5	79.4	81.0
CT scan	89.5	88.2	88.7	90.4	89.9	89.3	89.0	89.9	91.2	79.0	77.5	79.6
MRI scan	14.5	16.2	15.7	7.9	6.6	7.7	6.7	6.1	5.9	6.2	6.8	6.3

Abbreviations: ACE = angiotensin-converting enzyme; A2R = angiotensin-2 receptor; COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti-inflammatory drug, SSRI = selective serotonin reuptake inhibitor.
Data are percentages.
[a] Three levels of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1–2 (moderate), and ≥3 (high).

Table 2 Preadmission use of nonaspirin NSAIDs and 30-day mortality estimates after stroke

	30-d mortality risk	Hazard ratio (95% CI)		
		Unadjusted	Multivariable-adjusted[a]	Propensity score–matched[b]
Ischemic stroke				
No use of any NSAIDs	8.7 (8.4–9.0)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs[c]	8.8 (8.1–9.6)	1.01 (0.92–1.11)	1.02 (0.93–1.13)	0.99 (0.87–1.12)
New use	9.3 (8.1–10.6)	1.07 (0.92–1.24)	1.17 (1.00–1.35)	1.18 (0.95–1.47)
Long-term use	8.5 (7.6–9.5)	0.98 (0.87–1.11)	0.94 (0.83–1.07)	0.93 (0.79–1.09)
Nonselective NSAIDs[c]	8.1 (7.1–9.2)	0.93 (0.81–1.06)	1.00 (0.87–1.15)	1.02 (0.85–1.24)
New use	8.0 (6.6–9.6)	0.91 (0.75–1.11)	1.04 (0.85–1.26)	1.01 (0.80–1.28)
Long-term use	8.2 (6.8–9.7)	0.94 (0.78–1.13)	0.97 (0.80–1.17)	1.04 (0.83–1.30)
COX-2 inhibitors overall[c]	10.4 (9.1–11.9)	1.20 (1.04–1.40)	1.19 (1.02–1.38)	1.10 (0.89–1.36)
New use	11.4 (9.3–14.0)	1.33 (1.06–1.65)	1.42 (1.14–1.77)	1.21 (0.93–1.58)
Long-term use	9.7 (8.1–11.7)	1.12 (0.92–1.37)	1.05 (0.86–1.28)	1.02 (0.80–1.31)
Older COX-2 inhibitors	10.4 (9.0–11.9)	1.20 (1.03–1.40)	1.20 (1.03–1.40)	1.31 (1.04–1.64)
New use	11.4 (9.2–14.0)	1.32 (1.06–1.65)	1.42 (1.14–1.78)	1.44 (1.09–1.89)
Long-term use	9.7 (8.0–11.7)	1.12 (0.91–1.37)	1.06 (0.86–1.30)	1.22 (0.94–1.58)
Coxibs	10.8 (5.3–21.3)	1.23 (0.59–2.58)	0.87 (0.41–1.82)	0.97 (0.34–2.75)
New use	15.0 (5.1–39.6)	1.75 (0.56–5.43)	1.14 (0.37–3.53)	1.41 (0.37–5.31)
Long-term use	8.9 (3.4–22.0)	1.00 (0.37–2.67)	0.74 (0.28–1.97)	0.79 (0.24–2.65)
Intracerebral hemorrhage				
No use of any NSAIDs	35.1 (34.1–36.0)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs[c]	34.7 (32.1–37.5)	0.99 (0.89–1.09)	0.97 (0.88–1.08)	0.91 (0.80–1.04)
New use	32.0 (28.0–36.4)	0.89 (0.76–1.05)	0.90 (0.76–1.06)	1.06 (0.84–1.33)
Long-term use	36.5 (33.1–40.1)	1.05 (0.93–1.19)	1.02 (0.90–1.16)	0.98 (0.83–1.16)
Nonselective NSAIDs[c]	32.4 (29.0–36.1)	0.91 (0.79–1.05)	0.94 (0.81–1.08)	0.96 (0.79–1.15)
New use	30.6 (26.0–35.8)	0.85 (0.70–1.03)	0.88 (0.72–1.07)	0.89 (0.71–1.13)
Long-term use	34.3 (29.4–39.8)	0.98 (0.81–1.18)	1.00 (0.83–1.21)	1.03 (0.82–1.29)
COX-2 inhibitors overall[c]	34.5 (30.0–39.4)	0.96 (0.81–1.14)	0.93 (0.78–1.11)	0.95 (0.75–1.21)
New use	31.8 (25.1–39.8)	0.88 (0.66–1.17)	0.87 (0.66–1.15)	0.87 (0.63–1.21)
Long-term use	36.2 (30.4–42.7)	1.01 (0.82–1.25)	0.97 (0.78–1.21)	1.01 (0.77–1.32)
Older COX-2 inhibitors	33.4 (28.9–38.5)	0.93 (0.77–1.11)	0.91 (0.76–1.09)	0.86 (0.68–1.10)
New use	31.0 (24.2–39.3)	0.85 (0.63–1.14)	0.85 (0.64–1.15)	0.79 (0.57–1.11)
Long-term use	35.0 (29.1–41.7)	0.98 (0.78–1.22)	0.94 (0.75–1.18)	0.91 (0.69–1.20)
Coxibs	48.2 (31.5–68.1)	1.42 (0.82–2.44)	1.29 (0.75–2.23)	0.78 (0.37–1.61)
New use	41.7 (19.9–73.0)	1.22 (0.51–2.92)	1.05 (0.44–2.53)	0.68 (0.25–1.85)
Long-term use	53.3 (31.3–78.8)	1.58 (0.79–3.15)	1.51 (0.75–3.03)	0.86 (0.38–1.95)
Subarachnoid hemorrhage				
No use of any NSAIDs	24.5 (23.1–25.9)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs[c]	21.7 (18.3–25.6)	0.87 (0.71–1.07)	0.84 (0.69–1.03)	0.76 (0.59–0.98)
New use	15.4 (11.5–20.6)	0.59 (0.43–0.82)	0.64 (0.46–0.89)	0.65 (0.43–0.98)
Long-term use	28.1 (22.9–34.3)	1.19 (0.93–1.52)	1.03 (0.80–1.32)	0.97 (0.69–1.35)
Nonselective NSAIDs[c]	20.6 (16.4–25.8)	0.82 (0.63–1.07)	0.85 (0.65–1.11)	0.83 (0.59–1.18)
New use	15.1 (10.5–21.4)	0.58 (0.39–0.85)	0.61 (0.41–0.91)	0.58 (0.37–0.91)
Long-term use	29.0 (21.6–38.3)	1.23 (0.87–1.73)	1.22 (0.86–1.74)	1.25 (0.83–1.89)

Continued

Table 2 Continued

	30-d mortality risk	Hazard ratio (95% CI)		
		Unadjusted	Multivariable-adjusted[a]	Propensity score–matched[b]
COX-2 inhibitors overall[c]	22.8 (17.0–30.2)	0.92 (0.66–1.29)	0.90 (0.64–1.26)	1.06 (0.66–1.69)
New use	16.1 (9.9–25.7)	0.63 (0.37–1.06)	0.71 (0.42–1.20)	0.72 (0.39–1.33)
Long-term use	31.0 (21.6–43.1)	1.32 (0.87–2.02)	1.11 (0.72–1.72)	1.51 (0.89–2.58)
Older COX-2 inhibitors	22.2 (16.4–29.7)	0.90 (0.64–1.27)	0.89 (0.63–1.26)	0.78 (0.50–1.22)
New use	16.7 (10.2–26.5)	0.65 (0.38–1.10)	0.74 (0.44–1.26)	0.56 (0.31–1.02)
Long-term use	29.0 (19.8–41.2)	1.24 (0.79–1.93)	1.06 (0.67–1.66)	1.06 (0.63–1.81)
Coxibs	40.0 (11.8–87.4)	1.50 (0.38–6.01)	1.16 (0.28–4.77)	1.86 (0.19–8.65)
New use	—	—	—	—
Long-term use	—	—	—	—

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammatory drug.
Table cells with only a dash indicate subgroups with insufficient data for regression analyses.
[a] Multivariable model with adjustment for myocardial infarction, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, obesity, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease, alcoholism-related diseases, dementia, cancer, rheumatoid arthritis, connective tissue disease, osteoarthritis, osteoporosis, and concurrent use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists, β-blockers, calcium channel blockers, diuretics, nitrates, statins, aspirin, clopidogrel, vitamin K antagonists, systemic glucocorticoids, selective serotonin reuptake inhibitors, and bisphosphonates.
[b] Propensity score–matched model that matched NSAID users with nonusers based on their probability (propensity score ± 0.025) of using NSAIDs, conditioned on the distribution of baseline characteristics.
[c] Estimates are provided for current use and subcategories of new and long-term use. NSAIDs were categorized as nonselective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, tolfenamic acid, and indomethacin), older COX-2 inhibitors (diclofenac, etodolac, nabumetone, and meloxicam) or coxibs (celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib).

as ischemic strokes (table e-6), when restricting to primary diagnoses of stroke (table e-7) or CT- or MRI-confirmed cases (table e-8), and when using a 30-day exposure window (table e-9). The stratified analyses revealed no substantial effect modification of the HRs (table e-10).

DISCUSSION We found that preadmission use of COX-2 inhibitors was associated with increased mortality after ischemic stroke, while not affecting mortality from ICH or SAH. Preadmission use of nonselective NSAIDs was not associated with mortality after ischemic stroke or ICH. The effect of preadmission use of nonselective NSAIDs on SAH mortality was inconclusive.

The increased mortality rate associated with COX-2 inhibition in ischemic stroke was observed only among current users, which may indicate an actual drug effect. Such effect may be explained through several potential mechanisms. Given the thromboembolic properties of COX-2 inhibitors,[1–3] their use could potentially lead to larger and more often fatal thromboembolic occlusions compared with nonuse. The effect may also be mediated through adverse cardiovascular events[15,22] or stroke recurrence.[2,3] COX-2 inhibition may also impair the pathophysiologic response to a stroke. Thus, a cerebral infarct causes an inflammatory response at the site of injury and in the surrounding tissue, which upregulates neuronal COX-2 expression[23] and hence nitric oxide, PGE_2, and proinflammatory cytokines (including tumor necrosis factor-α and interleukin-1β).[24,25] Whether this upregulation of COX-2 promotes neuronal injury or protection is controversial,[7,26,27] because tumor necrosis factor-α mediates inflammatory neurotoxicity, while PGE_2 seems neuroprotective in cerebral ischemia.[7] Inhibiting the neuroprotective PGE_2 response may therefore be associated with poorer outcome among users of COX-2 inhibitors. Any ischemic preconditioning mediated by prior sublethal ischemic insults would also be counteracted by COX-2 inhibition.[28–30] Finally, we cannot exclude uncontrolled confounding, including the underlying comorbidity leading to NSAID use, as a potential explanation for our findings.

Our study adds to the increasing body of evidence concerning the vascular risk and prognostic impact associated with use of COX-2 inhibitors. The prognostic impact also needs to be considered when prescribing older or newer COX-2 inhibitors to patients at increased risk of thromboembolic events. Whereas prescription rates of coxibs have decreased dramatically after the withdrawal of rofecoxib in 2004, many older COX-2 inhibitors such as

Table 3 Preadmission use of individual nonaspirin NSAIDs and 30-day mortality estimates after ischemic stroke

	Ischemic stroke, hazard ratio (95% CI)		
	Unadjusted	Multivariable-adjusted[a]	Propensity score–matched[a]
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Ibuprofen (current use)	0.88 (0.76–1.02)	0.96 (0.83–1.12)	1.04 (0.84–1.28)
New use	0.87 (0.71–1.08)	1.00 (0.81–1.23)	1.04 (0.80–1.34)
Long-term use	0.88 (0.72–1.09)	0.93 (0.75–1.14)	1.05 (0.81–1.35)
Naproxen (current use)	1.06 (0.62–1.83)	1.25 (0.73–2.17)	1.20 (0.54–2.67)
New use	0.80 (0.33–1.92)	1.23 (0.51–2.95)	0.91 (0.32–2.60)
Long-term use	1.33 (0.67–2.66)	1.27 (0.64–2.55)	1.50 (0.60–3.73)
Etodolac (current use)	1.32 (1.01–1.74)	1.11 (0.84–1.46)	1.10 (0.74–1.63)
New use	1.77 (1.18–2.64)	1.53 (1.02–2.28)	1.48 (0.91–2.40)
Long-term use	1.09 (0.75–1.58)	0.89 (0.62–1.30)	0.90 (0.57–1.44)
Diclofenac (current use)	1.09 (0.90–1.32)	1.20 (0.99–1.46)	1.16 (0.88–1.53)
New use	1.13 (0.86–1.47)	1.28 (0.98–1.68)	1.20 (0.86–1.68)
Long-term use	1.06 (0.81–1.38)	1.13 (0.87–1.48)	1.13 (0.81–1.57)
Celecoxib (current use)	1.14 (0.43–3.04)	0.78 (0.29–2.07)	0.76 (0.21–2.78)
New use	1.50 (0.38–5.99)	1.12 (0.28–4.49)	1.00 (0.21–4.76)
Long-term use	0.92 (0.23–3.66)	0.59 (0.15–2.37)	0.62 (0.12–3.10)
Rofecoxib (current use)	2.08 (0.67–6.45)	1.47 (0.47–4.58)	1.50 (0.26–8.57)
New use	2.15 (0.30–15.23)	1.10 (0.16–7.85)	1.57 (0.15–16.40)
Long-term use	2.05 (0.51–8.18)	1.77 (0.44–7.10)	1.47 (0.22–9.70)

Abbreviations: CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.
[a] See description of the multivariable-adjusted and propensity score–matched models in the text and in the footnote to table 2.

diclofenac and etodolac are still frequently prescribed.[16] Use of diclofenac has previously been reported to more than double the risk of ischemic stroke[2] and our results indicated that diclofenac and etodolac users also have a worse outcome after ischemic stroke. If the association is truly causal, it constitutes a strong argument for increasing the efforts to ensure that patients with a high predicted risk of arterial thromboembolism (e.g., atrial fibrillation patients with high CHA_2DS_2-VASc score) are not prescribed COX-2 inhibitors when alternative treatment options are available. Of note, we studied the prognostic effect of NSAID use initiated before, not after, stroke admission. Consequently, our results do not necessarily contradict reports suggesting a role for COX-2 inhibitors in treating postischemic oxidative stress and inflammation.[31]

Several issues should be considered when interpreting our results. The nationwide population-based study design, within the setting of a tax-supported universal health care system and with complete follow-up for all patients, reduced selection biases.[10] The prescription data were virtually complete.[9] Although filled medication prescription data were used as a proxy for actual NSAID use, this was based on actual dispensing at pharmacies, rather than written prescriptions.[9,16] Copayments required upon dispensing of NSAIDs increased the likelihood of compliance. We lacked information on over-the-counter use of low-dose ibuprofen, which accounted for 30% to 35% of total ibuprofen sales and 15% to 25% of total NSAID sales during the study period.[16] However, with a user prevalence in our cohort of approximately 10%, the degree of misclassification was likely insufficient to affect the relative estimates substantially and in any case was nondifferential.[16] The positive predictive value of acute stroke diagnoses in the DNRP has been examined previously and was found to be 97% for ischemic stroke, 74% for ICH, and 67% for SAH.[13] The mortality data were complete.[10]

Our study did not have the advantage of random treatment assignment. Although we observed an equal distribution of baseline characteristics, especially after propensity score matching, we cannot exclude confounding. We did not have detailed data available on smoking, body weight, or indications for NSAID use. We did, however, adjust indirectly for lifestyle factors through COPD, hospital-diagnosed obesity, and ischemic heart disease. Moreover, smoking has previously been reported to predict late more than early case fatality rate from ischemic stroke.[18]

Also, the analysis stratified by COPD showed that smoking-related disease did not modify the results (table e-10). The point estimates associating nonselective NSAIDs and SAH mortality were similarly reduced for current and former users, which indicate confounding by indication rather than a drug effect. Moreover, because of the inhibiting effect of nonselective NSAIDs on platelets (through COX-1 inhibition), it seems biologically less plausible that preadmission use of nonselective NSAIDs would reduce mortality after SAH. The estimates from the multivariable and propensity score–matched analyses may differ slightly, depending on the exclusions due to matching and any potential treatment heterogeneity. The overall agreement between the results from the 2 approaches, however, supports the robustness of our findings.

We found that preadmission use of COX-2 inhibitors was associated with increased 30-day mortality after ischemic stroke, but not hemorrhagic stroke. Use of nonselective NSAIDs at time of admission was not associated with mortality from ischemic stroke or ICH.

AUTHOR CONTRIBUTIONS

M.S. and H.T.S. conceived the study idea and designed the study. H.T.S. and E.H.-P. collected the data. M.S. reviewed the literature, directed the analyses, organized the writing, and wrote the initial draft. The analyses were performed by E.H.-P. All authors participated in the discussion and interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version before submission. H.T.S. had full access to the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

STUDY FUNDING

The study was supported by the Department of Clinical Epidemiology's Research Foundation, Arvid Nilsson's Foundation, Aarhus University Research Foundation, and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 23, 2014. Accepted in final form September 2, 2014.

REFERENCES

1. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. Prostaglandins Other Lipid Mediat 2007;82:85–94.
2. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.
3. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf 2011;20:1225–1236.
4. Park HK, Lee SH, Chu K, Roh JK. Effects of celecoxib on volumes of hematoma and edema in patients with primary intracerebral hemorrhage. J Neurol Sci 2009;279:43–46.
5. Ahmad M, Zhang Y, Liu H, Rose ME, Graham SH. Prolonged opportunity for neuroprotection in experimental stroke with selective blockade of cyclooxygenase-2 activity. Brain Res 2009;1279:168–173.
6. Ayer R, Jadhav V, Sugawara T, Zhang JH. The neuroprotective effects of cyclooxygenase-2 inhibition in a mouse model of aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl 2011;111:145–149.
7. McCullough L, Wu L, Haughey N, et al. Neuroprotective function of the PGE2 EP2 receptor in cerebral ischemia. J Neurosci 2004;24:257–268.
8. Aid S, Bosetti F. Targeting cyclooxygenases-1 and -2 in neuroinflammation: therapeutic implications. Biochimie 2011;93:46–51.
9. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 2012;4:303–313.
10. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–549.
11. Schmidt M, Jacobsen JB, Johnsen SP, Bøtker HE, Sørensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. Neurology 2014;82:340–350.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 suppl): 30–33.
13. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology 2007;28:150–154.
14. Schmidt M, Christiansen CF, Horvath-Puho E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. J Thromb Haemost 2011;9:1326–1333.
15. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ 2011;343:d3450.
16. Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other non-steroidal anti-inflammatory drugs in Denmark: trends in utilization 1999–2012. Clin Epidemiol 2014;6:155–168.
17. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915–920.
18. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. Stroke 2011;42:2806–2812.
19. Andersen JS, Olivarius NDF, Krasnik A. The Danish National Health Service Register. Scand J Public Health 2011;39(7 suppl):34–37.
20. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Til S. Variable selection for propensity score models. Am J Epidemiol 2006;163:1149–1156.
21. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 2007;134:1128–1135.
22. Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. Arch Intern Med 2005;165:978–984.

23. Wang Q, Tang G, Yenari M. The inflammatory response in stroke. J Neuroimmunol 2007;184:53–68.
24. Maddahi A, Kruse LS, Chen QW, Edvinsson L. The role of tumor necrosis factor-α and TNF-α receptors in cerebral arteries following cerebral ischemia in rat. J Neuroinflammation 2011;8:107.
25. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. Nat Rev Immunol 2005;5:629–640.
26. Doré S, Otsuka T, Mito T, et al. Neuronal overexpression of cyclooxygenase-2 increases cerebral infarction. Ann Neurol 2003;54:155–162.
27. Graham SH, Hickey RW. Cyclooxygenases in central nervous system diseases: a special role for cyclooxygenase 2 in neuronal cell death. Arch Neurol 2003;60:628–630.
28. Kim EJ, Raval AP, Hirsch N, Perez-Pinzon MA. Ischemic preconditioning mediates cyclooxygenase-2 expression via nuclear factor-kappa B activation in mixed cortical neuronal cultures. Transl Stroke Res 2010;1:40–47.
29. Kim E, Raval AP, Defazio RA, Perez-Pinzon MA. Ischemic preconditioning via epsilon protein kinase C activation requires cyclooxygenase-2 activation in vitro. Neuroscience 2007;145:931–941.
30. Horiguchi T, Snipes JA, Kis B, Shimizu K, Busija DW. Cyclooxygenase-2 mediates the development of cortical spreading depression-induced tolerance to transient focal cerebral ischemia in rats. Neuroscience 2006;140:723–730.
31. Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. J Transl Med 2009;7:97.

Department of Clinical Epidemiology

Aarhus University and Aarhus University Hospital
Olof Palmes Allé 43-45
8200 Aarhus N
Denmark
Tel.: +45 87167212
Fax: +45 87167215
www.kea.au.dk