Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use

— Pharmacoepidemiological studies —

PhD dissertation

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Thesis papers

I. Schmidt M, Maeng M, Pedersen L, Lassen JF, Lash TL, Nielsen TT, Sørensen HT. Nonsteroidal Anti-inflammatory Drug Use and Cardiovascular Risks after Coronary Stent Implantation. **Pharmacotherapy**. 2011:31(5):458-468

II. 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(7):1326-33

III. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: a population-based case-control study. **BMJ**. 2011;343:d3450

IV. Schmidt M, Horváth-Puhó E, Christiansen CF, Petersen K, Bøtker HE, Sørensen HT. Preadmission Non-steroidal Anti-inflammatory Drug Use and 30-day Stroke Mortality. **Neurology** (In press).

V. 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;6:155-68

Abbreviations

CI	Confidence interval
COX	Cyclooxygenase
Coxibs	Newer COX-2 inhibitors
DNPR	Danish National Patient Registry
HR	Hazard ratio
IRR	Incidence rate ratio
MACE	Major adverse cardiovascular event
MRR	Mortality rate ratio
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PCI	Percutaneous coronary intervention
RR	Relative risk
TLR	Target lesion revascularization

Contents

1. Thesis structure

The cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) is controversial, because cyclooxygenase (COX)-2 inhibitors increase the risk of myocardial infarction, stroke, heart failure, and hypertension. This dissertation examines cardiovascular risks associated with use of non-aspirin NSAIDs that have not previously been examined in detail.

The dissertation is based on five papers, which are referred to in the text by their Roman numerals (I–V).[1-5] Papers I–IV are research studies,[1-4] whereas paper V is a methodology paper important for studies based on NSAID use.[5] The research studies are presented in detail.[1-4] The methodology paper — an ecologic study of the utilization of NSAIDs in Denmark between 1999–2012 and the potential of Danish prescription registries to capture individual-level use of NSAIDs — is incorporated into the text throughout the dissertation.[5]

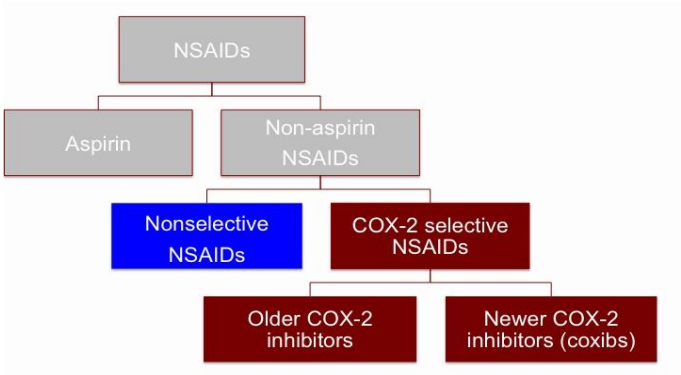
The dissertation consists of nine chapters. The introduction describes briefly the classification, use, and effects of NSAIDs, followed by a description of the established cardiovascular risks of NSAIDs, and ends with a review of the existing literature in relation to the hypotheses and objectives of the dissertation.

The succeeding three chapters summarize the study methods, results, and conclusions, and provide a discussion of the results in relation to the existing literature, applied methodology, and clinical implications.

The last chapters include summaries in English and Danish, references, and appendices with full versions of the papers.

2. Introduction

Figure 1: NSAID classification



2.1 NSAID classification

NSAIDs include aspirin (acetylsalicylic acid) and non-aspirin NSAIDs (Figure 1).[6] Aspirin was marketed in 1899 as a better tolerated form of sodium salicylate (discovered in 1763),[7] but was later also found associated with gastrointestinal erosions and ulcers.[8]

As a potentially safer alternative to aspirin, a range of non-aspirin NSAIDs were developed throughout the 1960s.[7] However, these drugs also exhibit gastrointestinal toxicity ranging from dyspepsia to ulcers, bleeding, and perforation,[9] including both nonulcer dyspepsia and silent ulceration.[8] This discrepancy between symptoms and ulceration constitutes a major challenge in the management of patients treated with (traditional) non-aspirin NSAIDs.[8]

The hypothesis that selective COX-2 inhibition would possess anti-inflammatory, analgesic, and antipyretic activity — without increasing the risk of adverse gastrointestinal events[10] — provided the rationale for the development of newer COX-2 inhibitors (coxibs), which were first introduced into clinical practice in 1999.[11] The coxibs can be ranked based on their relative COX-2 *vs*. COX-1 selectivity: lumiracoxib > etoricoxib > rofecoxib > valdecoxib > parecoxib > celecoxib.[11,12] Among the traditional non-aspirin NSAIDs, some also have a preference for COX-2 (older COX-2 inhibitors), whereas the remaining are classified as nonselective NSAIDs (Figure 1).

2.2 NSAID use in Denmark

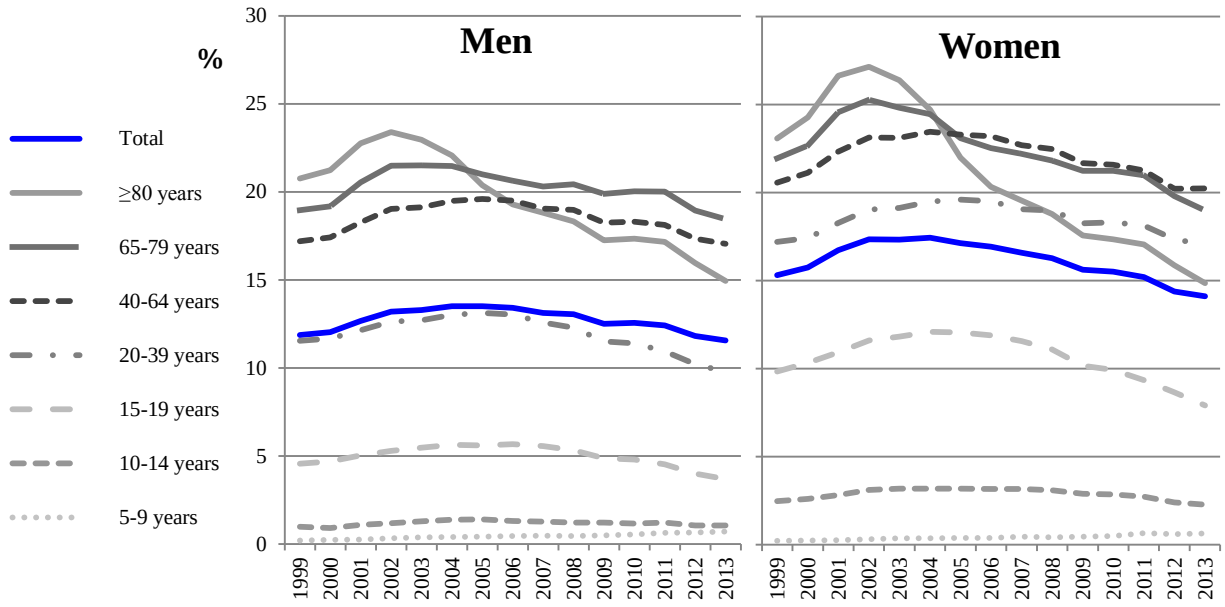
Aspirin and non-aspirin NSAIDs remain among the most commonly used drugs worldwide.[5] Aspirin relieves pain in high doses (500 mg), but is not an effective analgesic at low doses (75–150 mg). Low-dose aspirin, however, has an antithrombotic effect conferred by inhibition of platelet aggregation by irreversible blockage of the COX-1 enzyme.[6,13] Accordingly, the main indication for low-dose aspirin is prevention and treatment of occlusive vascular events in patients with ischemic heart disease, transient ischemic attack**,** or stroke.[14] Moreover, increasing evidence supports the effectiveness of long-term aspirin use for chemoprevention.[15]

Non-aspirin NSAIDs are designated to treat a range of pain and inflammatory conditions.[16,17] Non-aspirin NSAIDs may be indicated to treat non-inflammatory pain syndromes (*e.g.*, lower back pain, postoperative pain, or cancer-related pain) when the effect of non-pharmacological treatment and other analgesics, such as acetaminophen, is insufficient.[16] It may also be used for pain conditions when concurrent inhibition of prostaglandin synthesis is beneficial, *e.g.*, dysmenorrhea or ureteral stones.[16] The main indication, however, is treatment of inflammatory conditions with painful, stiff and/or swollen joints such as

arthritis or ankylosing spondylitis.[16,17] Non-aspirin NSAID use, however, does not improve prognosis of these conditions and should therefore be used in lowest effective dose for the shortest duration possible.[16,17] Still, long-term treatment may become necessary to treat symptoms of chronic inflammatory conditions.[16]

NSAIDs are available both as prescription and over-the-counter drugs.[5,18] Consistent with reports from other Western countries,[19] the proportion of Danish residents redeeming a prescription for a non-aspirin NSAID is around 60% within an eight-year period.[18] Annually, the overall prevalence of prescribed non-aspirin NSAID use in Denmark is around 15%,[5] with higher prevalence among women and the elderly (Figure 2).[5] In Denmark, coxibs and etodolac are used almost exclusively among individuals above 40 years, whereas ibuprofen, naproxen, and diclofenac are the most frequently used agents among younger individuals.[5] The potential chemopreventive effect of long-term low-dose aspirin use may increase the proportion of patients prescribed aspirin rather than non-aspirin NSAIDs.[15] Still, the prevalence of non-aspirin NSAID use is expected to increase due to the aging of the population and the concomitantly increasing prevalence of patients with painful degenerative and inflammatory rheumatic conditions.[20]

Figure 2. The one-year prevalence of the Danish population redeeming a prescription for non-aspirin NSAIDs between 1999 and 2013 in gender and age groups. Modified from Schmidt *et al*., Clin Epidemiol, 2014.[5]



2.3 NSAIDs' pharmacodynamic effects

NSAIDs exhibit their anti-inflammatory effect by inhibiting the COX enzyme, which is the rate-limiting enzyme in prostaglandin synthesis (Figure 3).[10] There are at least two major isoforms of the COX enzyme — COX-1 and COX-2.[10] Both isoforms catalyze the conversion of the unsaturated fatty acid arachidonic acid (C20:4) into prostaglandin H_2 through the intermediate product of prostaglandin G_2.[10] Prostaglandin H_2 is then finally converted by tissue-specific isomerases into bioactive lipids called prostanoids.[10] Acting through

multiple G-coupled protein receptors,[21] these prostanoids are mediators of a variety of biological effects, including pain, inflammation, and fever, and are also gastroprotective.

The COX-1 and COX-2 isoforms have quite similar kinetics, but elicit important differences in their regulatory mechanisms, cell localization, and function.[10] COX-1 is expressed constitutively in most tissues, *e.g.*, platelets, parietal cells, and kidney cells, and regulates normal cellular processes such as platelet aggregation, gastric cytoprotection, and kidney function.[10] Inhibition of the endogenous COX-1-mediated production of prostaglandins in the gastric mucosal cells accounts for the gastrointestinal toxicity of NSAIDs.[9]

In contrast, COX-2 is usually undetectable in most tissues, but is expressed in response to inflammation, *e.g.*, in atheromatous plaques and neoplasms.[10] Also, COX-2 is expressed in normal endothelial cells in response to shear stress.[22] Inhibition of COX-2 is associated with suppression of prostacyclin (prostaglandin I_2), which is the dominant prostanoid produced by endothelial cells.[10] Prostacyclin protects the endothelial cells during shear stress,[22] produces local smooth muscle cell relaxation and vasodilation, and interacts with platelets to antagonize aggregation.[23] Platelets contain only COX-1, which converts arachidonic acid to thromboxane A_2, the dominant COX product produced by platelets and a potent proaggregatory and vasoconstrictive agent.[23]

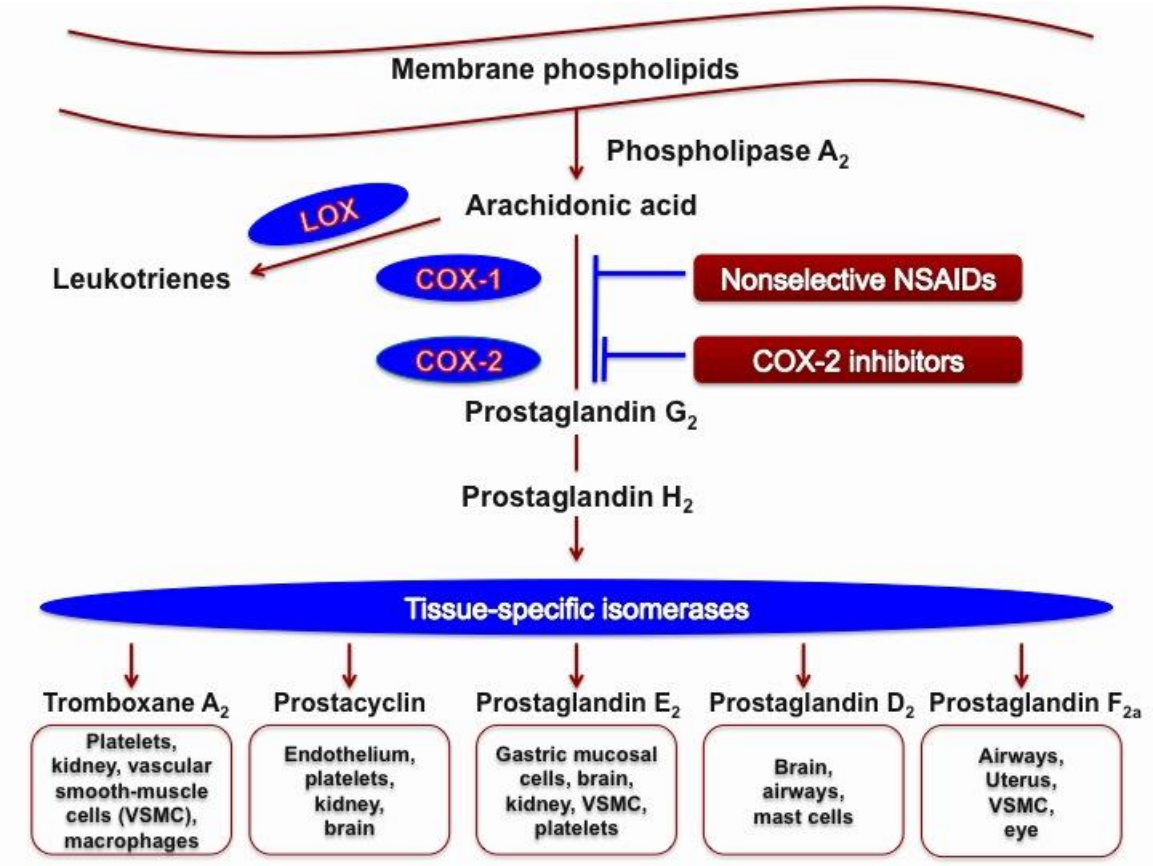


Figure 3. The effect of NSAIDs on the bio-synthesis of prostanoids from arachidonic acid. Adapted in part from FitzGerald GA *et al*., New Engl J Med, 2001.[5]

2.4 COX-2 inhibition and the cardiovascular system

Hemostasis of the cardiovascular system depends on equilibrium between prostacyclin and thromboxane A_2. Even before the approval of coxibs,[24,25] it was anticipated that such drugs could constitute a cardiovascular hazard.[24,25] The proposed underlying mechanism was that selective COX-2 inhibition would shift the prothrombotic/antithrombotic balance on the endothelial surfaces in favor of thrombosis by inhibiting the generation of COX-2-derived vascular prostacyclin while the COX-1-mediated generation of thromboxane A_2 was left unaffected.[10]

Other factors contributing to the cardiovascular hazard of selective COX-2 inhibition include acceleration of atherogenesis because prostacyclin has a protective role in the development of atherosclerosis,[26,27] blood pressure elevations (higher increase for COX-2 inhibitors than nonselective NSAIDs)[28,29] and risk or exacerbation of heart failure.[30-32] Also, a less protective effect of COX-2 up-regulation during myocardial ischemia may lead to larger infarct size, greater thinning of the left ventricular wall in the infarct zone, and an increased tendency to myocardial rupture.[33,34]

2.5 Established cardiovascular risks associated with non-aspirin NSAID use

The hypothesized thromboembolic risks of selective COX-2 inhibition were not tested in the clinical setting until years later. The first clinical data emerged in the Vioxx Gastrointestinal Outcome Research (VIGOR) study, in which the risks of upper gastrointestinal events were compared between rofecoxib (50 mg/day) and naproxen (500 mg twice/day) in 8,076 patients with rheumatoid arthritis.[35] In VIGOR, a 50% reduction in gastrointestinal events (relative risk (RR)=0.5, 95% confidence interval (CI): 0.3–0.6) among rofecoxib users coincided with a more than two-fold increased risk for the combined outcome of thrombotic cardiovascular events (RR=2.38, 95% CI: 1.39–4.00),[36] including a five-fold increased rate for myocardial infarction (20 *vs.* 4 events).[11,37] However, the lack of a placebo arm and a debated cardioprotective effect of naproxen rendered the cardiovascular risk of rofecoxib use controversial at the time.[10]

In the second major randomized controlled trial, the Celecoxib Long-term Arthritis Safety Study (CLASS) randomized use of celecoxib (800 mg twice/day) *vs*. ibuprofen (800 mg 3 times/day) or diclofenac (75 mg twice/day) in 8,059 patients with osteoarthritis or rheumatoid arthritis.[38] While the initial publication of the data suggested that celecoxib reduced the risk of adverse gastrointestinal events compared with its traditional NSAID comparators, this turned out not to be the case when the complete data became available.[39] CLASS demonstrated no increased risk of cardiovascular events (0.9% for celecoxib *vs*. 1.0% for ibuprofen/diclofenac).[36] Comparing the designs of VIGOR and CLASS, it should be noted that VIGOR included only patients with rheumatoid arthritis, who are known to have at 50% higher risk of myocardial infarction than patients with osteoarthritis or no arthritis.[40] Also, while low-dose aspirin use was precluded in VIGOR, it was used among 20% in CLASS, which may in part have neutralized the thrombogenic effect of celecoxib.[36]

Several years passed before the manufacturer withdrew rofecoxib from the market (September 30, 2004). This voluntary withdrawal was due to the results from the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.[41] APPROVe was a long-term, multicenter, randomized, placebo-controlled, double-blinded trial designed to determine the effect of three years of treatment with rofecoxib on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.[41] APPROVe showed that use of rofecoxib more than doubled the risk of cardiac events (hazard ratio (HR)=2.80, 95% CI: 1.44–5.45), and that the overall cardiovascular risk was not influenced by use of low-dose aspirin.[41] As a consequence of APPROVe, it became clear that the cardiovascular safety of all non-aspirin NSAIDs, including the traditional agents, needed a thorough evaluation.

Current evidence, as summarized in meta-analyses, supports that all non-aspirin NSAIDs increase the risk of heart failure and elevated blood pressure, whereas the risk of thrombotic events varies with the type of drug.[28,42] Use of coxibs is associated with the highest vascular risk,[42,43] whereas naproxen appears to have the least harmful cardiovascular risk profile.[42,43] Moreover, increasing evidence supports that traditional NSAIDs with a preference for COX-2, in particular diclofenac, have thrombogenic properties similar to coxibs.[42] Independent of treatment duration[44] and time passed since first myocardial infarction,[45] the associated cardiovascular risk of COX-2 selective inhibitors is a particular concern among patients with existing heart disease.[32,46]

The withdrawal of rofecoxib and subsequent increased focus on NSAID-associated cardiovascular risks have reduced the use of several non-aspirin NSAIDs in Denmark.[5] Most notably, use of coxibs nearly ceased after 2004.[5] Following recommendations from the Danish Medicines Agency in 2008[47] and the Danish Society for Cardiology in 2009[48] to prescribe diclofenac with caution due to its associated cardiovascular risks, diclofenac use has decreased by half since 2008.[5] In contrast, over-the-counter use as well as prescription use of ibuprofen has continued to increase throughout the same period, whereas naproxen use has remained stable despite the reported less harmful cardiovascular risk profile.[5]

According to the American Heart Association, selective COX-2 inhibitors increase the risks of myocardial infarction, stroke, heart failure, and hypertension.[23] However, it is less clear whether use of COX-2 inhibitors or other non-aspirin NSAIDs is also associated with adverse events in the growing proportion of patients with ischemic heart disease who receive percutaneous coronary intervention (PCI) with stent implantation (Figure 4). Use of non-aspirin NSAIDs may also influence the risk and prognosis of other major cardiovascular diseases. Thus, whether use of non-aspirin NSAIDs increases the risk of venous thromboembolism, atrial fibrillation, or a fatal outcome from stroke remains largely uninvestigated.

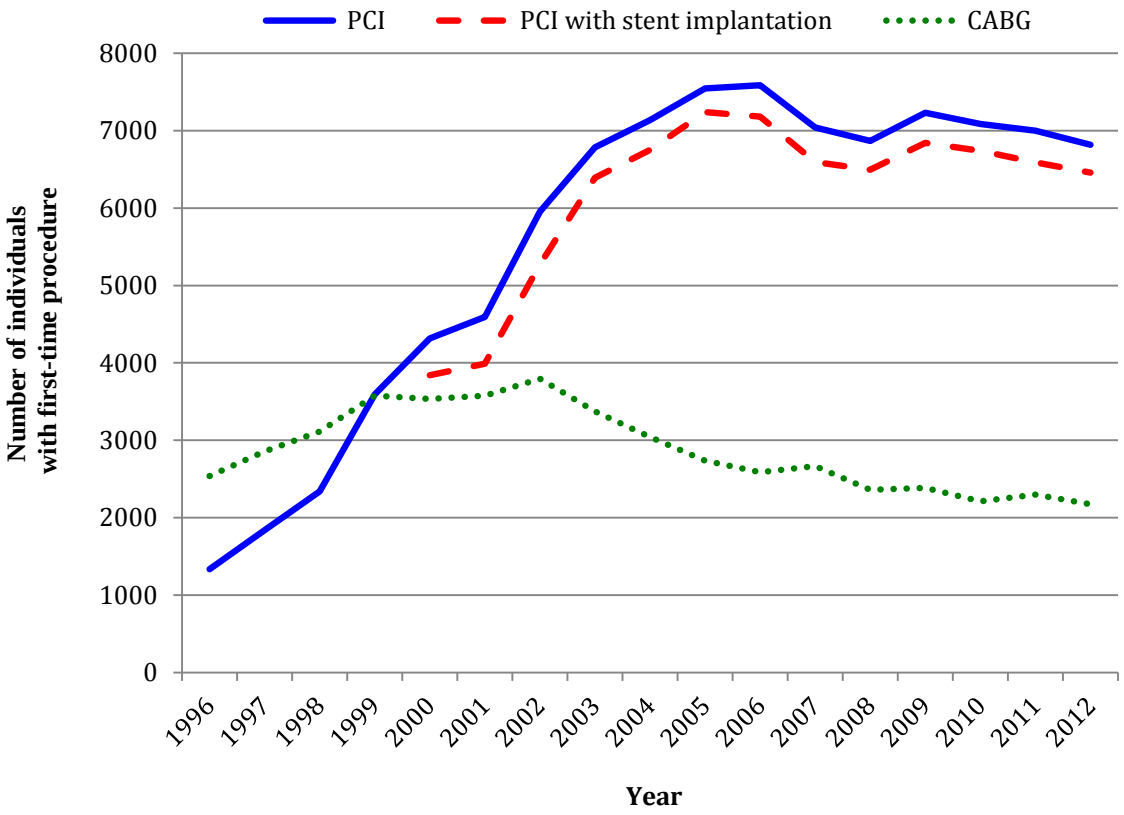


Figure 4. Number of individuals registered in the Danish National Patient Registry with a first-time percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during 1996–2012.

2.6 Literature review

To review the existing literature, we searched Medline using Medical Subject Headings (MeSH), creating first the search builder from "AND/OR" combinations of Major MeSH topics. If the search only revealed a few hits, non-Major MeSH topics were used instead. Titles and abstracts of all English written papers were then reviewed and relevant papers were selected according to the PICO criteria (population, intervention/exposure, comparison, and outcome).[49,50] Finally, related papers highlighted by Medline or Web of Knowledge for each selected paper were reviewed together with relevant papers from the reference list of the selected papers. An overview of the search terms and literature is provided in Table 1.

Table 1. Summary of literature

Study I: Non-aspirin NSAID use and stent-related outcomes			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Kang H *et al.*[51] - Eur Heart J - 2012	- RCT (Mini-COREA trial) - South Korea (five-center trial) - Randomization - 2006–2009	- DES-treated patients (n=909) - Celecoxib (200 mg twice/day for 3 months) - 6-month in-stent luminal loss (LL). Secondary: MACE (cardiac death, non-fatal MI, or TLR)	- Reduction in LL (for both paclitaxel- or zotarolimus-eluting stents). Reduced clinically driven TLR (5.7 *vs.* 3.2%, p=0.09), without increasing MACE (8.6 *vs.* 7.7%, p=0.84). - Open-label trial. Imprecise estimates for individual MACE components due to few events.
Engoren M *et al.*[52] - Ann Thorac Surg - 2011	- Cohort study - US - Cardiac surgery database - 1997–2006	- CABG patients - Postoperative ketorolac (15–30 mg i.v. loading dose, followed by 15–30 mg every 6 h as needed. - Graft occlusion (angiographically proven)	- aHR (ketorolac users *vs.* propensity score matched controls)=0.56 (0.45–0.69) for any graft occlusion and 0.71 (0.53–0.95) for all-cause mortality. - Not restricted to stent patients, which complicate comparison.
Schmidt M *et al.*[1] - Pharmacother - 2011	- Cohort study - Western Denmark - WDHR, NPR, PR, CRS, CDR - 2002–2005	- Patients with BMS or DES (n=13,001) - nsNSAIDs, older COXIs, coxibs (time-varying) - MACE (MI, stent thrombosis, TLR, or cardiac death)	- aHR=1.04 (0.83–1.31) for nsNSAIDs and 1.00 (0.81–1.25) for COX2Is. - Imprecise estimates for some subgroup analyses due to few events, in particular stent thrombosis. Small risks associated with individual NSAIDs cannot be ruled out.
Chung X *et al.*[53] - Circ Cardiovasc Interv - 2010	- RCT (COREA-TAXUS trial) - South Korea (two-center trial) - Randomization - 2004–2006	- DES-treated patients (n=274) - Celecoxib (400 mg before PCI, 200 mg twice/day for 6 months after) - 2-y MACE (cardiac death, non-fatal MI, TLR)	The early efficacy benefit at 6 months for celecoxib *vs.* non-use was maintained at 2 y (MACE: 6.9% *vs.* 19.7%; TLR: 6.2% *vs.* 18.2%) without an increased risk for cardiac death or MI (1.5% *vs.* 1.4). - Open-label trial. Small sample size. Only celecoxib examined.
Ray X *et al.*[54] - Circ Cardiovasc Qual Outcomes - 2009	- Cohort study - US, Canada, UK - Medicaid, Health database, GPRD - 1999–2004	- Patients with MI, PCI/CABG, or unstable angina (n=48,566) - nsNSAIDs and COX2Is - MACE (MI or out-of-hospital cardiac death)	- aHR with restriction to angioplasty/stent patients=0.99 (0.66–1.48) for naproxen, 1.28 (0.85–1.93) for ibuprofen, 1.00 (0.52–1.93) for diclofenac, 1.15 (0.85–1.56) for celecoxib, 1.49 (1.08–2.05) for rofecoxib. - Not restricted entirely to stent patients. First 45 days of follow-up not included.
Koo BK *et al.*[55] - Lancet - 2007	- RCT (COREA-TAXUS trial) - South Korea (two-center trial) - Randomization - 2004–2006	- DES-treated patients (n=274) - Celecoxib (200 mg twice/day for 6 months) - 6-month in-stent luminal loss (LL). Secondary: cardiac death, non-fatal MI, TLR.	Reduced LL among celecoxib users (0.49 mm, SD 0.47) compared with non-users (0.75 mm, SD 0.60). Absolute difference 0.26 mm (0.12–0.40). Also reduced risk of secondary endpoints, driven by a reduced need for TLR. - Open-label trial. Small sample size. Only celecoxib examined.
Gislason GH *et al.*[46] - Circulation - 2006	- Population-based cohort study with case-crossover analysis - Denmark (nationwide) - NPR, PR, CRS - 1995–2002	- Patients with first-time MI (n=58,432) - Ibuprofen, diclofenac, celecoxib, rofecoxib, and other NSAIDs - Re-hospitalization for MI (re-MI), all-cause death	- aHR for death=2.80 (2.41–3.25) for rofecoxib, 2.57 (2.15–3.08) for celecoxib, 1.50 (1.36–1.67) for ibuprofen, 2.40 (2.09–2.80) for diclofenac, 1.29 (1.16–1.43) for other. Dose-related risk of death. Also increased risks for re-MI for all drugs. - Not restricted to stent patients, which complicates comparison. Confounding by underlying disease severity cannot be excluded.

Study II: Non-aspirin NSAID use and venous thromboembolism risk			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Bergendal A *et al.*[56] - Pharmacoepidemiol Drug Saf - 2013	- Case-control study - Sweden (nationwide) - Thrombo Embolism Hormone Study - 2003–2009	- Females aged 18–64 y - Propionic-, acetic acid derivatives, coxibs - First-time VTE (n=1,433) - Matched population controls (n=1,402)	- aOR: 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.*[19] - Pharmacoepidemiol Drug Saf - 2011	- Case-control study - The Netherlands - PHARMO Record Linkage System - 1990–2006	- General population >18 y (source) - NSAIDs, acetaminophen, tramadol - First-time PE (n=4,433) - Matched controls (n=16,802)	- aOR(any NSAIDs): 2.39 (2.06–2.77) for current use, 1.23 (1.14–1.34) for past use, 4.77 (3.92–5.81) for new use, 2.14 (1.48–3.09) for long-term use. aOR highest for tNSAIDs (3.19, 2.73–3.72), diclofenac in any dose (3.85, 3.09–4.81) and >150 mg (6.64, 3.56–12.4). OR=1.74 (1.42–2.14) for acetaminophen, 4.07 (2.86–5.75) for tramadol. - Indications of at least some confounding by underlying pain indication.
Schmidt M *et al.*[2] - 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)	- aOR(nsNSAIDs)=2.51 (2.29–2.76) overall and 2.06 (1.85–2.29) for long-term users. aOR (COX2Is)=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 cannot be excluded.
Sundström *et al.*[57] - BJOG - 2008	- Nested case-control study - UK - GPRD - 1992–1998	- Women 15–49 y 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 (exposed: 10 cases and 12 controls), only mefenamic acid examined.
Lacut K *et al.*[58] - Haematologica - 2008	- Case-control study - France - The EDITH study - 2000–2004	- General population >18 y (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.*[59] - Thromb Res - 2008	- Animal experimental study - Belgium - 2008	- Murine venous thrombosis model - Rofecoxib (4 wk.) - VTE	- Enhanced prothrombotic effect detected in lean mice. - Not population-based clinical setting, only rofecoxib examined.
Huerta C *et al.*[60] - Arch Intern Med - 2007	- Nested case-control study - UK - GPRD - 1994–2000	- General population (source) - tNSAIDs (drugs not specified) - VTE (DVT/PE) (n=6,550) - Matched controls (n=10,000)	- aOR=1.86 (1.65–2.10) for VTE, 2.17 (1.89–2.50) for DVT, 1.60 (1.37–1.87) for PE. OR for VTE=2.82 (2.35–3.39) within 0–30 d, 1.68 (1.39–2.04) within 31–365 d, 1.26 (1.04–1.54) >1 y. No association for long-term users with osteoarthritis (estimates not provided). - No data on individual NSAIDs. No subgroups examined other than osteoarthritis.
Westgate EJ and FitzGerald GA[61] - PLoS Med - 2005	- Case report - US	- 25 y old woman: >3 y oral contraceptive use, nonsmoker, 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–y period of apparent tolerance) or prolonged stasis due to a 6–h car trip (despite having taking similar trips on multiple occasions).
Chan AL[62] - 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 except celecoxib were ruled out. The adverse reaction was determined as probable according to the Naranjo probability scale. - Risk of chance and confounding cannot be ruled out.
Layton D et al.[63] - Rheumatology (Oxford) - 2003	- Cohort study - England - NHS PR, GP-questionnaires - 1996–1997 (meloxicam); 1999 (rofecoxib)	- GP-treated general population cohort - Rofecoxib *vs.* meloxicam (reference) - Thromboembolic (cardiovascular, VTE, or cerebrovascular) events within 9 months	- Number of VTEs=6/15268 (0.05%) for rofecoxib and 20/19 087 (0.10%) for meloxicam users. aRR for VTE=0.29 (0.11–0.78). - COX-2 selective reference group makes comparison to non-users difficult. No data on other NSAIDs. Risk of non-response bias.
Tsai AW *et al.*[64] - 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) after adjustment for age-, race-, and sex. No association (estimate not provided) after further adjustment for BMI and diabetes. - No data on individual NSAIDs or new-/long-term use. Unclear if the null association relates to an increased, but non-significant HR due to limited sample size.
Bombardier et al.[35] - New Engl J Med - 2000	- RCT (VIGOR) - 301 centers in 22 countries - Randomization - 1999	- RA patients (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.[11,63,65] - Designed to evaluate gastrointestinal toxicity, but not powered to detect differences of individual thromboembolic events. VTE results not part of original paper.
Crofford LJ *et al.*[66] - Arthritis Rheum - 2000	- Case report - US - 1999	- 56 y old woman with systemic sclerosis and lupus anticoagulant - Celecoxib (200 mg/day) for leg pain	- PE two days after drug initiation. - Although temporal relationship, risk of chance and confounding cannot be ruled out. Risk of protopathic bias.

Study III: Non-aspirin NSAID use and atrial fibrillation risk			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Krijthe BP *et al*.[67] - BMJ Open - 2014	- Cohort study - The Netherlands - Rotterdam Study, PR, NPR, CRS - 1990–2009 (interval follow-up)	- Participants >55 y without AF (n=8,423) - NSAIDs (any type) (time-varying use) - AF (from ECG or MR) (n=857)	- aHR=1.76 (1.07–2.88) for current use and 1.84 (1.34–2.51) for recent past use (within 30 days after discontinuation), but not past use 31–180 days (1.00, 0.77–1.29) or >180 (1.04, 0.88–1.22) after discontinuation. - No data on individual NSAIDs, indications, and limited sample size.
Chao T *et al.*[68] - Int J Cardiol - 2013	- Case-control study - Taiwan (nationwide) - NHIRD - 2000–2009	- General population (source) - tNSAIDs and coxibs - First-time AF ≥18 y (n=7,280) - Matched controls (n=72,800)	- aOR(tNSAIDs or coxibs)=1.14 (1.06–1.23), 1.65 (1.38–1.97) for new use, 1.92 (1.49–2.48) for new use in HF; aOR(coxibs)=1.20 (0.95–1.28), 1.66 (1.14–2.41) in CKD and 1.71 (1.20–2.42) in chronic pulmonary disease; aOR(tNSAIDs *vs.* coxibs)=1.39 (1.18–1.64) - Imprecise coxib estimates potentially leading to type 2 error in interpretation.
Bäck M *et al.*[69] - Eur Heart J - 2012	- Population-based cohort study - Sweden (nationwide) - NPR, PR, CDR, CRS, other - 2005–2008	- General population >18 y (n=6,991,645) - tNSAIDs and coxibs (time-varying use) - First-time AF (n=139,323)	- aHR=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.*[3] - 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)	- aOR(nsNSAIDs)=1.17 (1.10–1.24), 1.46 (1.33–1.62) for new users. OR(COX2Is)=1.27 (1.20–1.34), 1.71 (1.56–1.88) for new users. OR(older COX2Is)=1.31 (1.22–1.40); aOR(coxibs)=1.20 (1.09–1.33). Highest risk for CKD or RA patients initiating COX2Is. - No data on AF subtypes or drug indications.
De Caterina R *et al*.[70] - Arch Intern Med - 2010	- Case-control study - UK - GPRD - 1996	- General population (source) - tNSAIDs - Paroxysmal and chronic AF (n=525/1035) - Matched controls 40–89 y (n=10,000)	- aOR for chronic AF (>1 wk.)=1.44 (1.08–1.91) for current and 1.80 (1.20–2.72) long-term (>1 y) use. aOR for paroxysmal AF(≤1 wk.)=1.18 (0.85–1.66) for current and 1.74 (1.11–2.71) for long-term use. - Imprecise estimates for individual NSAIDs.
Zhang J *et al.*[71] - JAMA - 2006	- Meta-analysis	- 116,094 participants in 114 RCTs - Coxibs - Arrhythmias (any) (n=286)	- aRR=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.

Study IV: Non-aspirin NSAID use and stroke mortality			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Rist PM *et al*.[72] - Eur J Intern Med - 2014	- Cohort study - US - Women's Healthy Study - Since 1993	- 39,860 women ≥45 y without NSAID use - NSAIDs (any) - Functional outcome after first-time TIA (n=702) or ischemic stroke (n=292)	- aHR=1.00 (0.77–1.29) for TIA, 1.48 (1.04–2.10) for modified Rankin Scale (mRS) score 0–1, 0.83 (0.52–1.33) for mRS 2–3, and 1.33 (0.68–2.59) for mRS 4–6. - Selfreported NSAID use (≥11 days in the past month) *vs.* non-use (<11 days in the past month). No data on individual NSAIDs.

Abbreviations: aRR=adjusted RR; AF=atrial fibrillation; AFL=atrial flutter; ARIC=The Atherosclerosis Risk In Communities; BMS=bare-metal stent; CABG=coronary artery bypass grafting; CDR=Cause of Death Registry; CHS=The Cardiovascular Health Study; CKD=chronic kidney disease; COX=cyclooxygenase; COX2Is=COX-2 selective inhibitors; coxibs=newer COX-2 inhibitors; CRS=Civil registration system or similar mortality/migration registry; DES=drug-eluting stent; DVT=deep vein thrombosis; GPRD=General Practice Research Database; HF=Heart failure; HR=hazard ratio; MACE=major adverse cardiovascular events; MR=medical records; MI=myocardial infarction; NHIRD=National Health Insurance Research Database; NSAID=(non-aspirin) non-steroidal anti-inflammatory drug; nsNSAIDs=nonselective NSAIDs; NPR=National Patient Registry; OR=odds ratio; PCI=percutaneous coronary intervention; PE=pulmonary embolism; PR=Prescription registry; PS=propensity score; RCT=randomized controlled trial; RR=relative risk; TIA=transient ischemic attacks; TLR=target-lesion revascularization; tNSAIDs=traditional NSAIDs, *i.e.*, nsNSAIDs or older COX2Is; UK=United Kingdom; US=United States; y=year; WDHR=Western Denmark Heart Registry; wk.=week.

Medline search algorithms: relevant papers out of total number of Medline hits + other relevant papers = total number of relevant papers:

- Study I: (("Anti-Inflammatory Agents, Non-Steroidal"[Majr]) AND ("Percutaneous Coronary Intervention"[Majr] OR "Stents"[Majr] OR "Myocardial Ischemia"[Majr])): 6/547 + 0 = 6 in total
- Study II: (("Anti-Inflammatory Agents, Non-Steroidal"[Majr]) AND ("Venous Thrombosis"[Mesh] OR "Pulmonary Embolism"[Majr] OR "Venous Thromboembolism"[Majr])): 1/57 + 11 = 12 in total
- Study III: ("Anti-Inflammatory Agents, Non-Steroidal"[Majr]) AND ("Arrhythmias, Cardiac"[Majr]): 1/48 + 4 = 5 in total
- Study IV: "("Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) AND ("Stroke"[Majr] OR "Intracranial Haemorrhages"[Majr])": 0/310 + 1 = 1 in total

2.7 Non-aspirin NSAID use and stent-related outcomes

The benefits of coronary stents come at the expense of an increased risk of stent-related events — most notably in-stent restenosis and thrombotic stent occlusion (stent thrombosis).[73,74] Stent thrombosis is a feared complication of stent implantation because it most often presents with death or as a large non-fatal myocardial infarction.[73,74] Stent thrombosis can occur acutely (within 24 hours), subacutely (within 30 days), late (within one year), or very late (> one year) after stent placement.[75] Compared with bare-metal stents, reports with 4-year outcomes initially indicated that drug-eluting stents were efficient in reducing the risk of target lesion revascularization (TLR) due to in-stent restenosis (from 20% to <10%), but roughly doubled the risk of late stent thrombosis (absolute risk of 1–2%).[73,74] Recent meta-analyses, however, provide evidence that drug-eluting stents reduce the risk of TLR compared with bare-metal stents without increasing the risk of any safety outcomes (death, myocardial infarction, or stent thrombosis).[76,77]

To prevent adverse arterial events, patients with coronary stents receive more aggressive antiplatelet treatment at least up to one year after stent implantation compared to patients without stents.[78] Due to the stent itself[73,74] and the antiplatelet regimen,[78] stent patients represent a subgroup of patients with ischemic heart disease, for whom the NSAID-associated cardiovascular risks need individual assessment. Data from low-risk populations[79] or patients with existing ischemic heart disease but without stents[44,46] cannot necessarily be extrapolated to stent patients due to the aggressive antiplatelet therapy,[78] the recent coronary intervention that may alter the cardiac safety of NSAIDs,[80] and the potential greater baseline risk.[73]

Previously, a randomized trial (COREA-TAXUS) of 274 stent patients found that six-month adjunctive celecoxib treatment after stent implantation was safe.[53,55] Unfortunately, the safety of other NSAIDs was not studied.[53,55] Another cohort study reported that patients undergoing coronary revascularization (with or without a history of myocardial infarction) had an increased risk of adverse cardiovascular events when diclofenac, ibuprofen, and higher doses of celecoxib and rofecoxib were used.[54] However, coronary revascularization was not restricted to or stratified by stent implantation.[54] Moreover, follow-up did not include the first 45 days after PCI, during which period non-aspirin NSAID use may be particular hazardous.[80] Finally, stent thrombosis, TLR, and cardiac death were not available for investigation as outcomes.[54]

2.8 Non-aspirin NSAID use and venous thromboembolism risk

Venous thromboembolism is a common disease affecting overall 1–2 per 1,000 individuals in Western populations per year.[81] The annual incidence rate, however, increases exponentially with age for both men and women,[82] from <0.5 per 1,000 persons below 40 years of age to about one per 100 persons aged 80 years or more.[82] The classic risk factors for venous thromboembolism include immobilization, recent surgery, trauma, cancer, pregnancy, and use of oral contraceptives or postmenopausal hormonal replacement therapy.[81] Based on the presence or absence of these classic risk factors, venous thromboembolism can

arbitrarily be categorized as provoked (=secondary) or unprovoked (=idiopathic/primary).[81] Venous thromboembolism is associated with increased morbidity and mortality.[81,83] It occurs predominantly in the deep vessels of the lower limbs (*i.e.*, deep vein thrombosis), with subsequent risk of pulmonary embolism and post-thrombotic syndrome.[84] Among patients with pulmonary embolism, 2–4% develop chronic thromboembolic pulmonary hypertension with disabling dyspnea both at rest and with exertion.[85] The recurrence rate after stopping anticoagulant drug therapy is overall 5% per year, and higher after unprovoked (8%) than provoked venous thromboembolism (3%).[86] Recurrent venous thromboembolism is therefore a major clinical problem and recent data show that patients with venous thromboembolism are at considerable increased risk of dying within the first 30 days after diagnosis (3% for deep vein thrombosis and 31% for pulmonary embolism), but also during the remaining 30 years of follow-up with venous thromboembolism as an important cause of death.[83]

By tradition, atherosclerotic and venous thrombosis have been considered two separate disease entities because arterial thrombi mainly comprise platelets, while venous thrombi mainly comprise red blood cells and fibrin.[87] However, the distinction between arterial and venous thrombosis is not trivial.[88,89] Platelets also play a role in venous thrombosis as explained by the biochemical interaction between platelets and the coagulation mechanism (platelet-fibrin units), which is essential for thrombus growth.[90,91] Moreover, these disorders are associated with increased risks of each other,[88,89] and treatment regimens previously only considered for arterial thrombosis may also be effective for venous thrombosis.[92,93]

Selective suppression of COX-2-derived prostacyclin may induce a prothrombotic state that not only affects the risk of arterial vascular events, as outlined previously, but also venous thromboembolism.[10,11] In fact, COX-2 is expressed in greater amounts in venous smooth muscle cells than in arterial cells.[94] Furthermore, prostaglandins stimulate the expression of thrombomodulin, a strong inhibitor of blood coagulation in human smooth muscle cells.[95] A reduced prostaglandin synthesis due to COX-2 inhibition may therefore have a prothrombotic effect.[95]

The association between non-aspirin NSAID use and venous thromboembolism has only been sparsely investigated. The original publication of the VIGOR trial failed to report all cardiovascular events.[35] It was later revealed that the rate of venous thrombosis had been five-fold higher in the rofecoxib group than in the naproxen group, indicating a strong COX-2-associated risk of venous thromboembolism.[11,63,65] However, the precision of the estimates was low (RR=0.17, 95% CI: 0.00–1.37 with rofecoxib as reference), because the trial was not powered to detect differences in individual thromboembolic events.[11,63,65] Subsequent observational studies have reported conflicting results on whether[57,60] or not[58,64] an association exists between traditional NSAIDs and venous thromboembolism. No study has yet examined the association with venous thromboembolism for both nonselective and COX-2 selective NSAIDs.

2.9 Non-aspirin NSAID use and atrial fibrillation risk

Atrial fibrillation is the most common rhythm disorder observed in clinical practice.[96] The incidence rate per 1,000 person-years is overall four, reflecting an increase from below 0.5 in individuals below 40 years of age to above 25 in individuals above 80 years of age.[96] The corresponding prevalence is 0.1% in individuals below 40 years of age and above 10% in individuals above 80 years of age.[96] In addition to age, other well-established risk factors include heart failure,[97] valvular heart disease,[97] hypertension,[97,98] hypertrophic cardiomyopathy,[99] cardiac surgery,[100] diabetes mellitus,[97,98] inflammation (even low-grade),[101,102] hyperthyroidism,[103] obstructive sleep apnea,[104] male sex,[97,98] and adult height.[98,105] Of clinical and public health importance, atrial fibrillation is associated with reduced quality of life[106] and increased risk of heart failure,[107] ischemic stroke,[108,109] and death.[110]

NSAIDs may reduce any inflammatory-associated risk of atrial inflammation.[102] However, NSAID use may also increase the risk of atrial fibrillation through several cardiovascular- and renal-related effects.[111] First, NSAIDs may elicit direct proarrhythmic effects that render the patient more susceptible to atrial fibrillation.[11] Thus, COX-2-derived prostacyclin acts as an endogenous antiarrhythmic agent through its inhibition of epicardial sympathetic nerve activity.[112-114] This inhibition may be particularly important during myocardial ischemia where thromboxane and prostacyclin are released from the acutely ischemic myocardium and their balance is related to the risk of arrhythmias.[115] Experimental animal studies have also shown that selective deletion of cardiomyocyte COX-2 expression in mice induces interstitial and perivascular fibrosis associated with an enhanced susceptibility to arrythmias[116] and that coxibs, independent of their COX-2 inhibition, may inhibit delayed rectifier potassium channels and thereby induce arrhythmia.[117]

Second, NSAIDs may increase the risk of atrial fibrillation through their frequently associated adverse renal effect.[118] Thus, NSAID-associated fluid retention and expansion of the plasma volume may lead to increased left atrial pressure/stretch and subsequent atrial fibrillation.[118] Even short-term use of NSAIDs (<14 days) has been shown to increase left ventricular end-diastolic and end-systolic dimensions on echocardiography.[119] As a result of decreased potassium excretion within the distal nephron, NSAID use may also cause proarrhythmic fluctuations in the potassium level.[118] Finally, an NSAID-associated risk of atrial fibrillation may in part be mediated through heart failure[120] and blood pressure elevations, with the latter occurring due to plasma volume expansion, increased peripheral resistance, and attenuation of diuretic and antihypertensive drug effects.[28,118]

The role of COX inhibition in atrial fibrillation occurrence has only sparsely been investigated in the clinical setting.[70,71] Data from a meta-analysis of 114 clinical trials suggested that use of rofecoxib was associated with an increased risk of any type of cardiac arrhythmia (RR=2.90, 95% CI: 1.07–7.88).[71] However, because only 286 incident arrhythmias were included, precision was low and risk of atrial fibrillation could not be examined separately.[71] Another study found that use of traditional NSAIDs was associated with a 44% increased risk of chronic atrial fibrillation.[71] As of yet, no study has examined the association between COX-2 inhibitors and risk of atrial fibrillation.[70]

2.10 Non-aspirin NSAID use and stroke mortality

Stroke is predicted to remain a leading cause of death and disability worldwide.[121] The incidence rate of hospitalized stroke per 1,000 person-years in Denmark is approximately three,[122] increasing from 1–2 in individuals below 45 years to 13–15 in those above 75 years.[121,122] Thus, more than two-thirds of all strokes occur among persons aged 65 years or older.[123] In this age group, both comorbidity and associated medical treatment, such as NSAID use, is highly prevalent.[5,124]

Comorbidity burden is an important prognostic factor for stroke mortality.[124] Numerous studies have examined whether non-aspirin NSAID use is associated with stroke incidence.[41,43,125] Although the evidence is inconsistent,[42,43] use of different coxibs and diclofenac has been reported to confer increased cerebrovascular risks.[41,43,125] The results from the APPROVe trial indicated a more than two-fold increased risk of cerebrovascular events (HR=2.32, 95% CI: 0.89–6.74) and a recent meta-analysis reported rate ratios more than 2.5-fold increased for ibuprofen (3.36, 95% CI: 1.00–11.60), diclofenac (2.86, 95% CI: 1.09–8.36), etoricoxib 2.67 (0.82–8.72), and lumiracoxib (2.81, 95% CI: 1.05–7.48). Still, it remains unclear whether non-aspirin NSAID use also affects stroke prognosis.

Given the reported thromboembolic properties of COX-2 inhibitors,[12,43,125] their use could potentially lead to larger and more often fatal thromboembolic occlusions compared with non-use. An effect of non-aspirin NSAID use on stroke mortality may also in part be mediated through stroke recurrence,[41,43,125] myocardial infarction,[41] or atrial fibrillation with subsequent risk of heart failure and ischemic stroke.[3] COX-2 inhibition may also impair the pathophysiological response to a stroke by inhibiting the neuroprotective effect of prostaglandin E_2.[126] Any ischemic preconditioning mediated by prior sublethal ischemic insults would also be counteracted by COX-2 inhibition.[127-129]

Despite the previous experimental studies on the role of COX enzymes in cerebral ischemia,[126,130-132] only one study has associated preadmission NSAID use with stroke outcome in the clinical setting.[72] The results from this study demonstrated that non-aspirin NSAID use was associated with an increased risk of stroke with mild functional outcome.[72] No study has examined the effect of preadmission NSAID use on short-term stroke mortality.

2.11 Hypotheses and objectives

We hypothesized that non-aspirin NSAID use increased the risk of stent thrombosis (study I), venous thrombosis (study II), atrial fibrillation (study III), and death from ischemic stroke (study IV). Any adverse effect of non-aspirin NSAID use on these outcomes would have major clinical and public health implications, especially in the elderly, where the prevalence of NSAID use and the occurrence of these diseases are high.

This dissertation therefore examined whether use of non-aspirin NSAIDs was associated with the risk of major adverse cardiovascular events (MACE) after coronary stent implantation (I), risk of venous thromboembolism (II), risk of atrial fibrillation (III), and 30-day stroke mortality (IV).

3. Methods

The methods used for each study are summarized in Table 2.

3.1 Setting

The Danish National Health Service provides universal tax supported healthcare, guaranteeing free and equal access to general practitioners and hospitals and partial reimbursement for prescribed medications, including NSAIDs.[133]

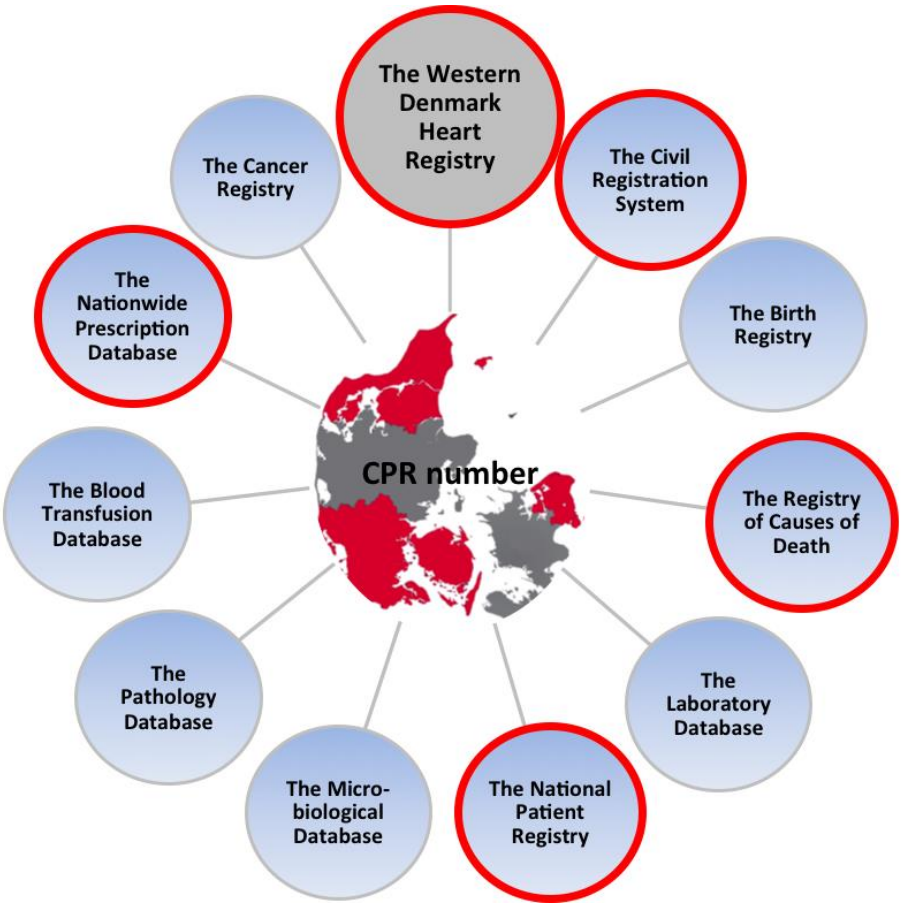


Figure 5. Record linkage potential of Danish medical registries using the Civil Personal Register (CPR) number. Red circles highlight the data sources used. Figure modified from Schmidt *et al.*, Clin Epidemiol, 2010.[106]

3.2 Data sources

Individual-level linkage of all Danish databases is possible using the unique Danish Civil Personal Register number (Figure 5), which is assigned to each Danish citizen at birth and to residents upon immigration.[134] The individual data sources used in this dissertation are described in more detail below. Each of these registries intends to cover all residents in their geographical area (Northern Denmark,[135] Western Denmark,[136] or entire Denmark[134,137-140]) within a given time period.[141] The Civil Registration System includes all inhabitants in Denmark and is therefore a population registry.[141] The others include members of the Danish population with some defining combination of traits, exposures, and events. Hence, these are population-based registries.[141]

Prescription registries (studies I–V)

Pharmacies in Denmark are equipped with electronic accounting systems, which are primarily used to secure reimbursement from the National Health Service.[138] For each redeemed prescription, the patient's Civil Personal Register number, the type of drug prescribed according to the Anatomical Therapeutic Chemical classification system,[142] pack size (number of pills and daily defined doses), and the date of drug dispensing are transferred electronically from the pharmacies to prescription registries.[138] Different dose units for the same pharmaceutical entity can also be identified separately in the prescription registries by use of product codes.[143]

We used three different sources of prescription data.[135,137,138] For study I, we used the Danish National Prescription Registry (*i.e.*, Register of Medicinal Product Statistics), which has complete nationwide coverage since January 1, 1995.[137] For studies II–III, we used the Aarhus University Prescription Database, which includes data on reimbursed medications dispensed at all community pharmacies in the North Denmark Region and the Central Denmark Region.[135] The coverage periods vary between parts (former counties) of the regions, but has since 1998 been complete for the study area of Northern Denmark, defined by the North Denmark Region and the northern part of the Central Denmark Region (excluding the former Vejle county).[135] This study area has (as of 2012) 1,611,864 inhabitants, which approximates to about 30% of the Danish population.[135] The accumulated population in study II (1999–2006) was 1,849,745 and in study III (1999–2008) 2,031,525 inhabitants. For study IV, we used the Danish National Database of Reimbursed Prescriptions, which has nationwide coverage of all reimbursed medications since January 1, 2004.[138]

The Civil Registration System (studies I–IV)

The Civil Registration System is an administrative registry, which has recorded vital statistics, including date of birth, change of address, date of emigration, and exact date of death, for the Danish population since April 2, 1968.[134]

The Western Denmark Heart Registry (study I)

The Western Denmark Heart Registry (WDHR) has collected patient and procedure data from all coronary interventions performed in Western Denmark since January 1, 1999.[136] Western Denmark covers a population of 3 million, which equals 55% of the total Danish population.[136] During our study period, the participating cardiac centers were high-volume centers performing more than 1,500 PCIs per year.[136,144] Interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, pre- or post-dilatation, choice of stent, direct stenting, and peri-procedural glycoprotein IIb/IIIa inhibitor) left to the operator's discretion.[144]

The Danish National Patient Registry (studies I–IV)

The Danish National Patient Registry (DNPR) records information on diagnoses and procedures for patients discharged from all Danish non-psychiatric hospitals since January 1, 1977.[139] Psychiatric inpatient admissions and all somatic and psychiatric emergency room and outpatient specialty clinic contacts have been included since 1995.[139] Each hospital discharge or outpatient visit is recorded with one primary diagnosis and one or more optional secondary diagnoses classified according to the International Classification of Diseases, 8th revision until the end of 1993 and the 10th revision thereafter.[139]

The National Registry of Causes of Death (study I)

The National Registry of Causes of Death has collected data on causes of death in Denmark since 1943.[140]

3.3 Study designs

Within the setting of the Danish population-based healthcare system,[133,141] we conducted two cohort studies (I and IV) and two case-control studies (II and III) (Table 2).[145]

Table 2. Summary of methods

	Study I	Study II	Study III	Study IV
Objectives	To examine whether non-aspirin NSAID use is associated with MACE after coronary stent implantation.	To examine whether non-aspirin NSAID use is associated with risk of venous thromboembolism.	To examine whether non-aspirin NSAID use is associated with risk of atrial fibrillation.	To examine whether preadmission non-aspirin NSAID use is associated with 30-day stroke mortality.
Design	Population-based cohort study.	Population-based case-control study.	Population-based case-control study.	Population-based cohort study.
Data sources	CRS, DNPR, WDHR, CDR, Danish National Prescription Registry.	CRS, DNPR, Aarhus University Prescription database.	CRS, DNPR, Aarhus University Prescription database.	CRS, DNPR, Danish National Database of Reimbursed Prescriptions.
Study region and period	Western Denmark; 1 January 2002 – 30 June 2005 (≥7 year prescription history for all).	Northern Denmark; 1 January 1999 – 31 December 2006 (≥1 year prescription history for all).	Northern Denmark; 1 January 1999 – 31 December 2008 (≥1 year prescription history for all).	Nationwide; 1 July 2004 – 31 December 2012 (≥6 months of prescription history for all).
Study population	Patients with first-time coronary stent implantation (n=13,001). 3 years of follow-up.	General population controls (n=82,218) matched to cases (n=8,368) on age and sex (risk-set sampling).	General population controls (n=325,918) matched to cases (n=32,602) on age and sex (risk-set sampling).	Patients with first-time stroke (n=100,043). 30 days of follow-up.
Exposures	Time-varying use of non-aspirin NSAIDs (current, new, long-term, former and no use).	Non-aspirin NSAIDs (current, new, long-term, former and no use).	Non-aspirin NSAIDs (current, new, long-term, former and no use).	Pre-admission use of non-aspirin NSAIDs (current, new, long-term, former and no use).
Outcomes/ cases	MACE, myocardial infarction, stent thrombosis, target lesion revascularization, cardiac death, and non-cardiac death.	Venous thromboembolism (overall and unprovoked), deep vein thrombosis, and pulmonary embolism.	Atrial fibrillation.	30-day all-cause mortality.
Covariables	Age, sex, diabetes, hypertension, cancer, Charlson Comorbidity Index level, indication for percutaneous coronary intervention, stent type, and time-varying use of statins, aspirin, clopidogrel, and proton pump inhibitors.	Age, sex, CVD, COPD or asthma, diabetes, liver disease, obesity, SCTD, osteoarthritis, RA, osteoporosis, renal failure, recent hospitalization, and use of antipsychotics, hormone replacement therapy, glucocorticoids, VKA.	Alcoholism, cancer, CVD, CKD, COPD or asthma, diabetes, hyperthyroidism, hypothyroidism, liver disease or chronic pancreatitis, RA, SCTD, and use of glucocorticoids.	MI, atrial fibrillation, intermittent claudication, diabetes, obesity, dementia, angina pectoris, heart valve disease, venous thromboembolism, CKD, hypertension, COPD, alcoholism, cancer, RA, SCTD, osteoarthritis, osteoporosis, CVD drugs, glucocorticoids, SSRI, bisphosphonates.
Statistics	Cox proportional-hazards regression.	Unconditional logistic regression.	Conditional logistic regression.	Cox proportional-hazards regression and logistic regression for calculating the propensity score.
Confounder control	Stratification, multivariable adjustment.	Restriction, stratification, multivariable adjustment, unmeasured confounder bias analysis.	Restriction, stratification, multivariable adjustment, unmeasured confounder bias analysis.	Restriction, propensity score matching (Greedy algorithm), multivariable adjustment, stratification.
Subgroups	Consistent use (≥2 prescriptions per year) *vs.* inconsistent (<2).	Age, sex, and presence/absence of cancer, CVD, diabetes, osteoarthritis, RA, SCTD, obesity, trauma or fracture, and recent hospital admission.	Age, sex, and presence/absence of CVD, CKD, osteoarthritis, RA, or SCTD.	Age, sex, presence/absence of RA, osteoarthritis, MI, atrial fibrillation, hypertension, and diabetes.
Sensitivity analyses	Change in exposure window of NSAID use from 60 to 15, 30, and 45 days.	Change in exposure window from 60 to 15, 30, 90, and 120 days; direct drug comparison with ibuprofen as reference; low *vs.* high tablet dose.	Direct drug comparison with ibuprofen as reference; low *vs.* high tablet dose; restriction to patients with primary diagnoses only, no previous use of digoxin/VKA, without inflammatory conditions, and undergoing cardioversion.	Change in exposure window from 60 to 30 days; Restriction to CT or MRI scan-confirmed diagnosis.

Abbreviations: Alcoholism=alcoholism-related disease; CDR=Cause-of-death registry; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; CRS=Civil Registration System; CVD=cardiovascular disease; CVD drugs=angiotensin-converting enzyme inhibitors, angiotensin-II receptor inhibitors, beta-blockers, calcium-channel blockers, diuretics, nitrates, statins, aspirin, clopidogrel, and VKA; DNPR=Danish National Patient Registry; MACE=major adverse cardiovascular events; RA=rheumatoid arthritis; SCTD=systemic connective tissue disease; SSRI=selective serotonin reuptake inhibitors; unprovoked=no pregnancy, major trauma, fracture, or surgery within 3 months preceding venous thromboembolism, or pre-existing cancer or a new cancer diagnosis within 3 months after venous thromboembolism; VKA=vitamin K antagonists; WDHR=Western Denmark Heart Registry.

3.4 Study populations and outcomes

3.4.1 Cohort studies (studies I and IV)

The cohort in study I was defined by all patients with a first-time coronary stent implantation in Western Denmark during 2002–2005. We did not include patients treated by balloon angioplasty without stent implantation. In study IV, we used the DNPR to identify all inpatient primary and secondary diagnoses of stroke during 2004–2012. Patients were included in the study if they received a hospital diagnosis of stroke, but not if they died at home without being hospitalized (approximately 90% of all stroke patients are hospitalized in Denmark).[146] Unspecified strokes, counting up to 40% of all stroke diagnoses in the DNPR, were classified as ischemic strokes because more than two-thirds of these were reported to be ischemic insults.[147] Restricting to incident strokes, we excluded patients diagnosed with stroke or hemiplegia (a secondary measure of previous stroke) in the DNPR before our study period.[124] The study periods were all chosen to ensure at least 6 months of prescription history for all study participants (Table 2).

The outcome measure in the cohort studies was time-to-event.[148] In study I, we defined MACE as the first occurrence of myocardial infarction, stent thrombosis, TLR, or cardiac death. We used the DNPR to identify myocardial infarction admissions.[139] Stent thrombosis and TLR were identified from the WDHR.[136] A committee of cardiac specialists, with members from each of the participating departments of cardiology in the WDHR,[149] reviewed the medical records and catheterization angiograms to adjudicate the occurrence of definite stent thrombosis as defined by the Academic Research Consortium:[75] angiographic confirmation of stent thrombosis and at least one of the following signs present within 48 hours: new onset of ischemic symptoms at rest, new electrocardiographic changes suggestive of acute ischemia, or typical rise and fall in cardiac biomarkers. We defined TLR as a re-PCI or coronary artery bypass grafting of the index lesion.[144] The same committee of cardiac specialists reviewed the original paper death certificates obtained from the National Registry of Causes of Deaths,[140] and classified death according to the underlying cause as cardiac or non-cardiac death. Cardiac death was defined as an evident cardiac death, PCI-related death, unwitnessed death, or death from unknown causes.[75] The outcome in the stroke cohort (IV) was 30-day all-cause mortality, which we obtained from the Civil Registration System.[134]

3.4.2 Case-control studies (studies II and III)

We used the DNPR to identify all cases in Northern Denmark with a first-time inpatient or outpatient diagnosis of venous thromboembolism during 1999–2006 (II) or atrial fibrillation during 1999–2008 (III).[139] We used both primary and secondary diagnoses.[139] The date of the first diagnosis was considered the index date for cases.

We then used the Civil Registration System to select up to 10 general population controls for each case, matched on age and sex.[134] We selected controls using risk-set sampling, *i.e.*, controls had to be alive

and at risk for a first venous thromboembolism/atrial fibrillation on the index date of the case to whom each was matched (Table 2).[150]

3.5 Non-aspirin NSAID use

3.5.1 Prescription and over-the-counter use

We used the prescription registries to identify prospectively all NSAID prescriptions redeemed by the study populations.[135,137,138] Except for diclofenac in a short period (July 16, 2007 to December 14, 2008),[5] the over-the-counter non-aspirin NSAID available in Denmark was 200 mg tablets of ibuprofen (since 27 March 1989).[151,152] Moreover, over-the-counter sales of ibuprofen have over time been restricted to persons aged ≥18 years (since 2011),[153] a maximum of one package per person per day (since 2011),[153] and pack sizes containing a maximum of 20 tablets (since 2013).[154]

Over-the-counter use in Denmark is far less common than in many other countries.[5,56] As a consequence, the potential for identifying NSAID use from prescription registries is substantially higher.[5] As of 2012, it has been estimated that the proportion of total sales of non-aspirin NSAIDs dispensed by prescription and thus captured in the Danish prescription registries is around 66% for ibuprofen and 100% for all other non-aspirin NSAIDs.[5]

3.5.2 Classification

We identified prescriptions for non-aspirin NSAIDs and classified them according to their COX-selectivity as nonselective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid), older COX-2 inhibitors (diclofenac, etodolac, nabumeton, and meloxicam), and coxibs (celecoxib, rofecoxib, and etoricoxib) (Figure 1).[12] Of note, there is an overlap between the older COX-2 inhibitors and coxibs in COX-2 selectivity when comparing the concentration of the drugs (IC_{50}) required to inhibit COX-1 and COX-2 activity by 50%.[12] Thus, the COX-1/COX-2 IC_{50} is 29 for diclofenac and 30 for celecoxib.[12] We therefore also included an overall group of COX-2 inhibitors by collapsing the groups of older COX-2 inhibitors and coxibs (Figure 1).[12] In all studies, we repeated the analyses for the six individual non-aspirin NSAIDs most frequently prescribed, which were ibuprofen, naproxen, diclofenac, etodolac, celecoxib, and rofecoxib.

3.5.3 User categories

We identified NSAID use both from preadmission use (II–IV) and in a time-varying manner throughout follow-up (I). We assumed a given prescription covered a maximum of 60 days, which we defined as current use, after which the participant was regarded as former user unless a new prescription was redeemed. If a true effect of NSAID use exists, we would expect the effect to be greater among current users than among

former users. We chose an exposure window of 60 days to capture most current users, as NSAID prescriptions seldom are provided for more than 60 days at a time in Denmark.[18,151] Also, sensitivity analyses of different exposure windows conducted in relation to previous studies suggested that a 60-day window was appropriate.[155,156] We defined persons with no filled NSAID prescriptions within six (IV) or 12 months (I–III) before their index date as non-users (reference group). Some side effects may arise shortly after therapy initiation[44,119] and inclusion of long-term users, who are more likely to tolerate the drug, may lead to underestimation of the NSAID-associated risks.[157] We therefore divided current users into two groups: new users, defined by having filled their first-ever prescription within 60 days before admission date, and long-term users, defined by having redeemed their first prescription more than 60 days before admission date. In study II the long-term user group was of particular interest because a longer period of use was expected to eliminate protopathic bias, *i.e.*, the association between new NSAID use and prodromal symptoms related to an incipient occurrence of venous thromboembolism.[158]

3.6 Covariables

To characterize the study populations, adjust for confounding, and examine the effect in subgroups of patients (effect measure modification), we obtained information on demographic data,[134] comorbidities (including the Charlson Comorbidity Index[159]) from inpatient and outpatient medical history,[136,139] procedures,[136,139] and comedication use.[135,137,138] When possible, we combined prescription and discharge data to increase sensitivity of covariables such as diabetes and chronic pulmonary disease.

3.7 Statistical analysis

The statistical analyses are summarized below and in Table 2. The full descriptions of the statistical analyses for each study are provided in Appendices I–IV.

For all studies, we initially created contingency tables for the main study variables.[160] In the time-to-event analyses, we followed all patients until date of a non-fatal outcome, death, emigration, or end of follow-up, whichever came first. We used Cox proportional hazards regression, with time since cohort entry as the underlying time scale, to calculate HRs as a measure of the incidence rate ratio (IRR). We used log-log plots to test the proportional hazards assumption graphically. We used logistic regression for the case-control analyses.[161] Because we used risk-set sampling of controls, the odds ratio (OR) estimates the IRR.[150] We calculated 95% 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 and no prior knowledge.[162]

We used different strategies to control for confounding depending on the individual study design (Table 2). In the design phase, we used restriction (I–IV) and propensity score matching (IV).[163,164] Calculating the propensity score, *i.e.*, the conditional probability of non-aspirin NSAID use given all

covariables,[165] we included potential confounders and risk factors in a logistic regression, but not factors associated exclusively with NSAID use.[163,166] Using a greedy matching algorithm,[167] we matched each NSAID user with the non-user with the closest propensity score.[167] The propensity score 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.[167] Of note, we did not propensity score match controls to cases in studies II and III because the control groups in these case–control studies were intended to resemble the population denominator that gives rise to the cases, rather than the cases.[168,169]

In the analyses phase, we used multivariable adjustment (I–IV) and stratification (I–IV). Generally, we compared the crude (I and IV)/age- and gender-matched estimates (II–III) with the adjusted estimates to evaluate the magnitude of confounding from the measured covariables. Confounder selection was based on a clinical evaluation of the expected association with both NSAID use and the outcomes.[170] In general, established risk factors that were prevalent in the study population were considered potential confounders. Also, potential risk factors with an expected strong association to NSAID use were also included as potential confounders when relevant. We stratified on clinically relevant subgroups of patients, including covariables that could potentially indicate underlying mechanisms for an association (*e.g.*, chronic kidney disease in study III).[171] Finally, we estimated by means of a rule-out approach how strongly a single unmeasured binary confounder would need to be associated with NSAID use and the outcome to fully explain our findings (II–III).[172]

We performed a range of sensitivity analyses to examine the extent to which our results were sensitive to changes in methods, analysis assumptions, or values of unmeasured variables (Table 2).[173] To examine the effect of different exposure definitions, we repeated the analyses for exposure windows below and above 60 days (I, II, and IV). We evaluated clinically relevant heterogeneity between drugs, by comparing the risks for individual NSAIDs with ibuprofen as referent exposure (II–III). Because all patients had a need for pain relief, this comparison likely reduced confounding by indication. We used the tablet dose from the last redeemed prescription as a proxy for total daily dose and examined the impact associated with low and high tablet dose (II–III). In study III, we furthermore restricted to primary hospital diagnoses (thereby detecting potential diagnostic surveillance bias), to patients without previous use of digoxin or a vitamin K antagonist (thereby excluding patients previously treated by their general practitioner with no previous hospitalization), to patients who underwent cardioversion within one year after the index date (thereby relating NSAID use to disease severity), and to patients without inflammatory conditions (thereby reducing confounding from systemic inflammation).

4. Results

The main findings are summarized in the following sections.

4.1 Non-aspirin NSAID use and stent-related outcomes (study I)

Independent of COX-2 selectivity, current use of non-aspirin NSAIDs was not associated with an increased rate of the composite outcome of MACE (Table 3). Specifically, the adjusted IRR for MACE was 1.04 (95% CI: 0.83–1.31) for current use of nonselective NSAIDs and 1.00 (95% CI: 0.81–1.25) for current use of COX-2 inhibitors compared with no use. Supporting the composite null result, there was also no substantial association with myocardial infarction, stent thrombosis, TLR, or cardiac death different from that seen among former users. Thus, although small increased IRRs were observed for current use of nonselective NSAIDs for myocardial infarction and for current use of nonselective NSAIDs and COX-2 inhibitors for cardiac death, these IRRs did not vary substantially from the IRRs observed for former users, suggesting that confounding by the underlying condition leading to NSAID use rather than a true drug effect influenced these outcomes. The adjusted IRR for non-cardiac death was 1.82 (95% CI: 1.29–2.55) for current use and 1.36 (95% CI: 1.04–1.78) for former use of nonselective NSAIDs, and 1.91 (95% CI: 1.40–2.61) for current use and 1.51 (95% CI: 1.17–1.97) for former use of COX-2 inhibitors. The results for stent thrombosis were inconclusive due to few events.

Table 3. Non-aspirin NSAID use and major adverse cardiovascular events after coronary stent implantation

	Nonselective NSAIDs			COX-2 inhibitors		
	Rate*	**Unadjusted IRR**	**Adjusted IRR†**	**Rate***	**Unadjusted IRR**	**Adjusted IRR†**
MACE						
No use	65	1	1	64	1	1
Former use	47	1.08 (0.91–1.30)	1.13 (0.94–1.35)	52	1.17 (0.98–1.41)	1.11 (0.93–1.33)
Current use	61	0.99 (0.79–1.25)	1.04 (0.83–1.31)	70	1.09 (0.88–1.35)	1.00 (0.81–1.25)
Myocardial infarction						
No use	19	1	1	19	1	1
Former use	20	1.19 (0.92–1.55)	1.22 (0.94–1.59)	20	1.17 (0.88–1.55)	1.07 (0.81–1.43)
Current use	23	1.24 (0.87–1.77)	1.30 (0.91–1.85)	17	0.89 (0.59–1.35)	0.80 (0.53–1.22)
Stent thrombosis						
No use	4.3	1	1	4.2	1	1
Former use	2.5	0.85 (0.34–2.13)	0.84 (0.33–2.09)	3.3	1.26 (0.54–2.92)	1.28 (0.55–2.96)
Current use	2.8	1.06 (0.47–2.39)	1.04 (0.46–2.36)	2.2	0.84 (0.34–2.06)	0.84 (0.34–2.07)
TLR						
No use	33	1	1	32	1	1
Former use	21	1.99 (0.76–1.27)	0.97 (0.76–1.26)	25	1.10 (0.85–1.42)	1.05 (0.82–1.36)
Current use	31	0.98 (0.72–1.35)	0.97 (0.71–1.34)	34	0.98 (0.72–1.34)	0.91 (0.67–1.25)
Cardiac death						
No use	18	1	1	18	1	1
Former use	9.4	1.01 (0.70–1.46)	1.18 (0.81–1.71)	12	1.35 (0.95–1.92)	1.33 (0.93–1.89)
Current use	20	1.10 (0.74–1.63)	1.24 (0.84–1.84)	28	1.52 (1.08–2.13)	1.40 (1.00–1.97)
Non-cardiac death						
No use	15	1	1	15	1	1
Former use	19	1.26 (0.96–1.65)	1.36 (1.04–1.78)	24	1.72 (1.32–2.22)	1.51 (1.17–1.97)
Current use	25	1.62 (1.16–2.28)	1.82 (1.29–2.55)	32	2.21 (1.62–3.01)	1.91 (1.40–2.61)

Abbreviations: MACE=major adverse cardiovascular event (*i.e.*, myocardial infarction, stent thrombosis, TLR, or cardiac death); NSAID=non-steroidal anti-inflammatory drug; TLR=target lesion revascularization.

*Rate per 1,000 person years.

†Adjusted for covariables listed in Table 2 using Cox proportional hazards regression.

4.2 Non-aspirin NSAID use and venous thromboembolism risk (study II)

Use of non-aspirin NSAIDs was associated with an increased risk of venous thromboembolism (Table 4). The adjusted IRR of venous thromboembolism associated with nonselective NSAIDs was 2.51 (95% CI: 2.29–2.76) for current use, 4.56 (95% CI: 3.85–5.40) for new use, and 2.06 (95% CI: 1.85–2.29) for long-term use. The adjusted IRR of venous thromboembolism associated with COX-2 inhibitors was 2.19 (95% CI: 1.99–2.41) for current use, 3.23 (95% CI: 2.69–3.89) for new use, and 1.92 (95% CI: 1.72–2.15) for long-term use. Former use of nonselective NSAIDs (1.44, 95% CI: 1.33–1.56) and COX-2 inhibitors (1.41, 95% CI: 1.30–1.54) were also moderately associated with an increased venous thromboembolism risk. Because the new user estimates may be influenced by protopathic bias, the two-fold increased risk of venous thromboembolism associated with long-term use likely provided the most valid estimate of the association. Still, the sensitivity analysis of different exposure windows indicated that our estimates might be underestimates of the true risk associated with NSAID use because NSAIDs often are prescribed for less than 60 days in Denmark (eTable 3 in Appendix II).

Supporting the robustness of our results, similarly increased risks were found for unprovoked venous thromboembolism, deep vein thrombosis, pulmonary embolism, individual NSAIDs, and low-dose and high-dose tablets (Tables 2–4 in Appendix II). Finally, we estimated that an unmeasured confounder that is highly prevalent (30%) and four times more frequent among users of COX-2 inhibitors than non-users would need to increase the risk of venous thromboembolism by a factor of 17 or more to explain our findings fully, if no increased risk actually existed (Figure 6). Even stronger confounders would be needed to explain the findings for current use of nonselective NSAIDs or new use of either subclass.

Table 4. Non-aspirin NSAID use and venous thromboembolism risk

	Incidence rate ratio for composite venous thromboembolism		
	No. of cases / No. of controls	**Unadjusted***	**Adjusted†**
No use	5,483 / 66,311	1 (reference)	1 (reference)
Nonselective NSAIDs			
Current use	794 / 2,971	3.24 (2.98–3.52)	2.51 (2.29–2.76)
New use	257 / 543	5.78 (4.97–6.72)	4.56 (3.85–5.40)
Long-term use	537 / 2,428	2.68 (2.43–2.95)	2.06 (1.85–2.29)
Former use	904 / 6,282	1.75 (1.63–1.89)	1.44 (1.33–1.56)
COX-2 inhibitors			
Current use	709 / 2,760	3.10 (2.84–3.38)	2.19 (1.99–2.41)
New use	198 / 546	4.40 (3.73–5.19)	3.23 (2.69–3.89)
Long-term use	511 / 2,214	2.77 (2.50–3.06)	1.92 (1.72–2.15)
Former use	806 / 5,092	1.91 (1.76–2.07)	1.41 (1.30–1.54)

Abbreviations: NSAID=non-steroidal anti-inflammatory drug
*Adjusted for the matching factors of age and gender.
†Adjusted for covariables listed in Table 2 using unconditional logistic regression.

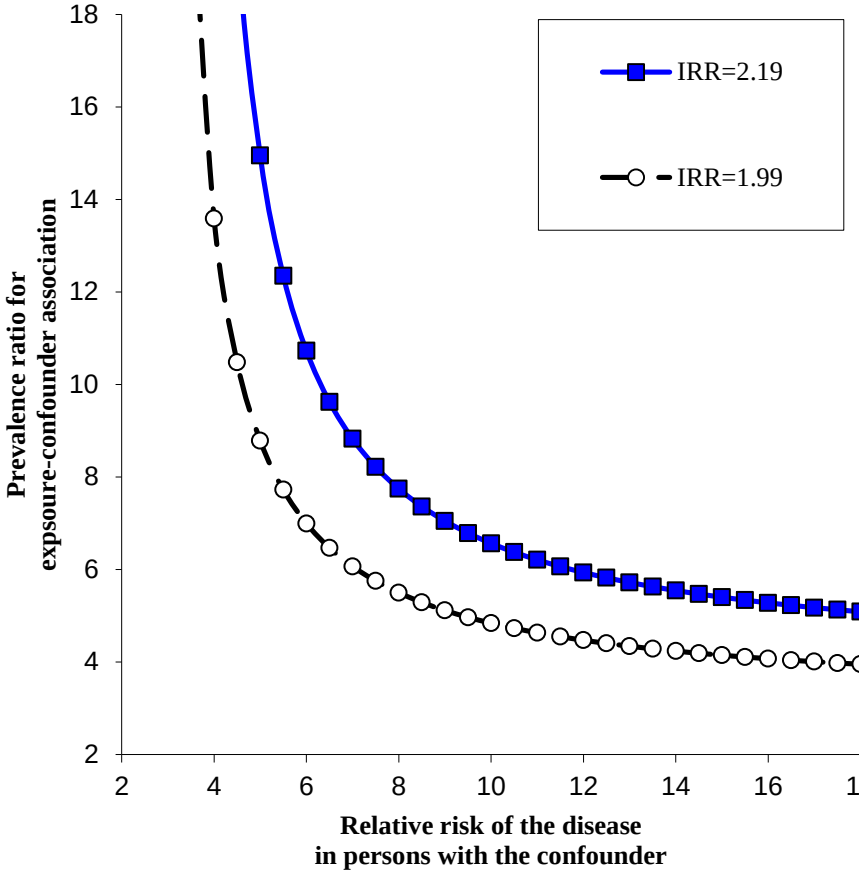


Figure 6. Required strength of an unmeasured confounder
Sensitivity analysis illustrating how strongly an unmeasured confounder would need to be associated with non-aspirin non-steroidal anti-inflammatory drug (NSAID) use and venous thromboembolism to fully explain our estimates. We assumed that the prevalence of the confounder was as common as smoking (30% of the population) and that 10% of the population used NSAIDs. The graphs depict the adjusted incidence rate ratio (IRR) for composite venous thromboembolism associated with current use of COX-2 inhibitors (solid line) along with the lower limit of the 95% confidence interval (dashed line).

4.3 Non-aspirin NSAID use and atrial fibrillation risk (study III)

We found that current use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation. Compared with non-users, the adjusted IRR was 1.17 (95% CI: 1.10–1.24) for nonselective NSAIDs and 1.27 (95% CI: 1.20–1.34) for COX-2 inhibitors (Table 5). Older COX-2 inhibitors and coxibs had similar effect estimates. The association was strongest for new users with a 40–70% relative risk increase, lowest for nonselective NSAIDs (adjusted IRR=1.46, 95% CI: 1.33–1.62) and highest for COX-2 inhibitors (1.71, 95% CI: 1.56–1.88). The IRR was highest in the elderly and among patients with chronic kidney disease or rheumatoid arthritis (Figure 7). The results were robust when restricting to patients without systemic inflammatory conditions (Figure 7). Consistently increased risks were observed for both high-dose and low-dose tablets of all individual NSAIDs, but for ibuprofen, naproxen, and diclofenac the effect was greater for high-dose than low-dose tablets. In the direct drug comparison (eTable 3 in Appendix 3), no NSAID had lower associated risk than ibuprofen, and diclofenac in particular conferred higher risk (1.19, 95% CI: 1.00–1.40 for new use).

Table 5. Non-aspirin NSAID use and atrial fibrillation risk

	No. of cases/controls	Incidence rate ratio	
		Unadjusted*	Adjusted†
No use	24,593/260,139	1.00 (reference)	1.00 (reference)
Nonselective NSAIDs			
Current use	1,385/10,985	1.33 (1.26–1.41)	1.17 (1.10–1.24)
New use	529/3,488	1.59 (1.44–1.75)	1.46 (1.33–1.62)
Long-term use	985/8,433	1.23 (1.14–1.32)	1.05 (0.98–1.13)
Former use	2,315/20,453	1.20 (1.14–1.25)	1.09 (1.04–1.14)
COX-2 inhibitors			
Current use	1,540/10,886	1.50 (1.42–1.59)	1.27 (1.20–1.34)
Older COX-2 inhibitors	977/6,981	1.49 (1.39–1.60)	1.31 (1.22–1.40)
Coxibs	448/3,119	1.51 (1.37–1.67)	1.20 (1.09–1.33)
New use	658/3,689	1.93 (1.76–2.11)	1.71 (1.56–1.88)
Long-term use	1,139/8,801	1.33 (1.24–1.43)	1.10 (1.03–1.18)
Former use	2,078/18,634	1.18 (1.13–1.24)	1.04 (0.99–1.09)
Older COX-2 inhibitors	1,396/12,892	1.11 (1.05–1.17)	1.01 (0.96–1.07)
Coxibs	596/5,152	1.23 (1.13–1.35)	1.02 (0.94–1.12)
Combination‡	79/468	1.79 (1.41–2.27)	1.47 (1.15–1.87)

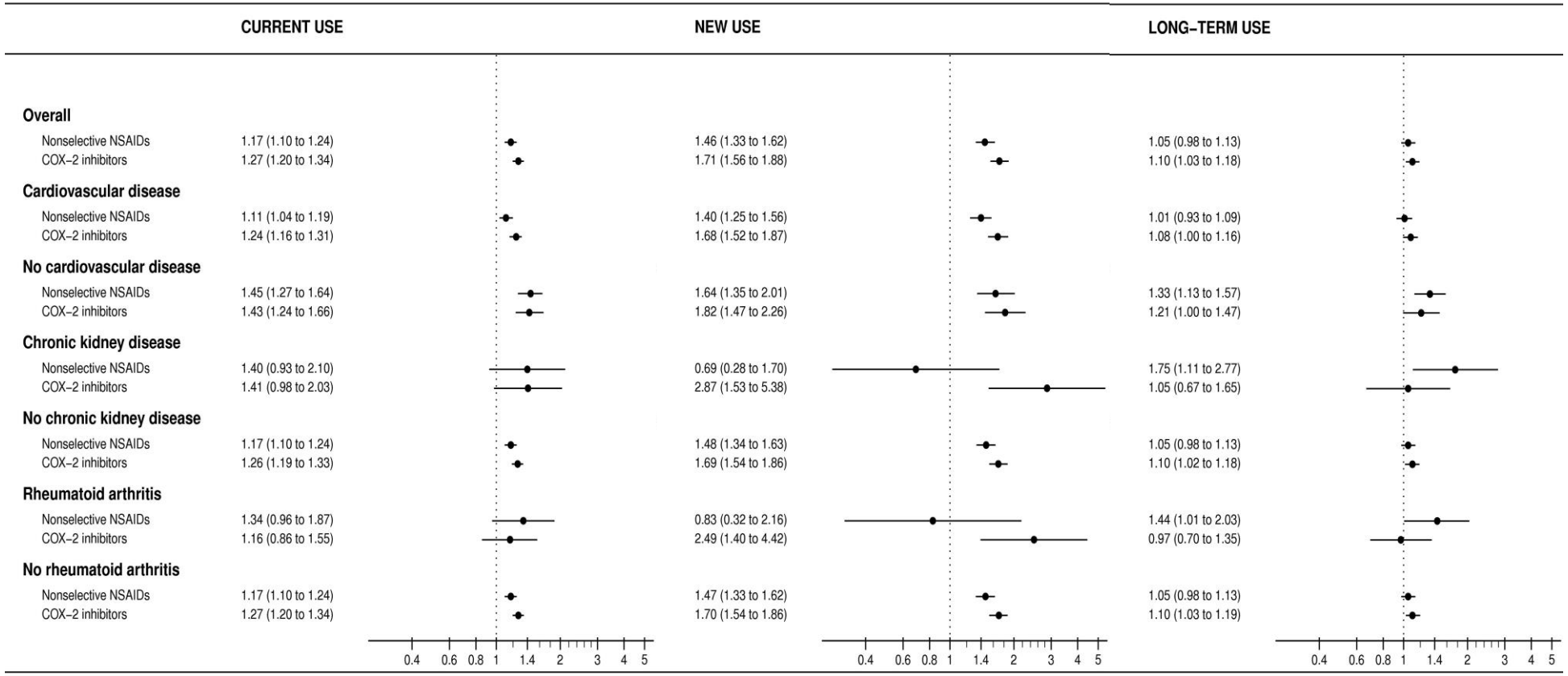
Abbreviations: NSAID=non-steroidal anti-inflammatory drug

*Age- and gender-matched.

†Adjusted for covariables listed in Table 2 using conditional logistic regression.

‡Current use of both nonselective NSAIDs and COX-2 inhibitors.

Figure 7. Adjusted incidence rate ratios associating use of non-aspirin non-steroidal anti-inflammatory drugs and atrial fibrillation risk in patient subgroups



4.4 Non-aspirin NSAID use and stroke mortality (study IV)

We identified 100,043 patients with first-time hospitalization for stroke, among whom 83,736 (84%) had ischemic stroke, 11,779 (12%) had intracerebral hemorrhage, and 4,528 (5%) had subarachnoid hemorrhage. A total of 10.8% were current NSAID users, 8.4% were former users, and 80.8% were non-users. 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.

We found that preadmission use of COX-2 inhibitors was associated with increased 30-day mortality following ischemic stroke, but not 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, driven by the effect among new users (1.31, 95% CI: 1.13–1.52).

The propensity score matching was successful (100% for ischemic stroke, 99.9% for intracerebral hemorrhage, and 99.2% for subarachnoid hemorrhage) resulting in equal distribution of characteristics among NSAID users and non-users (eTable 3 in Appendix IV). The propensity score matched analysis yielded similar results to the multivariable-adjusted analysis for the association between COX-2 inhibitors and ischemic stroke, with a 30-day MRR for ischemic stroke of 1.16 (95% CI: 1.01–1.34) among current users and 1.28 (95% CI: 1.07–1.54) among new users. The results were robust in numerous subgroups of patients and not sensitive to changes in the exposure window for NSAIDs (Table e7 in Appendix IV).

Comparing initiation of different types of COX-2 inhibitors, the increased MRR was driven by older COX-2 inhibitors (1.30, 95% CI: 1.12–1.52), being 1.51 (95% CI: 1.16–1.98) for etodolac and 1.21 (95% CI: 1.01–1.45) for diclofenac (Table 3 in Appendix IV). We observed no association between former use of COX-2 inhibitors and ischemic stroke mortality. Use of non-selective NSAIDs was not associated with 30-day mortality following ischemic stroke.

Table 6. Preadmission use of non-aspirin NSAIDs and 30-day mortality estimates following ischemic stroke.

	30-day mortality risk	30-day mortality rate ratio		
		Unadjusted	Multivariable-adjusted*	Propensity score matched†
No use of any NSAIDs	10.9 (10.6–11.1)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs (current use)	11.1 (10.5–11.8)	1.03 (0.96–1.10)	1.02 (0.96–1.09)	1.03 (0.94–1.12)
New use	11.4 (10.3–12.5)	1.05 (0.95–1.16)	1.11 (1.00–1.23)	1.15 (0.99–1.34)
Long-term use	11.0 (10.2–11.8)	1.01 (0.93–1.10)	0.97 (0.90–1.06)	1.00 (0.89–1.11)
Nonselective NSAIDs (current use)	10.8 (9.9–11.7)	0.99 (0.90–1.09)	1.06 (0.97–1.17)	1.11 (0.97–1.26)
New use	10.4 (9.1–11.7)	0.95 (0.83–1.09)	1.06 (0.93–1.21)	1.06 (0.90–1.25)
Long-term use	11.1 (9.9–12.5)	1.02 (0.91–1.16)	1.07 (0.94–1.21)	1.15 (0.98–1.33)
COX-2 inhibitors (current use)	12.7 (11.5–13.9)	1.18 (1.06–1.30)	1.14 (1.03–1.27)	1.16 (1.01–1.34)
New use	14.0 (12.2–16.0)	1.30 (1.12–1.51)	1.31 (1.13–1.52)	1.28 (1.07–1.54)
Long-term use	11.8 (10.4–13.3)	1.09 (0.96–1.25)	1.04 (0.91–1.19)	1.08 (0.91–1.28)
Older COX-2 inhibitors (current use)	12.6 (11.5–13.8)	1.17 (1.06–1.30)	1.16 (1.04–1.28)	1.18 (1.02–1.37)
New use	13.8 (12.0–15.9)	1.29 (1.11–1.50)	1.30 (1.12–1.52)	1.30 (1.08–1.56)
Long-term use	11.8 (10.4–13.3)	1.09 (0.95–1.25)	1.06 (0.93–1.22)	1.10 (0.93–1.31)
Coxibs (current use)	13.5 (8.5–21.0)	1.25 (0.76–2.04)	0.87 (0.53–1.42)	1.06 (0.53–2.15)
New use	22.9 (12.2–40.5)	2.27 (1.14–4.54)	1.48 (0.74–2.96)	1.93 (0.82–4.53)
Long-term use	9.5 (4.9–18.1)	0.86 (0.43–1.72)	0.61 (0.31–1.23)	0.73 (0.31–1.72)

Abbreviations: NSAID=non-steroidal anti-inflammatory drug

*Adjusted for covariables listed in Table 2 using Cox proportional hazards regression.

†Propensity score matched model that matched NSAID users with non-users based on their probability (propensity score ± 0.025) of using NSAIDs, conditioned on the distribution of covariables listed in Table 2.

5. Discussion

5.1 Main conclusions

We found that use of non-aspirin NSAIDs was not associated with MACE following coronary stent implantation. However, non-aspirin NSAIDs use was associated with an increased risk of venous thromboembolism, atrial fibrillation, and 30-day mortality following ischemic stroke, in particular when therapy with selective COX-2 inhibitors was initiated.

5.2 Comparison with existing literature

In the following subsections, we will provide an updated discussion of our findings taking both the literature published at the time of and after publication into consideration (Table 1).

5.2.1 Non-aspirin NSAID use and stent-related outcomes (study I)

No previous study has examined the cardiovascular risks, including stent thrombosis and TLR, associated with non-aspirin NSAID use in a large cohort of stent patients. An earlier Danish study of 58,432 patients with first-time myocardial infarction reported an increased risk of re-hospitalization for myocardial infarction and all-cause mortality for any use of ibuprofen, diclofenac, celecoxib, and rofecoxib.[46] The study, however, did not restrict to stent patients or include data on stent-related outcomes.[46] Also, naproxen was not studied separately.[46] A multisite cohort study included 48,566 patients from the US, Canada, and the UK with myocardial infarction, coronary revascularization (PCI or coronary artery bypass grafting), or unstable angina.[54] In this study, naproxen users had a lower rate of adverse cardiovascular events than users of ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib.[54] In the subgroup of patients with coronary revascularization with or without stent implantation, only rofecoxib showed an increased risk of the combined outcome of myocardial infarction and out-of-hospital death from ischemic heart disease, whereas there was no association for naproxen, ibuprofen, diclofenac, and celecoxib.[54] Assessing the efficacy of celecoxib in reducing neointimal hyperplasia after coronary stent implantation, the randomized COREA-TAXUS trial followed 274 patients after paclitaxel-eluting stent implantation.[53,55] Both the six-month[55] and two-year[53] outcomes from this trial suggested that the adjunctive use of celecoxib for six months after stent implantation in patients with ischemic heart disease was safe (no increased risk of MACE) and actually reduced the risk of TLR.[53,55] Similar results have recently been reported at six months in the Mini-COREA trial, which included 909 patients and a three-month treatment period with celecoxib, but otherwise had similar design and aim as the COREA-TAXUS trial.[51]

As NSAIDs are prescribed to alleviate pain from non-cardiac diseases, our finding that several of the drugs were associated with non-cardiac mortality to a higher extent than cardiac mortality was expected and supports that all-cause mortality associated with NSAID use is likely to be highly influenced by non-cardiac deaths. This finding is important because many studies have not been able to distinguish cardiac from non-cardiac mortality.

The mechanisms underlying our null results are not entirely clear considering the previously reported cardiovascular risks of particularly COX-2 inhibitors.[41,46,80] As an explanation, the potent platelet inhibition of post-intervention dual antiplatelet therapy with both clopidogrel and aspirin may have negated any excess thrombotic risk of non-aspirin NSAIDs. In support of this hypothesis, a previous study found that an almost two-fold (188%) increased shear stress-induced platelet aggregation due to selective COX-2 inhibition in the presence of an arterial stenosis was neutralized by low-dose (1 mg/kg) clopidogrel.[174]

In summary, among the few studies conducted additionally to ours in patients with coronary stent implantation, two randomized trials and one non-randomized cohort study support that use of diclofenac and celecoxib is not associated with excess cardiovascular risks in this patient subgroup.

5.2.2 Non-aspirin NSAID use and venous thromboembolism risk (study II)

In addition to the VIGOR trial results,[35] which indicated a five-fold higher rate of venous thromboembolism among rofecoxib users than naproxen users,[11,63,65] several other reports have provided evidence of an association between COX-2 inhibition and venous thromboembolism. In three case reports, FitzGerald[61] and others[62,66] have linked use of celecoxib[62,66] and valdecoxib[61] to the occurrence of deep vein thrombosis[62] and pulmonary embolism.[61,66] An enhanced prothrombotic effect of rofecoxib has also been reported in a murine venous thrombosis model.[59] A UK case-control study using 1992–1998 data from the General Practice Research Database found a five-fold or more increased odds of venous thromboembolism associated with use of mefenamic acid among women aged 15–49 previously diagnosed with menorrhagia (OR=5.54, 95% CI: 2.13–14.40).[57] In contrast, a case-control study including 402 cases of unprovoked first-time venous thromboembolic events found no association with NSAID use overall (OR=0.93, 95% CI: 0.44–1.98).[58]

Investigating multiple risk factors for venous thromboembolism, two previous studies included use of traditional NSAIDs.[60,64] Use of traditional NSAIDs was reported not to be associated with venous thromboembolism after confounder adjustment in a cohort study from the US (estimates not provided).[64] A UK case-control study of 6,550 patients found an adjusted OR for venous thromboembolism associated with current use of traditional NSAIDs of 1.86 (95% CI: 1.65–2.10).[60] Similar to our results, the risk increase was observed for both deep vein thrombosis and pulmonary embolism and also persisted for long-term users.[60] As an exception, authors reported that use longer than one month was not associated with an effect in patients with osteoarthritis.[60] Similar to the US study,[64] the estimate for the null association was, however, not provided and therefore it remains unclear whether the null finding was based solely on statistical significance, which would be influenced by the smaller sample size relative to our study.[60] No other subgroups of patients were examined in these two studies.[60,64] We found a consistent association for long-term use of all classes of non-aspirin NSAIDs and among patients with diseases of the musculoskeletal system or connective tissue, including osteoarthritis.

Following our study, two other studies have reported data in support of an association.[19] A case-control study from the Netherlands found that long-term NSAID use was associated with more than a two-fold increased risk of pulmonary embolism.[19] The risk was highest for diclofenac with an overall OR of 3.85 (95% CI: 3.09–4.81), increasing to 6.64 (95% CI: 3.56–12.4) for daily doses >150 mg.[19] The study also

indicated that the association in part may be explained by confounding from underlying medical conditions for which these drugs were prescribed, because painkillers not related to a prothrombotic state (acetaminophen and tramadol) also were associated with risk of pulmonary embolism.[19] Finally, a Swedish nationwide case-control study found that users of high cumulative doses of acetic acid derivatives and coxibs had the highest risks of venous thromboembolism, which indicates a correlation with COX-2 selectivity and dose.[56]

In summary, case reports, animal experimental studies, one randomized control trial, and several case-control studies, including ours, provide evidence of an association between use of COX-2 inhibitors and venous thromboembolism. Larger randomized trials are needed to establish whether the association is causal.

5.2.3 Non-aspirin NSAID use and atrial fibrillation risk (study III)

We found an increased risk of atrial fibrillation associated with use of non-aspirin NSAIDs. Notably, COX-2 inhibitors, in particular diclofenac, were associated with higher risks than nonselective NSAIDs, indicating a potential important pharmacological role of COX-2 inhibition.[12] The increased risk among new users may in part be attributable to direct proarrhythmic effects that render the patient more susceptible to atrial fibrillation as previously described. The adverse renal effects of NSAIDs (*e.g.,* fluid retention, electrolyte disturbances, and blood pressure destabilization)[28,118] may also be a contributing factor as indicated by the finding that patients with chronic kidney disease had a markedly higher risk when initiating therapy with COX-2 inhibitors.[28,118]

A UK case-control study of patients diagnosed in 1996 with chronic (n=1,035) or paroxysmal atrial fibrillation (n=525) found that current use of traditional NSAIDs (nonselective NSAIDs or older COX-2 inhibitors) was associated with an increased risk of chronic atrial fibrillation (OR=1.44, 95% CI: 1.08–1.91) and modestly associated with paroxysmal atrial fibrillation (OR=1.18, 95% CI: 0.85–1.66), *i.e.,* with magnitude of the association similar to our results.[70] In contrast to our results, long-term NSAID use (>1 year) was associated with the largest risk increase (OR=1.80, 95% CI: 1.20–2.72).[70] A meta-analysis, involving 116,094 patients using coxibs, identified 6,394 composite renal outcome events, but only 286 composite arrhythmia outcome events, of which ventricular fibrillation, cardiac arrest, and sudden cardiac death accounted for most.[71] Although rofecoxib was associated with an increased relative risk for the composite arrhythmia outcome (2.90, 95% CI: 1.07–7.88), the small number and types of arrhythmias available for analysis did not allow for an examination of atrial fibrillation risk.[71]

Following our study, three other studies have provided data that support our findings. First, a population-based cohort study from Sweden found an increased risk of atrial fibrillation associated with use of both traditional NSAIDs (HR=1.11, 95% CI: 1.09–1.13) and coxibs (HR=1.16, 1.05–1.29).[69] In this study, coxibs included either celecoxib or the more COX-2 selective etoricoxib.[69] Supporting our finding of an effect that is higher the more COX-2 selective, the risk increase was related to etoricoxib (1.35, 95% CI: 1.19–1.54), but not celecoxib (0.94, 0.79–1.11).[69] A nationwide case-control study from Taiwan found that any NSAID use was associated with an increased risk of atrial fibrillation (OR=1.14, 95% CI: 1.06–1.23), especially among new users (OR=1.65, 95% CI: 1.38–1.97) and patients with heart failure (OR=1.92, 95%

CI: 1.49–2.48).[68] Use of coxibs was associated with an OR for atrial fibrillation of 1.20 (95% CI: 0.95–1.28), increasing to 1.66 (95% CI: 1.14–2.41) among patients with chronic kidney disease and 1.71 (95% CI: 1.20–2.42) among patients with chronic pulmonary disease.[68] Finally, a cohort study using data from the Rotterdam Study also associated current NSAID use with an increased risk of atrial fibrillation (HR=1.76, 95% CI: 1.07–2.88).[67]

In summary, an increasing body of evidence stemming from case-control and cohort studies supports our finding of an association between non-aspirin NSAID use and atrial fibrillation, in particular for use of COX-2 inhibitors.

5.2.4 Non-aspirin NSAID use and stroke mortality (study IV)

The cohort study of functional outcome following ischemic stroke was conducted within the Women's Healthy Study among 39,860 female health professionals aged ≥45 years without previous cardiovascular disease.[72] Functional outcome was defined by the modified Rankin Scale (mRS) score based on the degree of impairment experienced by the patient at hospital discharge.[72] Compared with non-users, NSAID users had an adjusted HR of 1.00 (95% CI: 0.77–1.29) for transient ischemic attacks, 1.48 (95% CI: 1.04–2.10) for stroke with mRS=0–1, 0.83 (95% CI: 0.52–1.33) for mRS=2–3, and 1.33 (95% CI: 0.68–2.59) for mRS=4–6.[72] Because the women were not using NSAIDs at time of enrollment in the study, the estimates pertain to a new user effect.[72] However, the study was limited by self-reported NSAID use and lack of data on individual NSAIDs.[72] Any harmful effect of individual NSAIDs (*e.g.*, diclofenac) may therefore have been attenuated by grouping it with less harmful (non-selective) NSAIDs.[72] Finally, it should be noted that 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 post-ischemic oxidative stress and inflammation.[175]

In summary, no previous study has provided data on the association between preadmission use of non-aspirin NSAIDs and 30-day stroke mortality. The increased mortality rate associated with COX-2 inhibition in our study for ischemic stroke was observed only among current users, which could indicate a drug effect of COX-2 inhibitors through any of the pathways previously described.

5.3 Methodological considerations

5.3.1 Internal validity

All four studies in this dissertation were designed as etiological studies with the aim to examine whether non-aspirin NSAID use was causally related to the study outcomes.[176] However, before inferring causal relationships, the internal validity of each study must be evaluated to assess the potential risk of random and systematic errors that may have affected the estimates of association.[177] By random error (or chance), we refer to the precision of the estimates.[162] By systematic errors, we refer to selection bias, information bias, and confounding.[177] Selection and information biases are systemic errors arising from the study design and therefore cannot be corrected for by statistical analyses.[177] In contrast, confounding can be controlled for by both design (randomization, restriction, and matching) and statistical analyses (standardization, stratification, and adjustment).[177] Below we discuss in more detail the internal validity of each study.

5.3.2 Precision

The precision of the associations was evaluated using 95% CIs.[162] To avoid the persistent misconception that significance testing, expressed by comparison of p-values, is important for the interpretation of data, we interpreted the CIs as quantitative measures indicating the magnitude of effect and degree of precision, rather than as surrogate significance tests.[168]

The large number of outcomes and cases in our studies yielded statistically precise estimates for the primary analyses, which are therefore unlikely to have occurred by chance.[162] The precision was also high in most subgroup analyses, including analyses for individual NSAIDs and outcomes. As an exception, we cannot rule out small risks associated with use of individual NSAIDs and the individual components of MACE in study I, because the CIs for these estimates were wider. As the absolute risk of some outcomes was expected to be low[73,74] and there was no natural single outcome of interest, the primary outcome in study I (MACE) was a composite of several adverse outcomes. Aiming to increase statistical efficiency,[178] MACE had also been used as composite outcome in previous and subsequent studies on the topic.[51,53,54] Also, MACE is often used in clinical trials to reduce the required sample size and the cost of a trial by increasing the event rate in the control group.[179] The trade-off inherent in MACE is that the increased precision of the effect estimates comes at the expense of greater uncertainty in interpretation of the result.[180] It is recommended in general that composite outcomes include components that are similar in severity, frequency (in particular among the more and less severe components), and treatment effect (no substantial variability across components).[180] In practice, these criteria can rarely all be met[178] and our study I was no exception as, *e.g.*, TLR was a less severe, but more frequent complication than stent thrombosis, myocardial infarction, and cardiac death. Composite outcomes are particularly problematic when only one component of the composite outcome is affected or the direction of the effect differs across the individual components.[178] The latter scenario would not only reduce precision, but a strong association with one component may be obliterated by a less strong association in another more frequent component.[178] For transparency, we therefore reported on

the individual components separately and found no evidence that the null result was due to heterogeneous treatment effects. Finally, we note that in recent years (subsequent to our study I) MACE has increasingly been replaced by the composite of major adverse cardiac and cerebral event (MACCE) to acknowledge the importance of stroke as a thromboembolic and hemorrhagic complication to therapy and surgery.[181,182] Still, the choice of MACE was appropriate because study I focused on the stent-related cardiac outcomes.

5.3.3 Selection bias

By selection bias, we refer to the systematic error associated with selection of study participants according to exposure status in cohort studies or according to case or control status in case-control studies.[177] The bias arises when the association between exposure and outcome is different for study participants and non-participants.[177] Because the association among non-participants is rarely known, selection bias cannot be observed, but inferred.[177]

Our population-based designs within 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.[133,141] Moreover, the Civil Registration System allowed accurate accounting for censoring due to death or emigration.[134]

5.3.4 Information bias

Information bias occurs when exposure or outcome data are measured erroneously (misclassified).[177] If the misclassification of NSAID use or outcome data was dependent on the presence of its counterpart, it would have been differential and the direction of the bias would have been less predictable.[177] However, because information on NSAID use, hospital diagnoses, and confounding factors were collected prospectively, we avoided reliance upon self-reporting and thus the potential for differential misclassification due to recall bias.[177] Misclassification of NSAID use was non-differential if independent of the outcomes (and vice versa).[177] Non-differential misclassification most often biases the results towards null (in particular for binary exposure or disease variables).[177] However, if the misclassification depends on misclassification among other variables or if the exposure or disease variable has more than two levels, non-differential misclassification may produce bias away from the null.[177] Below we discuss how non-differential misclassification of NSAID use and the study outcomes may have influenced our results.

Misclassification of NSAID use

Data in Denmark's prescription databases are virtually complete, lacking only in-hospital medication use.[135,137,138] Because the prescription data are prospectively recorded, any misclassification of NSAID use because of "as-needed" prescriptions, non-adherence, or over-the-counter use would likely be non-differential, implying that the effect estimates for current users may be underestimates.[177] Because we categorized NSAID use into three exposure levels (non-use, former use, and current use), non-differential

misclassification between current and former NSAID use may have biased the effect estimates for former users away from the null.[177]

Owing to the reimbursement through the Danish National Health Service's insurance program, regular NSAID users have an economic incentive to obtain the drugs by prescription. Although we had to use redemption of a prescription as a proxy for actual NSAID use, the direct beneficial effects of NSAIDs on a wide range of symptoms also suggest high adherence for chronic users. Furthermore, we based information on NSAID use on actual dispensing at pharmacies for which patients pay a portion, and not just written prescriptions as other studies.[70]

We lacked information on over-the-counter use of NSAIDs. Low-dose (200 mg) ibuprofen accounted for practically all over-the-counter use of non-aspirin NSAIDs in our study periods (between 1999 and 2012), which equals 15–25% of total non-aspirin NSAID sales and 30–35% of total ibuprofen sales.[5] Over-the-counter use of ibuprofen could thus in principle explain part of the null result in study I. However, if NSAID use increased the cardiovascular risk in the stented cohort, we would expect a correlation between the NSAIDs' COX-2 selectivity and the risk for MACE.[42,43] Because we did not observe an increased risk associated with either older COX-2 inhibitors or coxibs, we have no reason to suspect that the null results for ibuprofen were due to non-differential misclassification. Moreover, the magnitude of misclassification bias due to over-the-counter use often has no practical impact on the relative risk estimates.[5] This fact can be illustrated from a hypothetical cohort study scenario where 15% of the population uses non-aspirin NSAIDs every day (as was the average proportion of use in the general Danish population between 1999 and 2012[5]), only two-thirds obtain the drug on prescription (worst-case scenario with ibuprofen), and there is an equal age distribution among new and long-term users.[5] In this scenario, there will be no misclassification of the apparently exposed individuals and only 5% (non-differential) misclassification of the apparently non-exposed (as one-third of 15% will be over-the-counter ibuprofen users who are not captured by the prescription registry).[5] Unless the relative risk estimate is very high, misclassification of this magnitude has no practical impact on the relative risk estimate among the exposed.[5]

Misclassification of outcomes

The individual components of MACE in study I were adjudicated by a specialist committee in relation to previous studies.[144,149] The positive predictive values of diagnoses in the DNPR have previously been validated using medical record review as standard reference and found to be approximately 92–100% for myocardial infarction,[183-185] 75–90% for venous thromboembolism,[93,186] 93–97% for atrial fibrillation,[187,188] 97% for ischemic stroke,[147] 74% for intracerebral hemorrhage,[147] 67% for subarachnoid hemorrhage,[147] and 98% overall for the comorbidities included in the Charlson Comorbidity Index.[184] Mortality data were virtually complete.[134] While the International Classification of Disease code used to identify atrial fibrillation also includes atrial flutter, our results were driven by atrial fibrillation because more than 90% of patients registered with this code have atrial fibrillation.[188] Study III was limited by its inability to separate paroxysmal, persistent, and permanent atrial fibrillation. However, we were able to restrict to atrial

fibrillation cases treated with cardioversion within one year after first diagnosis and thereby relating NSAID use to disease severity. We classified unspecified strokes as ischemic strokes and doing so inevitably misclassified some intracerebral hemorrhages (approximately 6%) as ischemic strokes.[147] Given the lack of association between NSAID use and mortality from intracerebral hemorrhage, such misclassification would bias the results for ischemic stroke towards the null and thus cannot explain our findings. Overall, coding errors of outcomes seem unlikely to have had an important influence on our results, and importantly the accuracy of the hospital diagnoses is unlikely to differ by previous medication exposure, so any misclassification would be non-differential.

5.3.5 Confounding

By confounding, we refer to the lack of exchangeability,[189] arising from the fact that the effect of NSAID use is mixed with the effect of another variable.[177] A confounder must be an independent cause or a proxy/marker for the cause, imbalanced across NSAID categories, and not on the causal pathway between NSAID use and the study outcomes.[177] As previously mentioned, we aimed to reduce potential confounding in both the design or analysis phases of our studies.

In study I, we lacked data on tobacco and alcohol use and had incomplete data on hypertension, all of which are associated with MACE and were likely to be more prevalent among NSAID users than non-users.[190] However, such confounding would bias results towards higher risks in NSAID users, and thus could not explain our null findings. Although we controlled for comorbidity using the Charlson Comorbidity Index, underreported Charlson comorbidities in the DNPR or unmeasured comorbidities may potentially lead to residual or uncontrolled confounding, respectively. However, the Charlson Comorbidity Index in its original form has proved to be an adequate tool for measuring the prognostic impact of comorbidity burden in patients with acute[191] and chronic[192] ischemic heart disease. Confounding by the underlying condition causing pain and leading to NSAID use is likely to influence death from non-cardiac causes and thus explains the association with non-cardiac mortality. Also, NSAIDs may have been prescribed for patients without clear contraindications, which could have led to better than average outcomes for the NSAID-treated patients.

In study II, we lacked data on the use of oral contraceptives, underlying conditions leading to NSAID use, body size, and immobilisation.[81] Because NSAID use was associated with venous thromboembolism among both men and women, oral contraceptives were unlikely to have confounded the effect estimates substantially. Former use was included as a marker of uncontrolled confounding by indication and was associated with venous thromboembolism occurrence, but much less than current use. To what extent physical limitations in mobility, due to for example lower back pain or chronic disease, influenced our results is unclear.

In study III, we lacked data on lifestyle factors, including smoking and body size, and underlying inflammatory conditions leading to NSAID use. In contrast to study II, former use was not associated with the outcome, indicating an effect of current use. Also, the effect estimates did not change when patients with

systemic inflammatory conditions, *e.g.*, rheumatoid arthritis, were excluded. Still, we note that it cannot be ruled out that new users may have more severe underlying inflammation compared with long-term users, which could have increased their risk of atrial fibrillation. In study II and III, we considered the case-control design an efficient alternative to the cohort design for the purpose of estimating relative measures of association, because the OR provides an unbiased estimate of the IRR owing to the risk-set sampling of controls.[150,168,169] Thus, we have no reason to suspect that the results of study II and III would have differed in a cohort setting.[93,169]

In study IV, we observed a balance in the measured variables between users and nonusers after propensity score matching.[167] Slight differences in the estimates between the propensity score matched analyses and the multivariable outcome model may in part be influenced by the exclusions due to matching and any potential treatment heterogeneity (the propensity score matched analysis estimated the average treatment effect in the treated).[163] A strength of propensity score matching is the statistical efficiency even in subgroup analyses where a decreasing number of events becomes a limiting factor for the number of covariables possible to include in the multivariable outcome model.[193,194] The overall agreement between the results from the two approaches is, however, not surprising considering they are based on the same set of covariables. Also, it should be noted that matching on the propensity score may still result in unmeasured variables, such as smoking or body weight being imbalanced between treated and untreated subjects (to the extent such variables are unrelated to the covariables already included in the calculation of the propensity score).[167] Still, the agreement between the two approaches supports the robustness of our findings.

In all studies, we note that we did adjust indirectly for unmeasured lifestyle factors by controlling for hospital-diagnosed chronic obstructive pulmonary disease, obesity, and ischemic heart disease (except in study I) and that our findings in studies II–III could not easily be explained by even a strong single unmeasured confounder. Still, due to the non-randomized design, we cannot exclude the potential risk of residual or unmeasured confounding.

5.3.6 Generalizability

Assuming high internal validity, our results are likely generalizable to most other industrial Western societies with comparable lifestyle, risk factor prevalence, and treatment regimens.[168] The Danish population is homogenous with regards to ethnicity, with a vast majority of Scandinavian and European citizens. The relative estimates of association are likely generalizable to other populations assuming no effect measure modification by environmental factors or ethnicity.[168]

5.4 Clinical implications

This dissertation adds to the increasing body of evidence about the cardiovascular risk and prognostic impact associated with use of non-aspirin NSAIDs. Current guidelines highlight the risk of myocardial infarction, stroke, heart failure, and hypertension associated with non-aspirin NSAID use.[23,48,195] We provide data to support that use of non-aspirin NSAIDs, in particular COX-2 inhibitors, is associated with cardiovascular risks not previously recognized.[23] Specifically, we add evidence that use of non-aspirin NSAIDs, especially COX-2 selective agents, is associated with risk of venous thromboembolism and atrial fibrillation. Our data also associate use of COX-2 inhibitors with an increased mortality following ischemic stroke. When no appropriate alternatives exist, the subgroup of patients with coronary stents on dual antiplatelet therapy, however, seems to tolerate the cardiovascular risks associated with non-aspirin NSAIDs.

Overall, our data support current recommendations that selective COX-2 inhibitors should be considered contraindicated in patients with cardiovascular disease.[23,48,195] They should also be avoided in patients with risk factors for cardiovascular disease, and only be used when there are no appropriate alternatives, and then, only in the lowest effective dose and for the shortest duration necessary to control symptoms.[23,48,195]

Physicians should be aware of the potential risk of atrial fibrillation when balancing patient-specific risks and benefits of prescribing treatment with non-aspirin NSAIDs.[196,197] Accordingly, efforts should be made to assess and treat modifiable risk factors for atrial fibrillation before and during treatment with non-aspirin NSAIDs.[17,48] Non-pharmacological treatment and other analgesics, such as acetaminophen, should be considered as agents to avoid initiation of non-aspirin NSAID therapy.[17,48] Due to the uncertainty of the nature of the association between non-aspirin NSAIDs and venous thromboembolism, it is too early to make recommendations. Regardless of the causality of this association, effective treatment of pain is warranted to reduce pain-related immobilization and the associated risk of venous thromboembolism.

6. Summary

The cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs) is controversial, because cyclooxygenase (COX)-2 inhibitors increase the risk of myocardial infarction, stroke, heart failure, and hypertension. To explore additional NSAID-associated cardiovascular risks, we examined whether use of non-aspirin NSAIDs was associated with risk of major adverse cardiovascular events (MACE) after coronary stent implantation (study I), risk of venous thromboembolism (study II), risk of atrial fibrillation (study III), and 30-day stroke mortality (study IV).

We conducted two cohort studies (I and IV) and two case-control studies (II and III). We identified use of NSAIDs from prescription registries and used medical databases to collect data on cardiovascular morbidity, comorbidity, and mortality.

In study I (2002–2005), we included 13,001 patients undergoing first-ever percutaneous coronary intervention with stent implantation in Western Denmark. Compared with non-users of NSAIDs, the adjusted incidence rate ratio (IRR) for MACE was 1.04 (95% CI: 0.83–1.31) for users of nonselective NSAIDs and 1.00 (95% CI: 0.81–1.25) for users of COX-2 inhibitors. Consistently, current use of non-aspirin NSAIDs was not associated with an increased rate of the individual MACE components (myocardial infarction, stent thrombosis, target lesion revascularization, and cardiac death) that was notably different from that seen among former users, suggesting no true adverse drug effect.

In study II (1999–2006), we identified 8,368 patients with a first-time hospital diagnosis of venous thromboembolism in Northern Denmark and 82,218 age- and sex-matched population controls. As compared with no use, the adjusted IRR for venous thromboembolism was 2.51 (95% CI: 2.29–2.76) for current use of non-selective NSAIDs and 2.19 (95% CI: 1.99–2.41) for current use of COX-2 inhibitors. Former users had substantially smaller increases than current users. The adjusted IRR for venous thromboembolism among long-term users were 2.06 (95% CI: 1.85–2.29) for non-selective NSAIDs and 1.92 (95% CI: 1.72–2.15) for COX-2 inhibitors. The long-term user estimates are less likely to be influenced by protopathic bias. Similarly increased risks were found for unprovoked venous thromboembolism (occurrence in the absence of pregnancy, cancer, major trauma, fracture, or surgery within three months preceding the venous thromboembolism), deep vein thrombosis, pulmonary embolism, and individual NSAIDs.

In study III (1999–2008), we identified 32,602 patients with a first-time hospital diagnosis of atrial fibrillation in Northern Denmark and 325,918 age- and sex-matched population controls. Compared with no use, the adjusted IRR associating current drug use with atrial fibrillation was 1.17 (95% CI: 1.10–1.24) for non-selective NSAIDs and 1.27 (95% CI: 1.20–1.34) for COX-2 inhibitors. Among new users, the adjusted IRR was 1.46 (95% CI: 1.33–1.62) for non-selective NSAIDs and 1.71 (95% CI: 1.56–1.88) for COX-2 inhibitors. Results for individual NSAIDs were similar.

In study IV (2004–2012), we included 100,043 patients with first-time hospitalization for stroke in

Denmark. After multivariate adjustment, the 30-day mortality rate ratio (MRR) for ischemic stroke was 1.14 (95% CI: 1.03–1.27) for current users of COX-2 inhibitors compared with non-users, driven by the effect among new users (1.31, 95% CI: 1.13–1.52). A propensity score matched analysis yielded similar results, with a 30-day MRR for ischemic stroke of 1.16 (95% CI: 1.01–1.34) among current users and 1.28 (95% CI: 1.07–1.54) among new users. Comparing different types of COX-2 inhibitors, the MRR was driven by new use of older traditional COX-2 inhibitors (1.30, 95% CI: 1.12–1.52), being 1.51 (95% CI: 1.16–1.98) for etodolac and 1.21 (95% CI: 1.01–1.45) for diclofenac. Mortality from hemorrhagic strokes was not associated with preadmission use of non-aspirin NSAIDs.

In conclusion, we found that use of non-aspirin NSAIDs was not associated with MACE following coronary stent implantation, but was associated with an increased risk of venous thromboembolism, atrial fibrillation, and 30-day mortality following ischemic stroke, especially when therapy with selective COX-2 inhibitors was initiated.

7. Dansk resume

Gigtmedicin lindrer smerte og hævelse ved en lang række sygdomme i bevægeapparatet. Gigtmedicin af typen NSAID kan øge risikoen for blodprop i hjertet, blodprop i hjernen, hjertesvigt og forhøjet blodtryk. Det er dog uvist hvorvidt gigtmedicin også øger risikoen for andre hjertekarsygdomme.

Formålet med denne afhandling var at undersøge om brugere af gigtmedicin har en øget risiko for hjerterelaterede komplikationer efter indsættelse af et metalgitter (stent) i en kranspulsåre pga. åreforkalkningssygdom (studie I). Derefter undersøgte vi, om brugere af gigtmedicin havde øget risiko for blodpropper i benene eller lungerne (studie II), forkammerflimmer (studie III), eller et dødeligt slagtilfælde (studie IV).

Studierne i denne afhandling inkluderede to kohortestudier (I og IV) og to case-control studier (II og III). Vi identificerede forbruget af gigtmedicin via danske receptregistre, og hjertekarsygdomme, andre kroniske sygdomme og død via Landspatientregistret og andre medicinske registre.

I studie I inkluderede vi 13.001 patienter behandlet med en stent i en kranspulsåre i perioden 2002–2005. Vi fandt ingen øget risiko for hjerterelaterede komplikationer hos disse patienter som følge af deres forbrug af gigtmedicin.

Studie II inkluderede 8.368 patienter med blodpropper i benene eller lungerne i perioden 1999–2006 i Region Midt eller Region Nord og 82.218 kontroller af samme køn og alder. Sammenlignet med ikke-brugere af gigtmedicin, var der en 2,5 gange øget risiko for sådanne blodpropper blandt brugere af nonselektive typer af gigtmedicin og en 2,2 gange øget risiko blandt brugere af såkaldte COX-2-hæmmere. Tidligere brugere havde en betydelig mindre risiko end nuværende brugere. Risikoen forblev 2 gange forøget blandt langtidsbrugere af de forskellige typer af gigtmedicin. Resultaterne var konsistente for både blodpropper i benene og lungerne og også for blodpropper der ikke var forudgået af andre provokerende faktorer som graviditet, kræft, traume, frakturer eller kirurgi inden for tre måneder.

Studie III inkluderede 32.602 patienter med debut af forkammerflimmer i Region Midt eller Region Nord i perioden 1999–2008 og 325.918 kontroller af samme køn og alder. Sammenlignet med ikke-brugere, var der en 17 % øget risiko for forkammerflimmer blandt brugere af non-selektive typer af gigtmedicin og 27 % øget for brugere af COX-2-hæmmere. Risikoen var endnu større hos personer der fornyligt var påbegyndt gigtmedicin, hvor den var 46 % øget for non-selektive typer af gigtmedicin og 71 % øget for COX-2-hæmmere. Resultaterne var konsistente også for de enkelte præparattyper.

Studie IV inkluderede 100.043 patienter, der var indlagt med slagtilfælde i Danmark i perioden 2004–2012. Risikoen for at dø inden for 30 dage efter en blodprop i hjernen var overordnet 14 % højere blandt brugere af COX-2-hæmmere end ikke-brugere, men hele 31 % øget blandt nye brugere. Vi fandt samme øgede risiko, når vi analyserede data med en alternativ statistisk metode kaldet propensity score matching. Ved sammenligning af forskellige COX-2-hæmmere var risikoen mest øget blandt nye brugere af ældre typer

af COX-2-hæmmere (30 %), og blandt disse 51 % øget for brugere af præparatet etodolac og 21 % øget blandt brugere af præparatet diclofenac. Brugere af gigtmedicin havde ingen øget dødelighed efter hjerneblødning som følge af deres gigtmedicin.

Samlet set viste vores studier, at brugere af gigtmedicin ikke havde en øget risiko for hjerterelaterede komplikationer efter behandling med en stent. Vi fandt dog, at brugere af gigtmedicin, og især personer der nyligt havde påbegyndt behandling med COX-2-hæmmere, havde en øget risiko for blodpropper i benene og lungerne, hjerteflimmer og en dødelig blodprop i hjernen.

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9. Appendices

Appendices I–V provide the full versions of papers I–V:

- **Appendix I**:

Paper I

- **Appendix II**:

Paper II

- **Appendix III**:

Paper III

- **Appendix IV**:

Paper IV

- **Appendix V**:

Paper V

Paper I

Nonsteroidal Antiinflammatory Drug Use and Cardiovascular Risks After Coronary Stent Implantation

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Study Objective. To determine whether use of nonselective nonsteroidal antiinflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2)–selective inhibitors in patients with coronary stents increased the 3-year rate of major adverse cardiovascular events (MACE).

Design. Population-based cohort study.

Data Sources. The Danish National Patient Registry, the Western Denmark Heart Registry, the Danish Nationwide Prescription Database, the Danish Civil Registration System, and the National Registry of Causes of Deaths.

Patients. A total of 13,001 patients who underwent first-ever percutaneous coronary intervention with stent implantation between January 1, 2002, and June 30, 2005.

Measurements and Main Results. All patients were followed for 3 years after stent implantation for MACE, defined as the first occurrence of myocardial infarction, stent thrombosis, target-lesion revascularization, or cardiac death. Patients' comorbidities were identified from the hospital registries; time-varying use of NSAIDs and concomitant drugs was determined from the Danish Nationwide Prescription Database. For each clinical outcome (MACE), the 3-year risk was computed. We used Cox proportional-hazards regression analysis to compute hazard ratios (HRs) as a measure of relative risk, controlling for potential confounders. During the follow-up period, 5407 patients (41.6%) redeemed at least one NSAID prescription. There were 686 hospitalizations for myocardial infarction (5.3% of patients), 146 for stent thrombosis (1.1%), and 1091 for target-lesion revascularization (8.4%). A total of 1220 patients (9.4%) died during the follow-up period; 637 (4.9%) died of cardiac causes. Compared with no NSAID use, the adjusted HR for MACE was 1.04 (95% confidence interval [CI] 0.83–1.31) for nonselective NSAID use and 1.00 (95% CI 0.81–1.25) for COX-2 inhibitor use.

Conclusion. Use of nonselective NSAIDs or COX-2 inhibitors was not associated with an increased rate of MACE in patients with coronary stents. However, we cannot rule out small risks associated with individual NSAIDs.

Key Words: angioplasty, coronary disease, cyclooxygenase-2 inhibitors, COX-2 inhibitors, nonsteroidal antiinflammatory drugs, NSAIDs, stents.

(Pharmacotherapy 2011;31(5):458–468)

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used to treat inflammatory conditions and pain.[1] By inhibiting cyclooxygenase (COX)-1–mediated production of prostaglandins,[1] nonselective NSAIDs can cause gastrointestinal toxicity[1] and nephrotoxic syndromes.[2] An alternative is selective COX-2 enzyme inhibitors.[3] The newer COX-2 inhibitors, introduced into

clinical practice in 1998, were developed as NSAIDs with an improved gastrointestinal adverse-effect profile.[1] The cardiovascular safety of traditional NSAIDs (older COX-2 inhibitors and nonselective NSAIDs) and newer COX-2 inhibitors requires thorough evaluation because randomized trials have demonstrated increased cardiovascular risk for several of these drugs.[4–8]

An increasing proportion of patients with ischemic heart disease undergo percutaneous coronary intervention (PCI) with stent implantation. The benefits of coronary stent placement accrue at the expense of increased risk of stent-related events—most notably stent thrombosis and in-stent restenosis.[9] Thus, as tertiary prophylaxis, these patients receive more aggressive antiplatelet treatment than patients without stents.[10, 11] Because of the stent itself and a post-intervention antiplatelet regimen that includes clopidogrel, patients with stents represent an important subpopulation of patients with coronary artery disease, for whom the risks of NSAID use need individual assessment.

The new COX-2 inhibitors and traditional NSAIDs increase the risk of reinfarction and death in patients with a history of acute myocardial infarction.[12] Only one study has investigated whether patients with a history of coronary revascularization (with or without a history of myocardial infarction) also have an increased risk of adverse cardiovascular events when using these drugs.[13] In that study, coronary revascularization (PCI or coronary artery bypass grafting [CABG]) was neither restricted nor stratified to patients with stents. In addition, follow-up did not include the first 45 days after index hospitalization, during which NSAID use may be particularly hazardous,[5] and there were no specific data on stent thrombosis, target-lesion revascularization, or cardiac death.[13]

Given the limited research on this important topic, we conducted a cohort study using population-based Danish data with complete follow-up, taking comorbidity, concomitant drugs, and multiple outcomes into consideration. Our objective was to determine whether use of nonselective NSAIDs or COX-2 inhibitors increased the 3-year rate of major adverse cardiovascular events (MACE) after coronary stent implantation.

Methods

Study Design and Setting

We conducted this population-based cohort study by using medical databases from western Denmark, which has a population of 3 million (55% of the total 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 drugs, including NSAIDs. Linkage among national registries is possible with use of a unique central personal registry number assigned to each Danish citizen at birth and to residents after immigration.[14]

Stent Cohort

We used the Western Denmark Heart Registry (WDHR)[15] to identify patients with first-ever PCIs performed between January 1, 2002, and June 30, 2005, and followed the patients for 3 years. We excluded patients treated by balloon angioplasty without stent implantation. Since 1999, the WDHR registry has collected patient and procedure data from all coronary interventions in western Denmark.[15] We defined the first PCI with stent implantation as the index PCI and the date of procedure as the index date.

Procedures and Postintervention Drugs

The participating cardiac centers were high-volume centers performing more than 1000 PCIs/year. Interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, before or after dilatation, choice of stent, direct stenting,

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use of periprocedural glycoprotein IIb-IIIa inhibitor) left to the physician's discretion.[16]

The recommended postintervention antiplatelet protocol included lifelong low-dose aspirin 75–150 mg/day and clopidogrel with a loading dose of 300 mg followed by a maintenance dose of 75 mg/day. The recommended duration of clopidogrel treatment was 1–12 months until November 2002 (when guidelines were updated) and 12 months thereafter.[15] If patients experienced a new event within the first year, then the duration of clopidogrel was extended to 12 months from the day of the new event. The proportion of patients who continued to receive clopidogrel for periods longer than 12 months was 8.7% overall (9.4% of clopidogrel users).

Nonsteroidal Antiinflammatory Drug Use

We used the Danish Nationwide Prescription Database[17] to identify prospectively all NSAID prescriptions redeemed by the stent cohort. This registry has, since 1995, recorded prescriptions dispensed from all pharmacies in Denmark.[17] Pharmacies are equipped with electronic accounting systems primarily used to secure reimbursement from the National Health Service. For each redeemed prescription, the pharmacy transfers the following information to the prescription database: the patient's central personal registry number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date the drug was dispensed.

Except for ibuprofen 200 mg/tablet, all nonaspirin NSAIDs are available by prescription only.[18] Regular users of ibuprofen typically are registered in the database because the cost is partly refunded when the drug is prescribed by a physician.

We identified prescriptions for nonaspirin nonselective 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, 19] Because of an overlap in COX-2:COX-1 selectivity ratio,[3] we collapsed older and newer COX-2 inhibitors into one group.[3] The exposure variables consisted in the primary analyses of the NSAID subclasses of nonselective NSAIDs and COX-2 inhibitors, and in the secondary analyses of the six individual NSAIDs most frequently prescribed in our data.

Exposure to NSAID use was assessed in a time-varying manner. Within 60 days before the index date and during follow-up, we assumed a given prescription covered a maximum of 60 days (current use), after which the patient was regarded as a former user until 365 days after the prescription was redeemed, unless a new prescription was redeemed. We chose an exposure window of 60 days to capture most current users, as NSAID prescriptions seldom are provided for more than 60 days at a time in Denmark.[18, 20] We defined nonusers as persons with no redeemed prescriptions of nonselective NSAIDs or COX-2 inhibitors within 365 days.

Clinical Outcomes

Within 3 years of the index PCI, we ascertained the occurrence of myocardial infarction, stent thrombosis, target-lesion revascularization, cardiac death, and noncardiac death. We defined MACE as the first occurrence of myocardial infarction, stent thrombosis, target-lesion revascularization, or cardiac death. Blinded to the history of NSAID use, a committee of cardiac specialists,[15] with members from each of the participating departments of cardiology, reviewed relevant records to determine the occurrence of stent thrombosis and cardiac death. We obtained information on myocardial infarction and target-lesion revascularization from hospital registries, as described below.

Myocardial infarction

We used the Danish National Patient Registry (DNPR)[21] covering all Danish hospitals to identify myocardial infarction admissions. The DNPR contains data on dates of admission and discharge, inpatient and outpatient diagnoses from nonpsychiatric hospitals after 1977, and emergency department and outpatient clinic visits after 1995.[21] Each discharge is associated with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter.[21] We used ICD-10 code I21 to identify myocardial infarction.

Stent Thrombosis and Revascularization

By retrieving medical records and reviewing catheterization angiograms, the specialist committee adjudicated the occurrence of definite stent thrombosis as defined by the Academic

Research Consortium[15, 22]: angiographic confirmation of stent thrombosis and at least one of the following signs present within 48 hours: new onset of ischemic symptoms at rest, new electrocardiographic changes suggestive of acute ischemia, or typical rise and fall in cardiac biomarkers.[15, 22] We defined target-lesion revascularization as a repeat PCI or CABG of the index lesion, and identified it from the WDHR.

Cardiac Death

We obtained all-cause mortality from the Danish Civil Registration System.[23] 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.[23] The specialist committee then reviewed original paper death certificates obtained from the National Registry of Causes of Deaths,[24] which has collected data on dates and causes of death in Denmark since 1943.[24] As recorded on the paper death certificate, death was classified according to the underlying cause, as either cardiac or noncardiac death. Cardiac death was defined as an evident cardiac death, PCI-related death, unwitnessed death, or death from unknown causes.[25]

Other Patient Characteristics

We identified available cardiovascular risk factors potentially associated with NSAID use. We obtained information on comorbid conditions—diabetes mellitus, hypertension, and cancer—by reviewing discharge diagnoses from the DNPR between 1977 and the index date. To increase the sensitivity of the diabetes diagnosis, we added information from the WDHR on diabetes diagnosed at time of index PCI, and we also used the Nationwide Prescription Database to obtain data on any use of antidiabetic drugs since 1995. We categorized the level of comorbidity by using the Charlson Comorbidity Index,[26] a scoring system that has been adapted for use with hospital discharge data.[27, 28] Without scoring for diabetes or cancer, we computed the Charlson index score for each patient and defined three levels of comorbidity based on scores: 0 (low), 1–2 (moderate), and 3 or greater (high).[26] We retrieved procedure-specific data from the WDHR on PCI indication, year of index PCI, and stent type. From the Nationwide Prescription Database, we ascertained concomitant drug data for the following drugs used during the 3-year follow-up period: statins, aspirin, clopidogrel, vitamin K antagonists, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, calcium channel blockers, and proton pump inhibitors.

Statistical Analysis

According to NSAID use, we calculated the frequency of patients with stents in categories of medical and demographic variables. We followed all patients from index date until date of MACE, noncardiac death, emigration, or 3 years of follow-up, whichever came first. We computed cumulative 3-year risks and rates according to the time-varying NSAID use (current, former, and no use). We used Cox proportional hazards regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) as a measure of relative risk. In regression analyses, we controlled for age, sex, diabetes mellitus, hypertension, cancer, comorbidity level, PCI indication, and stent type. Furthermore, we controlled for time-varying use of statins, aspirin, clopidogrel, and proton pump inhibitors by using exposure windows of 120 days for each drug.

To examine the impact of different exposure definitions, we repeated the analyses for NSAID exposure windows of 15, 30, and 45 days. To examine whether differences in duration of use and time from therapy initiation affected the results, we performed two additional sensitivity analyses. First, we repeated the analyses stratifying on the number of redeemed prescriptions the year before index PCI and defined NSAID use as inconsistent (indicator for as-needed use) when patients had redeemed fewer than two prescriptions and as persistent when patients had redeemed at least two prescriptions. Second, because inclusion of long-term use may lead to underestimation of adverse effects arising shortly after therapy initiation, we repeated the analyses categorizing current use as either new use (the first redeemed prescription) or long-term use (all redeemed prescriptions after the first).[29]

To evaluate heterogeneity in cardiovascular risk among individual NSAIDs and examine individual outcomes, we repeated the analyses for the six most commonly used NSAIDs and for myocardial infarction, stent thrombosis, target-lesion revascularization, cardiac death, and noncardiac death, separately. Analyses were performed by using Statistical Analysis System, version 9.2 (SAS Institute Inc., Cary, NC).

Table 1. Characteristics of Patients with Coronary Stent Implantation According to Nonsteroidal Antiinflammatory Drug Use

Characteristic	Nonusers (n=7594)	All Current Users[a] (n=5407)	Ibuprofen Users (n=3004)	Naproxen Users (n=198)	Etodolac Users (n=590)	Diclofenac Users (n=1856)	Celecoxib Users (n=474)	Rofecoxib Users (n=297)
Age, median (yrs)	65	63	62	63	65	62	67	67
	Percentage of Patients							
Male	73.1	71.1	73.6	71.7	61.2	73.1	57.4	56.6
PCI indication								
STEMI	31.2	26.3	25.6	23.2	28.8	26.9	24.7	24.2
Non-STEMI or UAP	30.2	31.3	31.3	34.3	29.3	30.3	33.8	38.7
Stable angina pectoris	35.5	40.3	40.7	41.9	40.3	41.0	39.7	35.7
Other	3.1	2.1	2.3	0.5	1.5	1.7	1.9	1.3
Year of stent implantation								
2002	23.3	24.9	23.9	27.3	27.6	20.8	46.8	53.5
2003	28.2	29.2	28.7	24.7	27.6	28.7	33.8	32.7
2004	30.7	30.6	31.1	32.3	30.3	33.8	18.1	13.8
2005	17.8	15.3	16.3	15.7	14.4	16.6	1.3	0
Stent type								
Bare metal	67.4	68.9	67.0	67.7	72.0	67.3	84.2	89.6
Drug eluting	27.9	26.5	28.4	27.3	24.1	28.0	13.5	8.4
Both bare metal + drug eluting	4.7	4.6	4.6	5.1	3.9	4.7	2.3	2.0
Comorbidities								
Diabetes mellitus	13.1	14.8	13.7	11.6	14.6	15.2	18.1	16.8
Hypertension	2.8	3.3	3.0	4.5	3.1	3.7	4.6	4.0
Cancer	7.1	6.5	5.9	5.1	6.8	6.6	7.4	6.4
Comorbidity level[b]								
Low	67.7	64.8	67.2	69.2	61.9	63.7	52.7	53.5
Moderate	27.2	31.0	28.8	27.8	33.6	32.2	38.8	39.7
High	5.1	4.2	4.0	3.0	4.6	4.1	8.4	6.7
Concomitant drugs[c]								
Statin	89.7	94.3	95.6	93.4	93.4	94.9	89.5	81.5
Aspirin	93.5	97.2	97.6	97.0	96.8	97.8	96.4	95.3
Clopidogrel	93.7	97.9	98.4	97.5	98.1	98.1	97.3	96.3
Vitamin K antagonist	12.6	8.8	8.3	11.6	8.5	8.0	11.4	11.8
ACE inhibitor or ARB	60.2	61.8	61.1	59.6	61.4	62.4	60.8	66.0
β-Blocker	88.2	91.5	92.0	89.9	91.4	91.5	88.0	88.6
Calcium channel blocker	37.0	43.1	42.5	47.0	46.8	42.8	50.0	48.1
Proton pump inhibitor	30.5	40.5	37.2	35.9	51.5	41.2	61.2	60.3

PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

[a]Patients with a prescription redeemed within 60 days before stent implantation or during follow-up, of either ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, tolfenamic acid, diclofenac, etodolac, nabumeton, meloxicam, celecoxib, rofecoxib, valdecoxib, parecoxib, or etoricoxib.

[b]Three levels of comorbidity were defined based on Charlson index scores of 0 (low), 1–2 (moderate), and ≥ 3 (high).

[c]At least one redeemed prescription registered between index PCI and death, emigration, or end of follow-up.

Results

Patient Characteristics

A summary of the stent cohort characteristics is shown in Table 1. We identified 13,001 patients with stents, with a median age of 64 years, of whom 72.3% were male. During the 3-year follow-up period, 3627 patients (27.9%) redeemed at least one nonselective NSAID prescription and 3466 patients (26.7%) redeemed at least one COX-2 inhibitor prescription. A total of 5407 patients (41.6%) redeemed at least one of either nonselective NSAIDs or COX-2 inhibitors, among which 1686 (13.0%) redeemed at least one of each. The indications for PCI were ST-segment elevation myocardial infarction (29.2% of patients), non–ST-segment elevation myocardial infarction or unstable angina pectoris (30.7%), and stable angina pectoris (37.5%). Users of COX-2 inhibitors were older, more likely to be female, and had a higher prevalence of both moderate and high comorbidity compared with nonusers.

Table 2. Hazard Ratios for Clinical Outcomes Associated with Use of Nonselective NSAIDs or COX-2 Inhibitors

Outcome	No. of Patients	Rate[a]	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
		Nonselective NSAIDs		
MACE (n=2115)				
No use	1897	65.14	1	1
Former use	138	46.60	1.08 (0.91–1.30)	1.13 (0.94–1.35)
Current use	80	60.81	0.99 (0.79–1.25)	1.04 (0.83–1.31)
Myocardial infarction (n=686)				
No use	592	19.16	1	1
Former use	62	19.52	1.19 (0.92–1.55)	1.22 (0.94–1.59)
Current use	32	22.60	1.24 (0.87–1.77)	1.30 (0.91–1.85)
Stent thrombosis (n=146)				
No use	134	4.25	1	1
Former use	8	2.45	0.85 (0.34–2.13)	0.84 (0.33–2.09)
Current use	4	2.77	1.06 (0.47–2.39)	1.04 (0.46–2.36)
Target-lesion revascularization (n=1091)				
No use	985	33.08	1	1
Former use	65	21.30	1.99 (0.76–1.27)	0.97 (0.76–1.26)
Current use	41	30.51	0.98 (0.72–1.35)	0.97 (0.71–1.34)
Cardiac death (n=637)				
No use	577	18.15	1	1
Former use	31	9.40	1.01 (0.70–1.46)	1.18 (0.81–1.71)
Current use	29	19.94	1.10 (0.74–1.63)	1.24 (0.84–1.84)
Noncardiac death (n=583)				
No use	486	15.28	1	1
Former use	61	18.50	1.26 (0.96–1.65)	1.36 (1.04–1.78)
Current use	36	24.75	1.62 (1.16–2.28)	1.82 (1.29–2.55)
		COX-2 Inhibitors		
MACE (n=2115)				
No use	1897	63.95	1	1
Former use	129	52.14	1.17 (0.98–1.41)	1.11 (0.93–1.33)
Current use	89	70.36	1.09 (0.88–1.35)	1.00 (0.81–1.25)
Myocardial infarction (n=686)				
No use	610	19.37	1	1
Former use	53	19.88	1.17 (0.88–1.55)	1.07 (0.81–1.43)
Current use	23	17.22	0.89 (0.59–1.35)	0.80 (0.53–1.22)
Stent thrombosis (n=146)				
No use	134	4.17	1	1
Former use	9	3.30	1.26 (0.54–2.92)	1.28 (0.55–2.96)
Current use	3	2.21	0.84 (0.34–2.06)	0.84 (0.34–2.07)
Target-lesion revascularization (n=1091)				
No use	984	32.41	1	1
Former use	64	25.25	1.10 (0.85–1.42)	1.05 (0.82–1.36)
Current use	43	33.54	0.98 (0.72–1.34)	0.91 (0.67–1.25)
Cardiac death (n=637)				
No use	565	17.42	1	1
Former use	34	12.36	1.35 (0.95–1.92)	1.33 (0.93–1.89)
Current use	38	27.88	1.52 (1.08–2.13)	1.40 (1.00–1.97)
Noncardiac death (n=583)				
No use	473	14.58	1	1
Former use	66	23.99	1.72 (1.32–2.22)	1.51 (1.17–1.97)
Current use	44	32.29	2.21 (1.62–3.01)	1.91 (1.40–2.61)

NSAID = nonsteroidal antiinflammatory drug; COX = cyclooxygenase; HR = hazard ratio; MACE = major adverse cardiovascular event (myocardial infarction, stent thrombosis, target-lesion revascularization, or cardiac death); CI = confidence interval.

[a]Rate/1000 person-years.

[b]Adjusted for age, sex, diabetes mellitus, hypertension, cancer, Charlson Comorbidity Index score, indication for percutaneous coronary intervention, stent type, and time-varying use of statins, aspirin, clopidogrel, and proton pump inhibitors.

Table 3. Adjusted Hazard Ratios for Clinical Outcomes Associated With Use of Individual NSAIDs

NSAID	MACE	Myocardial Infarction	Target-Lesion Revascularization	Cardiac Death	Noncardiac Death
Ibuprofen (n=3004)					
No use	1	1	1	1	1
Former use	1.09 (0.90–1.32)	1.14 (0.86–1.53)	0.95 (0.72–1.25)	1.17 (0.78–1.74)	1.25 (0.93–1.68)
Current use	0.95 (0.73–1.23)	1.21 (0.81–1.81)	0.90 (0.63–1.29)	1.08 (0.68–1.73)	1.89 (1.31–2.74)
Naproxen (n=198)					
No use	1	1	1	1	1
Former use	0.83 (0.37–1.84)	1.32 (0.49–3.54)	0.48 (0.12–1.93)	0.67 (0.09–4.76)	2.39 (1.13–5.05)
Current use	2.60 (1.43–4.70)	1.38 (0.35–5.54)	2.49 (1.12–5.57)	3.55 (1.33–9.51)	0.83 (0.12–5.90)
Etodolac (n=590)					
No use	1	1	1	1	1
Former use	1.08 (0.69–1.68)	1.35 (0.74–2.46)	0.95 (0.49–1.84)	1.36 (0.61–3.06)	1.88 (1.15–3.06)
Current use	0.46 (0.22–0.96)	0.75 (0.28–2.00)	0.26 (0.07–1.05)	0.48 (0.12–1.94)	0.37 (0.09–1.50)
Diclofenac (n=1856)					
No use	1	1	1	1	1
Former use	1.09 (0.86–1.38)	0.96 (0.66–1.41)	1.05 (0.75–1.47)	1.36 (0.87–2.14)	0.97 (0.66–1.45)
Current use	1.04 (0.77–1.41)	0.86 (0.49–1.52)	0.92 (0.59–1.43)	1.38 (0.84–2.27)	2.19 (1.45–3.30)
Celecoxib (n=474)					
No use	1	1	1	1	1
Former use	1.40 (0.99–1.99)	1.28 (0.72–2.29)	1.42 (0.89–2.28)	1.27 (0.60–2.71)	2.21 (1.42–3.44)
Current use	1.05 (0.66–1.68)	0.85 (0.32–2.28)	0.80 (0.38–1.68)	1.96 (1.07–3.58)	2.53 (1.38–4.63)
Rofecoxib (n=297)					
No use	1	1	1	1	1
Former use	0.70 (0.40–1.24)	0.77 (0.32–1.87)	0.77 (0.36–1.62)	0.22 (0.03–1.60)	1.15 (0.60–2.19)
Current use	1.21 (0.73–2.02)	0.61 (0.15–2.45)	1.49 (0.77–2.88)	1.31 (0.58–2.94)	2.04 (0.96–4.35)

Data are adjusted hazard ratio (95% confidence interval).
NSAID = nonsteroidal antiinflammatory drug; MACE = major adverse cardiovascular event (myocardial infarction, stent thrombosis, target-lesion revascularization, or cardiac death).

Table 4. Sensitivity Analysis Examining the Impact of Different Exposure Windows on the Adjusted Hazard Ratio of Major Adverse Cardiovascular Events

Drug Category	Exposure Window[a]			
	15 Days	30 Days	45 Days	60 Days
Nonselective NSAIDs				
Former use	1.19 (1.01–1.41)	1.29 (1.10–1.52)	1.17 (0.99–1.40)	1.13 (0.94–1.35)
Current use	0.74 (0.45–1.21)	0.87 (0.62–1.20)	1.05 (0.81–1.35)	1.04 (0.83–1.31)
COX-2 inhibitors				
Former use	1.11 (0.93–1.32)	1.19 (1.00–1.41)	1.11 (0.93–1.33)	1.11 (0.93–1.33)
Current use	0.67 (0.42–1.05)	0.86 (0.64–1.15)	1.00 (0.79–1.27)	1.00 (0.81–1.25)

Data are adjusted hazard ratio (95% confidence interval).
NSAID = nonsteroidal antiinflammatory drug; COX = cyclooxygenase.
[a]Number of days exposed from a prescription redemption.

Clinical Outcomes

As Table 2 shows, during the 3-year follow-up there were 686 hospitalizations (5.3%) for myocardial infarction, 146 (1.1%) for stent thrombosis, and 1091 (8.4%) for target-lesion revascularization. A total of 1220 patients (9.4%) died; 637 (4.9%) died of cardiac causes. With nonuse as the reference, the unadjusted HR for MACE was 0.99 (95% CI 0.79–1.25) for current use of nonselective NSAIDs and 1.09 (95% CI 0.88–1.35) for current use of COX-2 inhibitors. Confounder adjustments changed these results very little (adjusted HR 1.04, 95% CI 0.83–1.31 for nonselective NSAIDs and 1.00, 95% CI 0.81–1.25 for COX-2 inhibitors). Supporting the composite null result, there was no substantial association between current use of nonselective NSAIDs or COX-2 inhibitors and myocardial infarction, stent thrombosis, target-lesion revascularization, or cardiac death (Table 2). Although small increased HRs were observed for current use of nonselective NSAIDs for myocardial

Table 5. Sensitivity Analysis Examining the Impact of Duration of NSAID Use Before and After Index PCI on the Adjusted Hazard Ratio of Major Adverse Cardiovascular Events

	No. of Redeemed Prescriptions 1 Year Before Index PCI		No. of Redeemed Prescriptions During Follow–up	
Drug	0–1 (inconsistent use)	≥ 2 (consistent use)	1 (new use)	≥ 2 (long-term use)
Nonselective NSAIDs				
Former use	1.24 (1.02–1.51)	0.77 (0.50–1.18)	1.16 (0.96–1.39)	0.98 (0.69–1.37)
Current use	0.97 (0.72–1.29)	1.14 (0.77–1.69)	1.06 (0.81–1.39)	0.79 (0.50–1.26)
COX-2 inhibitors				
Former use	1.18 (0.96–1.45)	0.88 (0.58–1.32)	1.20 (0.99–1.45)	0.81 (0.56–1.18)
Current use	1.21 (0.95–1.54)	0.62 (0.39–0.99)	1.08 (0.85–1.38)	0.69 (0.43–1.11)
Ibuprofen				
Former use	1.18 (0.95–1.46)	0.74 (0.47–1.19)	1.20 (0.99–1.47)	0.84 (0.57–1.24)
Current use	0.90 (0.65–1.24)	0.98 (0.62–1.53)	0.93 (0.67–1.27)	0.87 (0.53–1.43)
Naproxen				
Former use	0.88 (0.33–2.34)	0.67 (0.17–2.72)	0.56 (0.20–1.54)	1.56 (0.46–5.29)
Current use	2.08 (0.87–5.02)	3.21 (1.41–7.30)	3.77 (2.02–7.02)	0.70 (0.08–5.83)
Etodolac				
Former use	0.92 (0.54–1.55)	1.69 (0.74–3.85)	0.97 (0.60–1.58)	1.79 (0.76–4.20)
Current use	0.45 (0.19–1.08)	0.46 (0.12–1.88)	0.52 (0.23–1.16)	0.20 (0.03–1.52)
Diclofenac				
Former use	1.05 (0.79–1.40)	1.12 (0.70–1.79)	1.19 (0.93–1.52)	0.88 (0.53–1.46)
Current use	1.46 (1.06–2.01)	0.32 (0.13–0.79)	1.10 (0.77–1.57)	0.73 (0.37–1.42)
Celecoxib				
Former use	1.73 (1.18–2.54)	0.78 (0.34–1.77)	1.22 (0.82–1.81)	1.36 (0.67–2.76)
Current use	1.06 (0.59–1.92)	1.12 (0.52–2.42)	1.12 (0.67–1.87)	0.57 (0.17–1.91)
Rofecoxib				
Former use	0.95 (0.52–1.72)	0.19 (0.03–1.33)	0.68 (0.37–1.25)	1.02 (0.36–2.92)
Current use	1.19 (0.64–2.22)	1.16 (0.47–2.86)	1.24 (0.70–2.19)	0.97 (0.22–4.38)

Data are adjusted hazard ratio (95% confidence interval).
PCI = percutaneous coronary intervention; NSAID = nonsteroidal antiinflammatory drug; COX = cyclooxygenase.

infarction and for current use of nonselective NSAIDs and COX-2 inhibitors for cardiac death, these HRs did not separate substantially from the HRs observed for former users, suggesting that confounding by the under-lying condition leading to NSAID use, rather than a true drug effect, increased the cardiac mortality. The adjusted HR for noncardiac death was 1.82 (95% CI 1.29–2.55) for current use and 1.36 (95% CI 1.04–1.78) for former use of nonselective NSAIDs, and 1.91 (95% CI 1.40–2.61) for current use and 1.51 (95% CI 1.17–1.97) for former use of COX-2 inhibitors.

The adjusted HRs associating individual NSAIDs with all outcomes are shown in Table 3. Because of few events, the HRs for stent thrombosis were inconclusive and therefore are not shown. Compared with nonuse, there was no substantial difference between current and former use of ibuprofen, etodolac, diclofenac, celecoxib, and rofecoxib and the HRs for MACE, myocardial infarction, target-lesion revascularization, and cardiac death. Current naproxen use was consistently associated with increased rates for all cardiac outcomes (adjusted HR for MACE 2.60, 95% CI 1.43–4.70). The noncardiac mortality rate was consistently higher for all NSAIDs, except etodolac and naproxen.

Supporting the null finding, the sensitivity analyses showed that the adjusted HR for MACE changed very little with decreasing exposure windows (Table 4; results for individual NSAIDs are not shown). Furthermore, we found that the rate of MACE associated with NSAID use did not increase regardless of whether the NSAID use was defined as inconsistent, consistent, new, or long-term (Table 5).

Discussion

In this population-based cohort study, current use of nonselective NSAIDs or COX-2 inhibitors was not associated with an increased rate of MACE notably different from that seen among former users, suggesting no true adverse drug effect of NSAIDs in patients with coronary stents. The fact that several NSAIDs were associated with noncardiac death was expected because NSAIDs are prescribed to alleviate pain from

noncardiac diseases that may eventually become fatal. Nonetheless, this finding is important because studies on this subject often are not able to distinguish cardiac mortality from noncardiac mortality. Thus, increased all-cause mortality associated with NSAID use is likely to be highly influenced by noncardiac deaths. Surprisingly, naproxen use was associated with adverse cardiovascular events. Because of the limited number of events and the nonrandomized design, we cannot exclude small cardiovascular risks associated with use of other individual NSAIDs. Stent thrombosis is a feared complication to stent implantation because of its high case-fatality rate.[9] However, even if individual NSAIDs increased the relative rate for stent thrombosis substantially, the absolute risk associated with NSAID use would remain low due to the rare occurrence rate of stent thrombosis.[9]

To our knowledge, our study is the first to examine the cardiovascular risks in a large cohort of patients all of whom had coronary stents, taking multiple outcomes into consideration. An earlier study of 58,432 Danish patients with first-time myocardial infarction reported an increased risk of reinfarction and all-cause mortality for any use of ibuprofen, diclofenac, celecoxib, and rofecoxib.[12] Not all patients underwent stent implantation, however, and naproxen was not studied separately.[12] In a cohort of 48,566 patients from the United Kingdom, United States, and Canada, with myocardial infarction, coronary revascularization (PCI or CABG), or unstable angina, naproxen had better cardiovascular safety than ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib.[13] In a subgroup of patients with coronary revascularization, only rofecoxib showed an increased risk of the combined outcome of myocardial infarction and out-of-hospital death from coronary artery disease. Supporting our null results, a randomized controlled trial from South Korea with 2-year follow-up of 274 patients receiving 6-month adjunctive celecoxib treatment after paclitaxel-eluting stent implantation showed no increased risk of MACE during its use or after its discontinuation.[30]

The question of which NSAID has the best cardiovascular safety profile is particularly important for patients with existing coronary artery disease, including the subgroup of patients with stents. Data from low-risk populations as well as from patients with existing coronary artery disease without stents cannot necessarily be extrapolated to patients with stents because the latter may have greater baseline absolute risk,[9] they receive aggressive antiplatelet therapy,[10, 11] and their recent coronary intervention may alter the cardiac safety of NSAIDs.[5]

One group of authors concluded that naproxen is safer than ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib in patients with coronary artery disease.[13] In contrast, naproxen use was associated with increased cardiovascular risk in our stent cohort. In patients with stents who received aspirin therapy, an increased cardiovascular risk from naproxen use could be due to pharmacodynamic interactions because both naproxen and ibuprofen interfere with the irreversible inhibitory effect of aspirin.[31] Thus, naproxen in combination with aspirin could undermine the sustained inhibition of platelet COX-1 necessary for cardioprotection from aspirin.[31] Alternatively, we cannot rule out that naproxen, because it is considered the safest nonselective NSAID,[8, 32, 33] was prescribed more often to high-risk patients, which would bias the effect estimates away from the null. Other studies have, however, also found naproxen associated with increased cardiovascular risk.[34, 35]

The mechanisms underlying our near-null results are not clear considering the previously reported cardiovascular risks of COX-2 inhibitors.[4–6, 12] The highly cardioprotective effect of postintervention dual antiplatelet therapy with both clopidogrel and aspirin, however, may have negated any excess thrombotic cardiovascular risk of NSAIDs. The irreversible COX-1 inhibition by aspirin thus may protect against the excess cardiovascular risk of COX-2 inhibitors, when balancing the COX inhibition. Moreover, patients examined in previous studies on this topic did not receive clopidogrel consistently,[12, 13] which is an important difference because increased platelet activity by COX-2 inhibitors in the presence of arterial stenosis may be preventable by low-dose clopidogrel.[36]

Limitations

A number of issues should be considered when interpreting our results. The population-based design within the setting of a tax-supported universal health care system largely removed selection bias stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. Data in the prescription database are virtually complete.[37] Although we had to use redemption of a prescription as a proxy for actual NSAID use, the direct beneficial effects of

NSAIDs on a wide range of symptoms and the copayment requirements suggest high adherence. Furthermore, we based information on drug exposure on actual dispensing at pharmacies. Unfortunately, we did not have detailed information on dosage available. We lacked information on over-the-counter use of low-dose ibuprofen (200 mg/tablet), which accounts for approximately 15% of total NSAID sales in Denmark.[20] Such misclassification of drug exposure would bias the effect estimates toward the null. If NSAID use increased the cardiovascular risk in the stent population, we would expect a correlation between the COX-2 selectivity of the NSAIDs and the risk.[4–8] Because we did not observe an increased risk associated with either older or newer COX-2 inhibitors, we have no reason to suspect that the null results for ibuprofen were due to nondifferential misclassification.

Using the WDHR to ascertain the study outcomes has been previously validated,[15] and the DNPR and the Nationwide Prescription Database have been shown to be accurate.[17, 38, 39] Information on drug use, hospitalizations, and confounding factors were collected independently from medical databases, thus avoiding reliance on self-reporting and reducing the potential for differential information bias.[40]

Although we controlled for important predictors of cardiovascular events, it is possible that confounding by unmeasured variables influenced our results. We lacked information on tobacco and alcohol use and had incomplete data on hypertension, all of which increase the risk of second events and are likely to be more prevalent among NSAID users than nonusers.[41] However, this confounding would bias results toward higher risks in NSAID users and, thus, could not explain our near-null findings. Although we controlled for comorbidity by using the Charlson Comorbidity Index, residual confounding by comorbidity, in particular the underlying condition causing pain and leading to NSAID use, is likely to have increased noncardiac death and thus explain the association between use of most NSAIDs and noncardiac mortality. Also, NSAIDs may have been prescribed for patients without clear contraindications, which could have led to better than average outcomes for the NSAID-treated patients.

Conclusion

Our study suggests that use of nonselective NSAIDs or COX-2 inhibitors is not associated with an increased rate of MACE in patients with coronary stents. However, we cannot rule out small risks associated with use of individual NSAIDs.

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Paper II

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ORIGINAL ARTICLE

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

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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.

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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

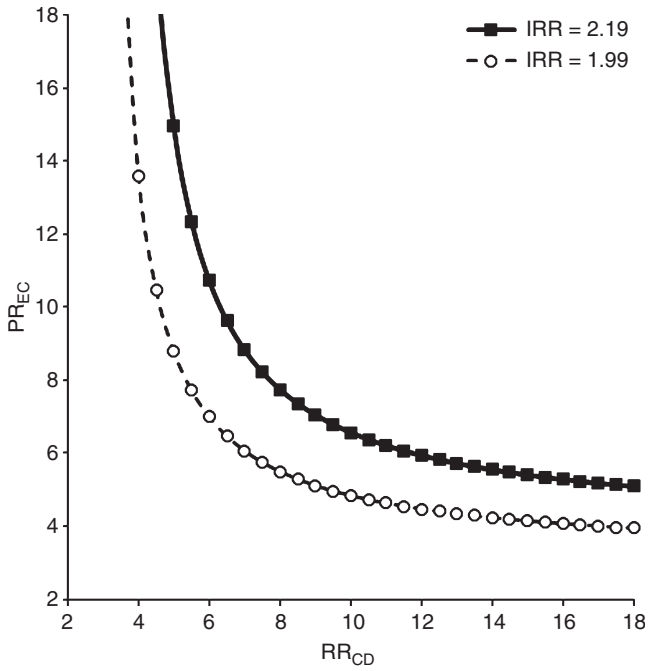

Fig. 1. Required strength of an unmeasured confounder. Sensitivity analysis illustrating how strongly an unmeasured confounder would need to be associated with NSAID use (prevalence ratio for exposure–confounder association [PR_{EC}]) and venous thromboembolism (VTE) (relative risk of the disease in 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

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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.

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Supporting Information

eTable 1. Incidence rate ratios associating individual NSAID use with deep venous thrombosis and pulmonary embolism.

	Incidence rate ratio (95% confidence interval)			
	Deep venous thrombosis		Pulmonary embolism	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
Ibuprofen				
Current use	4.02 (3.63-4.46)	3.14 (2.81-3.51)	2.78 (2.39-3.24)	2.16 (1.84-2.54)
Recent use	1.86 (1.69-2.05)	1.56 (1.41-1.73)	1.72 (1.50-1.96)	1.39 (1.21-1.60)
Naproxen				
Current use	2.13 (1.41-3.22)	1.62 (1.04-2.54)	1.82 (1.01-3.25)	1.34 (0.72-2.49)
Recent use	1.52 (1.11-2.07)	1.25 (0.90-1.73)	1.72 (1.16-2.54)	1.34 (0.89-2.02)
Etodolac				
Current use	2.69 (2.08-3.50)	2.00 (1.52-2.64)	2.52 (1.81-3.50)	1.89 (1.33-2.67)
Recent use	2.75 (2.25-3.36)	2.08 (1.68-2.59)	1.67 (1.22-2.30)	1.18 (0.85-1.65)
Diclofenac				
Current use	3.56 (3.11-4.08)	2.60 (2.25-3.01)	2.85 (2.35-3.45)	2.01 (1.64-2.46)
Recent use	1.98 (1.76-2.23)	1.53 (1.35-1.74)	1.85 (1.57-2.17)	1.36 (1.15-1.61)
Celecoxib				
Current use	3.37 (2.63-4.32)	2.04 (1.56-2.68)	2.78 (2.01-3.86)	1.64 (1.16-2.33)
Recent use	2.28 (1.82-2.85)	1.62 (1.27-2.05)	2.10 (1.58-2.79)	1.42 (1.05-1.92)
Rofecoxib				
Current use	3.53 (2.70-4.62)	2.43 (1.81-3.25)	2.86 (2.01-4.09)	1.97 (1.35-2.88)
Recent use	2.15 (1.70-2.72)	1.45 (1.13-1.86)	1.70 (1.24-2.34)	1.11 (0.79-1.56)

See user definitions in the text or on Table 1.

*Adjusted for the matching factors of age and sex.

†Additional adjustments for the potential confounders listed in Table 1.

eTable 2. Stratified analyses of the adjusted incidence rate ratios associating NSAID use and venous thromboembolism.

	Composite venous thromboembolism				Unprovoked venous thromboembolism			
	Nonselective NSAIDs		COX-2 inhibitors		Nonselective NSAIDs		COX-2 inhibitors	
	Current use	Recent use	Current use	Recent use	Current use	Recent use	Current use	Recent use
Overall	2.51 (2.29-2.76)	1.44 (1.33-1.56)	2.19 (1.99-2.41)	1.41 (1.30-1.54)	2.71 (2.40-3.05)	1.38 (1.24-1.54)	2.15 (1.88-2.46)	1.46 (1.30-1.64)
Female	2.38 (2.10-2.69)	1.40 (1.26-1.57)	1.94 (1.71-2.21)	1.35 (1.20-1.51)	2.78 (2.36-3.26)	1.32 (1.13-1.53)	1.84 (1.54-2.20)	1.33 (1.14-1.56)
Male	2.71 (2.36-3.11)	1.49 (1.32-1.68)	2.61 (2.24-3.03)	1.50 (1.32-1.72)	2.65 (2.21-3.18)	1.46 (1.25-1.71)	2.68 (2.19-3.28)	1.64 (1.38-1.95)
Age group								
<55 years	3.98 (3.32-4.78)	1.60 (1.36-1.89)	3.70 (2.96-4.62)	1.84 (1.51-2.23)	4.65 (3.73-5.79)	1.58 (1.29-1.92)	4.47 (3.39-5.89)	1.81 (1.43-2.29)
55–70 years	2.51 (2.12-2.96)	1.48 (1.28-1.72)	2.38 (1.99-2.85)	1.59 (1.35-1.86)	2.41 (1.93-3.01)	1.45 (1.19-1.75)	2.36 (1.86-2.30)	1.60 (1.30-1.98)
≥71 years	1.86 (1.61-2.15)	1.29 (1.14-1.47)	1.66 (1.44-1.91)	1.19 (1.05-1.35)	1.92 (1.58-2.33)	1.16 (0.96-1.39)	1.39 (1.13-1.72)	1.19 (0.99-1.42)
Cancer								
No	2.62 (2.37-2.89)	1.43 (1.31-1.56)	2.13 (1.91-2.38)	1.50 (1.36-1.65)	-	-	-	-
Yes	2.02 (1.60-2.54)	1.49 (1.23-1.82)	2.34 (1.88-2.92)	1.08 (0.88-1.34)	-	-	-	-
Cardiovascular disease								
No	3.81 (3.30-4.40)	1.63 (1.43-1.86)	3.09 (2.60-3.67)	1.75 (1.50-2.03)	4.15 (3.47-4.97)	1.61 (1.37-1.90)	3.34 (2.67-4.17)	1.75 (1.45-2.11)
Yes	1.91 (1.69-2.15)	1.32 (1.19-1.47)	1.85 (1.65-2.08)	1.26 (1.14-1.41)	1.95 (1.66-2.29)	1.24 (1.07-1.43)	1.71 (1.45-2.02)	1.28 (1.11-1.49)
Diabetes mellitus								
No	2.67 (2.43-2.94)	1.43 (1.31-1.55)	2.28 (2.06-2.52)	1.43 (1.31-1.57)	2.89 (2.56-3.27)	1.36 (1.22-1.53)	2.24 (1.95-2.58)	1.48 (1.31-1.67)
Yes	1.20 (0.84-1.71)	1.60 (1.20-2.13)	1.36 (0.96-1.94)	1.22 (0.90-1.67)	1.05 (0.62-1.79)	1.61 (1.10-2.35)	1.29 (0.78-2.15)	1.27 (0.82-1.97)
Musculoskeletal or connective tissue disease*								
No	2.78 (2.51-3.09)	1.38 (1.25-1.51)	2.41 (2.15-2.70)	1.36 (1.23-1.51)	3.02 (2.64-3.45)	1.37 (1.21-1.54)	2.46 (2.11-2.86)	1.47 (1.29-1.68)
Yes	1.65 (1.35-2.02)	1.65 (1.39-1.96)	1.62 (1.34-1.95)	1.53 (1.29-1.81)	1.69 (1.27-2.23)	1.42 (1.10-1.84)	1.42 (1.08-1.87)	1.39 (1.09-1.79)
Obesity								
No	2.59 (2.36-2.85)	1.47 (1.36-1.60)	2.25 (2.04-2.49)	1.42 (1.30-1.55)	2.80 (2.48-3.17)	1.43 (1.28-1.59)	2.17 (1.89-2.49)	1.47 (1.30-1.65)
Yes	1.48 (0.98-2.23)	0.96 (0.64-1.43)	1.33 (0.87-2.02)	1.39 (0.94-2.03)	1.29 (0.69-2.43)	0.65 (0.36-1.19	1.80 (1.00-3.25)	1.38 (0.78-2.45)
Trauma or fracture								
No	2.58 (2.35-2.84)	1.46 (1.34-1.59)	2.21 (1.99-2.44)	1.44 (1.31-1.57)	-	-	-	-
Yes	1.62 (1.20-2.20)	1.16 (0.85-1.59)	1.85 (1.31-2.63)	1.03 (0.73-1.44)	-	-	-	-
Recent hospital admission								
No	2.63 (2.38-2.90)	1.49 (1.36-1.63)	2.32 (2.09-2.59)	1.42 (1.29-1.57)	2.84 (2.51-3.21)	1.42 (1.27-1.59)	2.11 (1.83-2.43)	1.48 (1.31-1.67)
Yes	1.66 (1.33-2.07)	1.20 (0.99-1.44)	1.51 (1.22-1.87)	1.35 (1.13-1.62)	1.30 (0.86-1.96)	0.94 (0.62-1.43)	2.17 (1.38-3.40)	1.12 (0.76-1.64)

See covariate definitions in the text or in Table 1 and user definitions and description of the adjusted model in the text or in Table 2.
*Osteoarthritis, rheumatoid arthritis, or systemic connective tissue disease

eTable 3. Sensitivity analysis examining the impact of different exposure windows on the rate of venous thromboembolism.

		Adjusted incidence rate ratio (95% confidence interval)			
Exposure window*	**No use**	**Nonselective NSAIDs**		**COX-2 selective inhibitors**	
		Current use†	**Recent use‡**	**Current use†**	**Recent use‡**
15 days	1	3.91 (3.40-4.49)	1.57 (1.46-1.68)	3.05 (2.63-3.54)	1.52 (1.41-1.63)
30 days	1	3.13 (2.80-3.50)	1.50 (1.39-1.61)	2.54 (2.26-2.86)	1.46 (1.34-1.58)
60 days	1	2.51 (2.29-2.76)	1.44 (1.33-1.56)	2.19 (1.99-2.41)	1.41 (1.30-1.54)
90 days	1	2.26 (2.08-2.46)	1.43 (1.31-1.57)	2.06 (1.88-2.25)	1.39 (1.26-1.53)
120 days	1	2.15 (1.99-2.33)	1.41 (1.28-1.55)	1.98 (1.82-2.15)	1.36 (1.23-1.51)

See description of the adjusted model in the text or in Table 2.

*Number of days exposed from prescription redemption.

†Defined by an exposure window from last prescription redemption which covered the index date.

‡Defined by an exposure window from the most recent prescription redemption (within 365 days before index date), which did not cover the index date.

ATC and ICD codes

ATC codes for NSAIDs

Nonselective NSAIDs; ibuprofen: M01AE01, M01AE51; naproxen: M01AE02; ketoprofen: M01AE03, M01AE53; dexibuprofen: M01AE14; piroxicam: M01AC01; tolfenamic acid: M01AG02; indomethacin: M01AB01.

Older COX2Is; diclofenac: M01AB05, M01AB55; etodolac: M01AB08; nabumeton: M01AX01; meloxicam: M01AC06.

Newer COX2Is: celecoxib: M01AH01; rofecoxib: M01AH02; valdecoxib: M01AH03; parecoxib: M01AH04; etoricoxib: M01AH05; lumiracoxib: M01AH06.

ATC codes for co-medications

Antipsychotics: N05A.

Hormone replacement therapy: G03C, G03F.

Oral glucocorticoids: H02AB.

Vitamin K antagonists: B01AA03, B01AA04.

ICD codes defining VTE

DVT: ICD-8: 451.00; ICD-10: I80.1-3.

PE: ICD-8: 450.99; ICD-10: I26.

ICD and ATC codes defining co-morbidities

Cancer: ICD-8: 140-209; ICD-10: C00-C99.

Pregnancy: ICD-8:630-680; ICD-10:O00-O99.

Trauma or fracture: ICD-8: 800-929, 950-959; ICD-10: S00-T14.

Cardiovascular diseases: ICD-8: 393-398, 400-404, 410-414, 427.09, 427.10, 427.19; ICD-10: I05-I09, I10-I15, I20-I25, I50; ATC: C09 or C02 before 1 January 1996 (angiotensin-converting enzyme inhibitors or angiotensin-II receptor inhibitors), C07 (beta-blockers), B01AC06 or N02BA01 (aspirin), B01AC04 (clopidogrel), C10AA or B04AB01 (statins), C08 (calcium channel antagonists), C02 (antihypertensive drugs), C03 (diuretics), C01DA if two or more prescriptions (nitrates)

Diabetes mellitus: ICD-8: 249, 250; ICD-10: E10, E11, H36.0; ATC: A10A, A10B.

COPD or asthma: ICD-8: 491, 492, 493; ICD-10: J41, J42, J43, J44, J45, J46; ATC: R03.

Liver disease: ICD-8: 571; ICD-10: K70.0, K70.3, K71.7, K73, K74, K76.0, B18, I85.

Obesity: ICD-8: 277; ICD-10: E65-E68.

Osteoarthritis: ICD-8: 713; ICD-10: M15-19, M47.

Osteoporosis: ICD-8: 723.09; ICD-10: M80-M82.

Renal failure: ICD-8: 581-584; ICD-10: N17-N19.

Rheumatoid arthritis: ICD-8: 712; ICD-10: M05-M06.

Systemic connective tissue disease: ICD-8: 716, 734, 446, 135.99; ICD-10: M30–M36, M45.

Paper III

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RESEARCH

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

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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

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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.

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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.

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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).

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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.

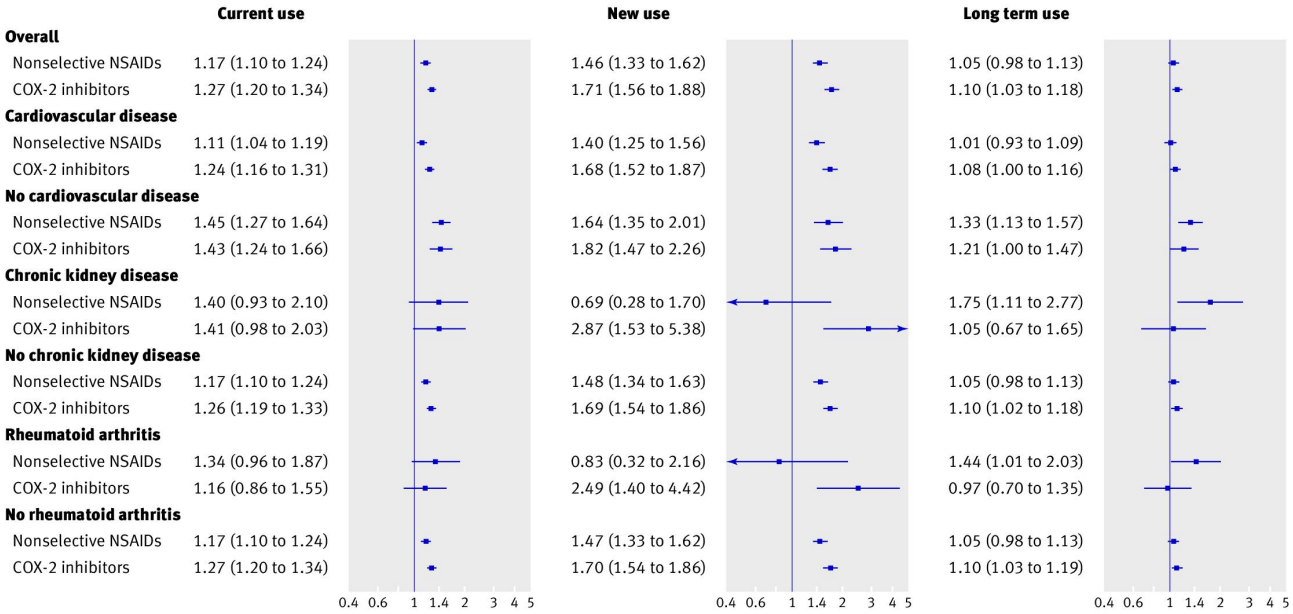
††Current use of both non-selective NSAIDs and COX 2 inhibitors.

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

Webappendix: Registry codes

Medication (ATC codes)

Nonselective NSAIDs; ibuprofen: M01AE01, M01AE51; naproxen: M01AE02; ketoprofen: M01AE03, M01AE53; dexibuprofen: M01AE14; piroxicam: M01AC01; tolfenamic acid: M01AG02

Older COX-2 inhibitors; diclofenac: M01AB05, M01AB55; etodolac: M01AB08; nabumeton: M01AX01; meloxicam: M01AC06.

Newer COX-2 inhibitors: celecoxib: M01AH01; rofecoxib: M01AH02; valdecoxib: MM01AH03; parecoxib: MM01AH04; etoricoxib: M01AH05.

Oral glucocorticoids: H02AB.

Thyroid drugs (levothyroxinnatrium): H03AA01.

Digoxin: C01AA05.

Vitamin K antagonists: B01AA.

Diseases (ICD and ATC codes)

Atrial fibrillation or flutter: ICD-8: 427.93-94; ICD-10: I48.9

Alcoholism-related disease other than those affecting the liver or pancreas: ICD-8: 291, 303, 979, 980; ICD-10: F10, G31.2, G62.1, G72.1, I42.6, K29.2, R78.0, T51.0, T51.9, Z72.1; ATC: N07BB01 (any prescription for disulfiram).

Cancer: ICD-8: 140-207; ICD-10: C00-C96.

Cardiovascular disease: ICD-8: 393-398, 400-404, 410-414, 427.09, 427.10, 427.19; ICD-10: I05-I09, I10-I15, I20-I25, I50; ATC: C09, B01AC06, N02BA01, C07, C08, C03, C01DA, C10AA, B04AB, C02.

Chronic kidney disease; ICD-8: 249.02, 250.02, 582, 583, 584, 590.09, 593.20, 753.10, 753.19, 792; ICD-10: E10.2, E11.2, E14.2, N03, N05, N11.0, N14; N16, N18-N19, N26.9, Q61.1-Q61.4.

Chronic obstructive pulmonary disease or asthma: ICD-8: 491, 492, 493; ICD-10: J41, J42, J43, J44, J45, J46; ATC: R03.

Diabetes mellitus: ICD-8: 249-250 (except 249.02 and 250.02); ICD-10: E10-E11 (except E10.2 and E11.2), O24 (except O24.4), H36.0; ATC: A10B, A10A.

Hyperthyroidism: ICD-8: 242; ICD-10: E05; ATC: H03B.

Hypothyroidism: ICD 8: 243-44; ICD-10: E02-3; ATC: H03AA01.

Inflammatory bowel disease: ICD-8: 563.01, 563.19, 569.04; ICD-10: K50-51.3

Liver disease or chronic pancreatitis; ICD-8: 571.09-571.11, 571.19, 571.90, 571.91-571.93, 571.99, 577.10, 577.11, 456.00, 456.01, 456.09; ICD-10: K70.0, K70.3, K71.7, K73, K74, K76.0, B18, I85, K86.0, K86.1.

Osteoarthritis: ICD-8: 713; ICD-10: M015-19, M47.

Psoriatic arthritis: ICD-8: 696.09; ICD-10: M07.

Rheumatoid arthritis: ICD-8: 712; ICD-10: M05-M06.

Systemic connective tissue disease: ICD-8: 716, 734, 446, 135.99; ICD-10: M30–M36, M45.

Procedures (Danish procedure codes)

Cardioversion: BFFA0

Paper IV

MS ID#: NEUROLOGY/2014/580225

Title: Preadmission use of non-steroidal anti-inflammatory drugs and 30-day stroke mortality

Running head: NSAID use and 30-day stroke mortality

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Supplemental Data: Table e1-8, electronic file name: Supplemental Data

Counts: Abstract: 250 words; Text: 2769 words; Title: 85 characters (incl. spaces and punctuation); References: 28; Tables/Figures: 4

Key words: Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors; stroke; mortality; cohort study

Contributorship: 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.

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Dr. Morten Schmidt reports no disclosures.
Statistician Erzsébet Hováth-Puhó reports no disclosures.
Dr. Christian Fynbo Christiansen reports no disclosures.
Dr. Karin L. Petersen reports no disclosures.
Dr. Hans Erik Bøtker reports no disclosures.
Dr. Henrik Toft Sørensen reports no disclosures.

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.

Data sharing: No additional data available.

ABSTRACT

Objectives: To examine whether preadmission use of *nonselective* non-steroidal anti-inflammatory drugs (NSAIDs) and *selective* cyclooxygenase (COX)-2 inhibitors 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 during 2004-2012 (n=100,043) and subsequent mortality. We categorized NSAID use as current (prescription redemption within 60 days before hospital admission), former, and non-use. Current use was further classified as new or long-term use. Cox regression was used to compute 30-day mortality rate ratios (MRRs), controlling for potential confounding through multivariable adjustment and propensity-score matching.

Results: The 30-day adjusted MRR for ischaemic stroke was 1.14 (95% confidence interval (CI): 1.03-1.27) for current users of COX-2 inhibitors compared with non-users, driven by the effect among new users (1.31, 95% CI: 1.13-1.52). The propensity-score-matched analysis yielded similar MRRs for ischaemic stroke: 1.16 (95% CI: 1.01-1.34) among current users and 1.28 (95% CI: 1.07-1.54) among new users. Comparing the different COX-2 inhibitors, the MRR was driven by new use of older traditional COX-2 inhibitors (1.30, 95% CI: 1.12-1.52) among which it was 1.51 (95% CI: 1.16-1.98) for etodolac and 1.21 (95% CI: 1.01-1.45) for diclofenac. There was no association for former users. Mortality from intracerebral haemorrhage and subarachnoid haemorrhage 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 following ischaemic stroke, but not haemorrhagic stroke. Preadmission use of nonselective NSAIDs was not associated with mortality from ischaemic or haemorrhagic stroke.

INTRODUCTION

Non-aspirin non-steroidal 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 ischaemic stroke,[2,3] but it remains unclear whether preadmission use of COX-2 inhibitors also affects the outcome of an ischaemic 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 oedema, neuroinflammation, and infarct size in rodent stroke models.[4-6] In contrast, other studies have found a neuroprotective role of COX-2-derived prostaglandin E2 (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 following stroke, which indicates a therapeutic potential for nonselective NSAIDs.[8]

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 following ischaemic stroke, intracerebral haemorrhage (ICH), or subarachnoid haemorrhage (SAH).

METHODS

Setting

Since 1 January 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 1 July 2004 through 31 December 2012, in order to ensure the availability of at least a 6-month prescription history for all study participants. The Danish population included in this study period 6,379,918 inhabitants.

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.[9] Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark using the unique civil registration 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 non-psychiatric 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, classified according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.[12]

We used the DNRP to identify all inpatient primary and secondary diagnoses of ischaemic stroke, ICH, and SAH during the study period. Of note, patients are included in the DNRP if they receive a hospital diagnosis of stroke, but not if they die at home without being hospitalized. We classified unspecified strokes (40% of all stroke diagnoses) as ischaemic strokes because more than two-thirds of all unspecified strokes are known to be ischaemic strokes.[13]

Our study included only patients with incident stroke. Thus, 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] Due to their low positive predictive value, we also excluded emergency room diagnoses of stroke in the absence of a subsequent inpatient diagnosis.[13] The DNRP provided information on diagnostic procedures (computed tomography (CT) or magnetic resonance imaging (MRI)) performed during hospitalization.

NSAID use

We used the nationwide prescription database to identify prospectively all NSAID prescriptions filled by stroke patients before their admission date.[9] 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 civil registration 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.[9] Except for ibuprofen in the 200 mg per tablet dose, all non-aspirin NSAIDs are available by prescription only.[14] Regular users of ibuprofen are typically registered in the prescription database, because the cost is partly refunded when the drug is prescribed by a physician.[14]

We identified prescriptions for non-selective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, tolfenamic acid, and indomethacin) and COX-2 inhibitors. COX-2 inhibitors were subcategorized as older COX-2 inhibitors (diclofenac, etodolac, nabumeton, and meloxicam) or coxibs (celecoxib, rofecoxib, valdecoxib, parecoxib, 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 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.[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 would expect the effect to be greater among current than former users. We defined persons with no filled NSAID prescriptions during the 180 days before their admission date as non-users. Because some side effects may arise shortly after therapy initiation, inclusion of long-term users may lead to underestimation of these complications.[16] For this reason, we further categorized current users into two groups: new users, defined as having filled their first-

ever prescription within 60 days before their admission date; and long-term users, defined as having filled additional prescriptions more than 60 days before their admission date.

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)[17] 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). In order to increase the sensitivity 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]

Comedications

We used the prescription database to ascertain concurrent use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists (ARBs), beta-blockers, calcium channel blockers, diuretics, nitrates (if ≥2 prescriptions), statins, aspirin, clopidogrel, vitamin K antagonists, systemic glucocorticoids, selective serotonin reuptake inhibitors (SSRIs), 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 gender, age group (<60, 60-69, 70-79, or ≥80 years), comorbidities, comedication use, and whether CT or MRI was performed during the hospital admission. 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 as measures of mortality rate ratios (MRRs) within 30 days for current, new, long-term, and former use compared with non-use.

We applied two different statistical methods to reduce confounding. First, we used a multivariable model adjusting for the known prognostic factors, other potential confounders, and comedication use as defined above. To increase the positive predictive value of the stroke diagnosis, we repeated the analysis including only patients who had a CT or MRI scan registered in the DNPR during their hospital admission.

To examine the sensitivity of the estimates to differences in exposure definitions, we also repeated the analysis using a 30-day instead of 60-day exposure window. We stratified analyses by gender, age group, and presence/absence of rheumatoid arthritis, osteoarthritis, myocardial infarction, atrial fibrillation or flutter, hypertension, and diabetes mellitus.

Secondly, 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 described above.[18] We then computed the probability of current NSAID use (=the propensity score) for all stroke patients and visually illustrated the propensity score distribution among current users and non-users. Using a greedy matching algorithm, we matched each NSAID user with the non-user with the closest propensity score.[19] 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.[19] 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 non-users.[19] The proportional hazard assumption was visually assessed by log–log plots.

Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). All ICD and ATC codes are provided in Table e-1.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Danish Data Protection Agency (record number record number 2011-41-5755). As 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 83,736 (84%) had ischaemic stroke (median age: 74 years), 11,779 (12%) had ICH (median age: 72 years), and 4,528 (5%) had SAH (median age: 58 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 stroke patients with ICH or SAH was 16.5% among current NSAID users and 15.7% among non-users. There was substantial overlap in propensity score distributions among NSAID users and non-users before matching (Figure 1) and we achieved virtually complete matching of controls to current NSAID users (100% for ischaemic stroke, 99.9% for ICH, and 99.2% for SAH). The most notable difference in patient characteristics before matching (Table 1 and Table e-2) was that a higher proportion of NSAID users had obesity, COPD, rheumatic disease, osteoarthritis, or glucocorticoid use than non-users. After matching, the characteristics of NSAID users and non-users were equally distributed (Table e-3).

Overall 30-day mortality among NSAID non-users was 11% for ischaemic stroke, 35% for ICH, and 24% for SAH. After multivariable adjustment (Table 2), current use of nonselective NSAIDs was not associated with mortality from ischaemic stroke compared with non-users (MRR=1.06, 95% confidence interval (CI): 0.97-1.17). However, the 30-day MRR for ischaemic stroke was 1.14 (95% CI: 1.03-1.27) for current users of COX-2 inhibitors, driven by the effect among new users (MMR=1.31, 95% CI: 1.13-1.52). The propensity-score-matched analysis yielded similar results, with a 30-day MRR for ischaemic stroke of 1.16 (95% CI: 1.01-1.34) among current users and 1.28 (95% CI: 1.07-1.54) among new users. Comparing initiation of different types of COX-2 inhibitors and the statistical precision, the effect was driven by older COX-2 inhibitors (multivariable-adjusted MRR: 1.30, 95% CI: 1.12-1.52), among which it was 1.51 (95% CI: 1.16-1.98) for etodolac users and 1.21 (95% CI: 1.01-1.45) for diclofenac users (Table 3). The results for individual NSAID types and ICD and SAH are presented in Table e-4. We observed no association between former use of COX-2 inhibitors and ischaemic stroke mortality (Table e-5). Use of non-selective NSAIDs and COX-2 inhibitors was not associated with 30-day mortality following ICH and SAH (Table 2 and Table e-5). New users of non-selective NSAIDs had a reduced MRR for SAH (0.61, 95% CI: 0.41-0.91), but similar reductions were seen for former users (MRR: 0.69, 95% CI: 0.49-0.97) (Table e-5). The results were robust in the analysis restricted to CT- or MRI-confirmed cases (Table e-6) and when using a 30-day exposure window (Table e-7). The stratified analyses revealed no substantial effect modification of the MRRs (Table e-8).

DISCUSSION

Preadmission use of COX-2 inhibitors was associated with increased mortality following ischaemic stroke, while preadmission use of nonselective NSAIDs and COX-2 inhibitors was not associated with mortality following ICH or SAH.

The increased mortality rate associated with COX-2 inhibition in ischaemic stroke was observed only among current users, which indicates 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 potentially could lead to larger thromboembolic occlusions that would increase mortality, compared with non-use. The effect may also be mediated through adverse cardiovascular events or stroke recurrence. COX-2 inhibition may also impair the pathophysiological response to a stroke. Thus, a cerebral infarct causes an inflammatory response at the site of injury and in the surrounding tissue, which up-regulates neuronal COX-2 expression[20] and hence nitric oxide, PGE_2, and proinflammatory cytokines (including tumour necrosis factor (TNF)-a and interleukin-1b).[21,22] Whether this up-regulation of COX-2 promotes neuronal injury or protection is controversial,[7,23,24] because TNF-a 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 ischaemic preconditioning mediated by prior sublethal ischaemic insults would also be counteracted by COX-2 inhibition.[25-27] 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 following the withdrawal of rofecoxib in 2004, many older COX-2 inhibitors such as diclofenac are still frequently prescribed.[14] Use of diclofenac has previously been reported to more than double the risk of ischemic stroke[2] and our study adds evidence that diclofenac users also have a worse outcome following 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 post-ischaemic oxidative stress and inflammation.[28]

Strengths and limitations

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. The prescription data were virtually complete.[9] Although prescription data were used as a proxy for actual NSAID use, this was based on actual dispensing at pharmacies, rather than written prescriptions.[9,14] Co-payments required upon dispensing of NSAIDs increased the likelihood of compliance. We lacked information on over-the-counter use of low dose (200 mg/tablet) ibuprofen, which accounted for 30%-35% of total ibuprofen sales and 15%-25% of total NSAID sales during the study period.[14] 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 non-differential.[14] The positive predictive value of acute stroke diagnoses in the DNRP has been examined previously and found to be 97% for ischaemic stroke, 74% for ICH, and 67% for SAH.[13] Because we classified *unspecified strokes* as ischaemic strokes, we inevitably misclassified some ICH (approximately 6%) as ischaemic strokes.[13] Given the lack of association between NSAID use and ICH mortality, such misclassification would bias the results for ischaemic stroke towards the null and thus cannot explain our findings. 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 as previously mentioned. We adjusted indirectly for lifestyle factors through COPD, hospital-diagnosed obesity, and ischemic heart disease, but did not have detailed data available on smoking or body

weight. The point estimates associating non-selective NSAIDs and SAH mortality were similarly reduced for current and former users, indicating no drug effect. 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 two approaches, however, supports the robustness of our findings.

We found that preadmission use of COX-2 inhibitors was associated with increased 30-day mortality following ischaemic stroke, but not haemorrhagic stroke. Use of nonselective NSAIDs at time of admission was not associated with mortality from ischaemic or haemorrhagic stroke.

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Table 1. Characteristics of stroke patients according to preadmission NSAID use.

	NSAID use								
	Ischaemic stroke			Intracerebral haemorrhage			Subarachnoid haemorrhage		
	Current use	Former use	No use	Current use	Former use	No use	Current use	Former use	No use
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number (%)	9133 (100)	7167 (100)	67 436 (100)	1213 (100)	890 (100)	9676 (100)	489 (100)	345 (100)	3694 (100)
Gender (female)	4893 (53.6)	3654 (51.0)	32 192 (47.7)	649 (53.5)	435 (48.9)	4592 (47.5)	303 (62.0)	219 (63.5)	2093 (56.7)
Age, years									
<60	1590 (17.4)	1454 (20.3)	12 545 (18.6)	230 (19.0)	219 (24.6)	2412 (24.9)	257 (52.6)	176 (51.0)	2001 (54.2)
60-69	1931 (21.1)	1567 (21.9)	14 496 (21.5)	244 (20.1)	158 (17.8)	2050 (21.2)	105 (21.5)	76 (22.0)	776 (21.0)
70-79	2704 (29.6)	2013 (28.1)	17 976 (26.7)	355 (29.3)	244 (27.4)	2456 (25.4)	62 (12.7)	56 (16.2)	510 (13.8)
≥80	2908 (31.8)	2133 (29.8)	22 419 (33.2)	384 (31.7)	269 (30.2)	2758 (28.5)	65 (13.3)	37 (10.7)	407 (11.0)
Comorbidity level*									
Low	3894 (42.6)	3081 (43.0)	31 786 (47.1)	530 (43.7)	409 (46.0)	4926 (50.9)	303 (62.0)	186 (53.9)	2391 (64.7)
Moderate	3709 (40.6)	2839 (39.6)	24 700 (36.6)	499 (41.1)	341 (38.3)	3288 (34.0)	142 (29.0)	128 (37.1)	1009 (27.3)
High	1530 (16.8)	1247 (17.4)	10 950 (16.2)	184 (15.2)	140 (15.7)	1462 (15.1)	44 (9.0)	31 (9.0)	294 (8.0)
Individual comorbidities									
Myocardial infarction	722 (7.9)	618 (8.6)	6089 (9.0)	64 (5.3)	68 (7.6)	591 (6.1)	12 (2.5)	16 (4.6)	118 (3.2)
Angina pectoris	1375 (15.1)	1209 (16.9)	10 515 (15.6)	134 (11.0)	125 (14.0)	1143 (11.8)	39 (8.0)	34 (9.9)	256 (6.9)
Atrial fibrillation or flutter	1059 (11.6)	903 12.6 ()	9451 (14.0)	137 (11.3)	110 (12.4)	1311 (13.5)	28 (5.7)	20 (5.8)	195 (5.3)
Heart valve disease	357 (3.9)	317 (4.4)	3098 (4.6)	29 (2.4)	46 (5.2)	408 (4.2)	12 (2.5)	7 (2.0)	69 (1.9)
Intermittent claudication	295 (3.2)	215 (3.0)	2068 (3.1)	30 (2.5)	9 (1.0)	173 (1.8)	5 (1.0)	2 (0.6)	47 (1.3)
Venous thromboembolism	362 (4.0)	300 (4.2)	2461 (3.6)	49 (4.0)	28 (3.1)	342 (3.5)	12 (2.5)	6 (1.7)	75 (2.0)
Obesity	550 (6.0)	382 (5.3)	2385 (3.5)	66 (5.4)	36 (4.0)	276 (2.9)	21 (4.3)	15 (4.3)	104 (2.8)
Diabetes mellitus	1301 (14.2)	1040 (14.5)	8881 (13.2)	118 (9.7)	79 (8.9)	943 (9.7)	37 (7.6)	23 (6.7)	198 (5.4)
Chronic kidney disease	186 (2.0)	175 (2.4)	1841 (2.7)	19 (1.6)	24 (2.7)	281 (2.9)	7 (1.4)	5 (1.4)	58 (1.6)

Hypertension	2444 (26.8)	1914 (26.7)	16 931 (25.1)	271 (22.3)	223 (25.1)	2255 (23.3)	81 (16.6)	64 (18.6)	506 (13.7)
COPD	2237 (24.5)	1747 (24.4)	13 423 (19.9)	268 (22.1)	191 (21.5)	1767 (18.3)	91 (18.6)	88 (25.5)	638 (17.3)
Alcoholism-related disease	669 (7.3)	525 (7.3)	4235 (6.3)	89 (7.3)	78 (8.8)	784 (8.1)	42 (8.6)	27 (7.8)	263 (7.1)
Dementia	236 (2.6)	210 (2.9)	2346 (3.5)	49 (4.0)	22 (2.5)	393 (4.1)	6 (1.2)	4 (1.2)	50 (1.4)
Cancer	1433 (15.7)	1095 (15.3)	9610 (14.3)	222 (18.3)	160 (18.0)	1452 (15.0)	49 (10.0)	32 (9.3)	317 (8.6)
Rheumatoid arthritis	304 (3.3)	184 (2.6)	1100 (1.6)	43 (3.5)	22 (2.5)	143 (1.5)	20 (4.1)	10 (2.9)	41 (1.1)
Connective tissue disease	318 (3.5)	247 (3.4)	1822 (2.7)	39 (3.2)	27 (3.0)	217 (2.2)	16 (3.3)	10 (2.9)	59 (1.6)
Osteoarthritis	2623 (28.7)	1836 (25.6)	10 089 (15.0)	295 (24.3)	211 (23.7)	1283 (13.3)	97 (19.8)	61 (17.7)	349 (9.4)
Osteoporosis	565 (6.2)	422 (5.9)	3383 (5.0)	85 (7.0)	68 (7.6)	526 (5.4)	29 (5.9)	15 (4.3)	105 (2.8)
Comedication									
ACE or A2R inhibitors	2654 (29.1)	1941 (27.1)	17 213 (25.5)	284 (23.4)	202 (22.7)	1917 (19.8)	99 (20.2)	62 (18.0)	510 (13.8)
β-blockers	1927 (21.1)	1493 (20.8)	13 769 (20.4)	180 (14.8)	162 (18.2)	1571 (16.2)	47 (9.6)	38 (11.0)	328 (8.9)
Calcium channel blockers	1590 (17.4)	1220 (17.0)	10 360 (15.4)	133 (11.0)	87 (9.8)	943 (9.7)	55 (11.2)	40 (11.6)	270 (7.3)
Diuretics	3034 (33.2)	2101 (29.3)	18 108 (26.9)	311 (25.6)	200 (22.5)	2007 (20.7)	91 (18.6)	52 (15.1)	446 (12.1)
Nitrates	213 (2.3)	126 (1.8)	1267 (1.9)	16 (1.3)	8 (0.9)	123 (1.3)	4 (0.8)	2 (0.6)	22 (0.6)
Statins	1608 (17.6)	1249 (17.4)	10 732 (15.9)	172 (14.2)	140 (15.7)	1337 (13.8)	56 (11.5)	49 (14.2)	354 (9.6)
Acetylsalicylic acid	2466 (27.0)	1753 (24.5)	16 056 (23.8)	242 (20.0)	216 (24.3)	2008 (20.8)	56 (11.5)	47 (13.6)	355 (9.6)
Clopidogrel	156 (1.7)	159 (2.2)	1303 (1.9)	9 (0.7)	11 (1.2)	160 (1.7)	5 (1.0)	1 (0.3)	38 (1.0)
Vitamin K antagonists	344 (3.8)	317 (4.4)	3317 (4.9)	108 (8.9)	84 (9.4)	999 (10.3)	13 (2.7)	11 (3.2)	134 (3.6)
Systemic glucocorticoids	692 (7.6)	475 (6.6)	2887 (4.3)	58 (4.8)	46 (5.2)	361 (3.7)	19 (3.9)	16 (4.6)	91 (2.5)
SSRIs	1012 (11.1)	692 (9.7)	5808 (8.6)	141 (11.6)	82 (9.2)	913 (9.4)	37 (7.6)	25 (7.2)	258 (7.0)
Bisphosphonates	413 (4.5)	300 (4.2)	2158 (3.2)	64 (5.3)	38 (4.3)	342 (3.5)	22 (4.5)	11 (3.2)	79 (2.1)
CT or MRI scan during admission	7986 (87.4)	6239 (87.1)	59 285 (87.9)	1115 (91.9)	814 (91.5)	8842 (91.4)	440 (90.0)	315 (91.3)	3395 (91.9)
CT scan	7771 (85.1)	6030 (84.1)	57 451 (85.2)	1096 (90.4)	800 (89.9)	8642 (89.3)	435 (89.0)	310 (89.9)	3369 (91.2)
MRI scan	1005 (11.0)	903 (12.6)	8160 (12.1)	96 (7.9)	59 (6.6)	748 (7.7)	33 (6.7)	21 (6.1)	219 (5.9)

Abbreviations: ACE, angiotensin-converting enzyme; A2R, angiotensin-2 receptor; NSAIDs, nonsteroidal anti-inflammatory drugs, SSRIs, selective serotonin reuptake inhibitors
*Three levels of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1-2 (moderate), and ≥3 (high).

Table 2. Preadmission NSAID use and 30-day mortality estimates following stroke.

	Ischaemic stroke				Intracerebral haemorrhage				Subarachnoid haemorrhage			
	Risk	Mortality rate ratio (95% CI)			Risk	Mortality rate ratio (95% CI)			Risk	Mortality rate ratio (95% CI)		
		Unadjusted	Multivariable-adjusted*	Propensity-score-matched†		Unadjusted	Multivariable-adjusted*	Propensity-score-matched†		Unadjusted	Multivariable-adjusted*	Propensity-score-matched†
No use of any NSAIDs	10.9 (10.6-11.1)	1 (reference)	1 (reference)	1 (reference)	35.1 (34.1-36.0)	1 (reference)	1 (reference)	1 (reference)	24.5 (23.1-25.9)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs‡	11.1 (10.5-11.8)	1.03 (0.96-1.10)	1.02 (0.96-1.09)	1.03 (0.94-1.12)	34.7 (32.1-37.5)	0.99 (0.89-1.09)	0.97 (0.88-1.08)	0.91 (0.80-1.04)	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	11.4 (10.3-12.5)	1.05 (0.95-1.16)	1.11 (1.00-1.23)	1.15 (0.99-1.34)	32.0 (28.0-36.4)	0.89 (0.76-1.05)	0.90 (0.76-1.06)	1.06 (0.84-1.33)	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	11.0 (10.2-11.8)	1.01 (0.93-1.10)	0.97 (0.90-1.06)	1.00 (0.89-1.11)	36.5 (33.1-40.1)	1.05 (0.93-1.19)	1.02 (0.90-1.16)	0.98 (0.83-1.16)	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‡	10.8 (9.9-11.7)	0.99 (0.90-1.09)	1.06 (0.97-1.17)	1.11 (0.97-1.26)	32.4 (29.0-36.1)	0.91 (0.79-1.05)	0.94 (0.81-1.08)	0.96 (0.79-1.15)	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	10.4 (9.1-11.7)	0.95 (0.83-1.09)	1.06 (0.93-1.21)	1.06 (0.90-1.25)	30.6 (26.0-35.8)	0.85 (0.70-1.03)	0.88 (0.72-1.07)	0.89 (0.71-1.13)	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	11.1 (9.9-12.5)	1.02 (0.91-1.16)	1.07 (0.94-1.21)	1.15 (0.98-1.33)	34.3 (29.4-39.8)	0.98 (0.81-1.18)	1.00 (0.83-1.21)	1.03 (0.82-1.29)	29.0 (21.6-38.3)	1.23 (0.87-1.73)	1.22 (0.86-1.74)	1.25 (0.83-1.89)
COX-2 inhibitors‡	12.7 (11.5-13.9)	1.18 (1.06-1.30)	1.14 (1.03-1.27)	1.16 (1.01-1.34)	34.5 (30.0-39.4)	0.96 (0.81-1.14)	0.93 (0.78-1.11)	0.95 (0.75-1.21)	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	14.0 (12.2-16.0)	1.30 (1.12-1.51)	1.31 (1.13-1.52)	1.28 (1.07-1.54)	31.8 (25.1-39.8)	0.88 (0.66-1.17)	0.87 (0.66-1.15)	0.87 (0.63-1.21)	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	11.8 (10.4-13.3)	1.09 (0.96-1.25)	1.04 (0.91-1.19)	1.08 (0.91-1.28)	36.2 (30.4-42.7)	1.01 (0.82-1.25)	0.97 (0.78-1.21)	1.01 (0.77-1.32)	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 types	12.6 (11.5-13.8)	1.17 (1.06-1.30)	1.16 (1.04-1.28)	1.18 (1.02-1.37)	33.4 (28.9-38.5)	0.93 (0.77-1.11)	0.91 (0.76-1.09)	0.86 (0.68-1.10)	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	13.8 (12.0-15.9)	1.29 (1.11-1.50)	1.30 (1.12-1.52)	1.30 (1.08-1.56)	31.0 (24.2-39.3)	0.85 (0.63-1.14)	0.85 (0.64-1.15)	0.79 (0.57-1.11)	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	11.8 (10.4-13.3)	1.09 (0.95-1.25)	1.06 (0.93-1.22)	1.10 (0.93-1.31)	35.0 (29.1-41.7)	0.98 (0.78-1.22)	0.94 (0.75-1.18)	0.91 (0.69-1.20)	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	13.5 (8.5-21.0)	1.25 (0.76-2.04)	0.87 (0.53-1.42)	1.06 (0.53-2.15)	48.2 (31.5-68.1)	1.42 (0.82-2.44)	1.29 (0.75-2.23)	0.78 (0.37-1.61)	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	22.9 (12.2-40.5)	2.27 (1.14-4.54)	1.48 (0.74-2.96)	1.93 (0.82-4.53)	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	9.5 (4.9-18.1)	0.86 (0.43-1.72)	0.61 (0.31-1.23)	0.73 (0.31-1.72)	53.3 (31.3-78.8)	1.58 (0.79-3.15)	1.51 (0.75-3.03)	0.86 (0.38-1.95)	-	-	-	-

* 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, COPD, alcoholism-related diseases, dementia, cancer, rheumatoid arthritis, connective tissue disease, osteoarthritis, osteoporosis, and concurrent use of ACE inhibitors or ARBs, beta-blockers, calcium channel blockers, diuretics, nitrates, statins, aspirin, clopidogrel, vitamin K antagonists, systemic glucocorticoids, SSRIs, and bisphosphonates.

† Propensity-score-matched model that matched NSAID users with non-users based on their probability (propensity score ± 0.025) of using NSAIDs, conditioned on the distribution of baseline characteristics.

‡ 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, nabumeton, and meloxicam) or coxibs (celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib).

Table 3. Preadmission use of individual NSAIDs and 30-day mortality rate ratio following ischaemic stroke.

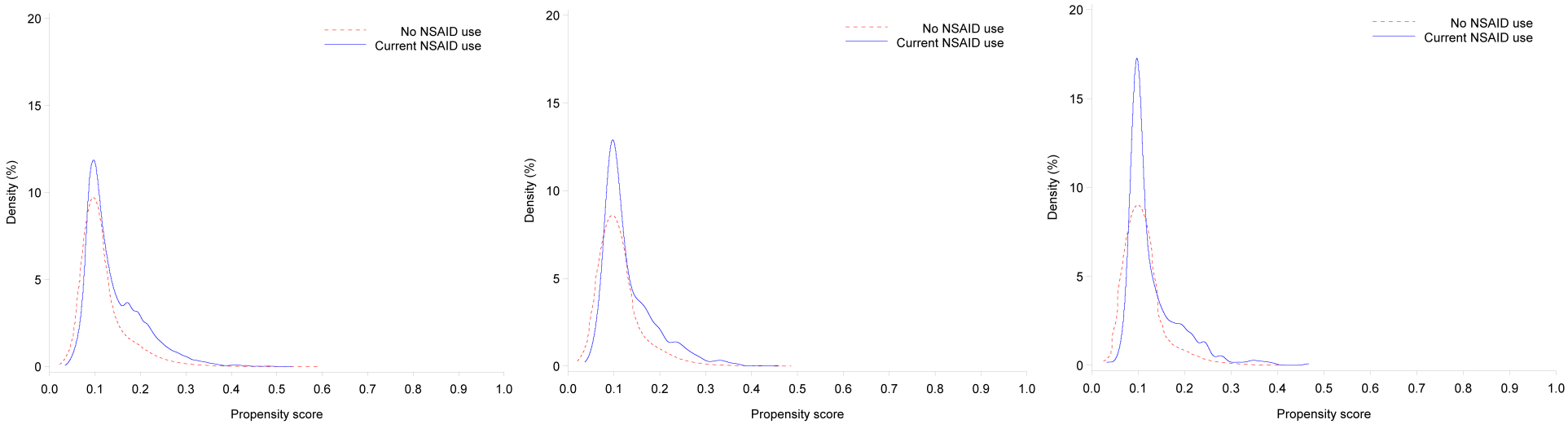
	Mortality rate ratio (95% CI)		
	Ischaemic stroke		
	Unadjusted	Multivariable-adjusted*	Propensity-score matched*
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Ibuprofen (current use)	0.94 (0.85-1.04)	1.02 (0.92-1.13)	1.02 (0.89-1.18)
New use	0.93 (0.80-1.07)	1.05 (0.91-1.21)	1.01 (0.85-1.20)
Long-term use	0.95 (0.83-1.09)	1.00 (0.87-1.15)	1.03 (0.87-1.23)
Naproxen (current use)	1.10 (0.77-1.58)	1.26 (0.87-1.81)	1.64 (0.91-2.95)
New use	0.99 (0.56-1.75)	1.35 (0.77-2.39)	1.48 (0.72-3.08)
Long-term use	1.19 (0.74-1.91)	1.20 (0.74-1.93)	1.77 (0.91-3.43)
Etodolac (current use)	1.39 (1.16-1.65)	1.17 (0.98-1.40)	1.04 (0.81-1.34)
New use	1.77 (1.36-2.31)	1.51 (1.16-1.98)	1.34 (0.97-1.84)
Long-term use	1.19 (0.94-1.50)	1.00 (0.80-1.27)	0.90 (0.67-1.20)
Diclofenac (current use)	1.08 (0.95-1.22)	1.15 (1.01-1.31)	1.08 (0.90-1.29)
New use	1.13 (0.94-1.36)	1.21 (1.01-1.45)	1.13 (0.91-1.41)
Long-term use	1.03 (0.86-1.23)	1.10 (0.92-1.31)	1.03 (0.82-1.28)
Celecoxib (current use)	1.24 (0.66-2.30)	0.83 (0.44-1.54)	0.75 (0.33-1.69)
New use	1.32 (0.50-3.52)	0.94 (0.35-2.51)	0.79 (0.26-2.39)
Long-term use	1.19 (0.53-2.64)	0.76 (0.34-1.70)	0.72 (0.27-1.88)
Rofecoxib (current use)	1.54 (0.69-3.42)	1.06 (0.47-2.35)	1.03 (0.34-3.14)
New use	3.07 (1.15-8.19)	1.84 (0.69-4.91)	2.05 (0.58-7.25)
Long-term use	0.76 (0.19-3.05)	0.57 (0.14-2.28)	0.51 (0.11-2.43)

*See description of the multivariable-adjusted and propensity-score-matched models in the text and in the footnote to Table 2.

Figure 1. Propensity score distributions among NSAID users and non-users.

A. Ischaemic stroke **B. Intracerebral haemorrhage** **C. Subarachnoid haemorrhage**

The propensity score for NSAID use is the probability given baseline variables that any patient in either exposure group would be using NSAIDs.



Supplemental data

Table e-1. ICD and ATC codes

Stroke		
Ischaemic stroke		ICD-8: 433-434; ICD-10: I63-64
ICH		ICD-8: 431; ICD-10: I61
SAH		ICD-8: 430; ICD-10: I60
CT scan		ICD-10: UXCA
MRI scan		ICD-10: UXMA
NSAIDs		ATC: M01A, except M01AX05
Nonselective NSAIDs		
Ibuprofen		ATC: M01AE01, M01AE51
Naproxen		ATC: M01AE02
Ketoprofen		ATC: M01AE03, M01AE53
Dexibuprofen		ATC: M01AE14
Piroxicam		ATC: M01AC01
Tolfenamic acid		ATC: M01AG02
COX-2 inhibitors		
Older COX2Is		
Diclofenac		ATC: M01AB05, M01AB55
Etodolac		ATC: M01AB08
Nabumeton		ATC: M01AX01
Meloxicam		ATC: M01AC06
Newer COX2Is (coxibs)		
Celecoxib		ATC: M01AH01
Rofecoxib		ATC: M01AH02
Etoricoxib		ATC: M01AH05
Comedications		
ACE or A2R Inhibitors		ATC: C09.A-D
Acetylsalicylic acid		ATC: B01AC06, N02BA01
Bisphosphonates		ATC: M05BA-B
Calcium channel blockers		ATC: C08
Clopidogrel		ATC: B01AC04
SSRIs		ATC: N06AB
Statins		ATC: C10AA, C10B, B04AB
Systemic glucocorticoids		ATC: H02AB
Vitamin K antagonists		ATC: B01AA03, B01AA04
Other cardiovascular drugs		
Beta-blockers		ATC: C07
Diuretics		ATC: C03
Nitrates		ATC: C01DA
Thrombolytic therapy		ATC: BOHA1
Charlson Comorbidity Index		
Diseases	**Weights**	
Myocardial infarction	1	ICD-8: 410; ICD-10: I21; I22; I23
Congestive heart failure		ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease		ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease		ICD-8: 430-438; ICD-10: I60-I69, G45, G46
Dementia		ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30
Chronic pulmonary disease		ICD-8: 490-493, 515-518, ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease		ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease		ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28
Mild liver disease		B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes without end-organ damage		ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes with end-organ damage	2	ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8
Hemiplegia		ICD-8: 344; ICD-10: G81, G82
Moderate to severe renal disease		ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Non-metastatic solid tumour		ICD-8: 140-194; ICD-10: C00-C75
Leukaemia		ICD-8: 204-207; ICD-10: C91-C95
Lymphoma		ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96
Moderate to severe liver disease	3	ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic cancer	6	ICD-8: 195-198, 199; ICD-10: C76-C80

AIDS	ICD-8: 079.83; ICD-10: B21-B24
Individual comorbidities	
Myocardial infarction	ICD-8: 410; ICD-10: I21, I22, I23
Congestive heart failure	ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
Angina pectoris	ICD-8: 413; ICD-10: I20.9, I25.1, I25.9
Intermittent arterial claudication	ICD-8: 443.89-443.99; ICD-10: I73.9
COPD	ICD-8: 491-492; ICD-10: J41-44; ATC: R03
Venous thromboembolism	ICD-8: 451.00; ICD-10: I80.1-3, I26
Atrial fibrillation or flutter	ICD-8: 427.93, 427.94; ICD-10: I48
Heart valve disease	ICD-8: 394-398; ICD-10: I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22
Hypertension	ICD-8: 400-404; ICD-10: I10-I15
Obesity	ICD-8: 277; ICD-10: E65-E68
Diabetes mellitus	ICD-8: 249-250; ICD-10: E10-E14, O24 (except O24.4), H36.0; ATC: A10B, A10A
Chronic kidney disease	ICD-8: 249.02, 250.02, 753.10-753.19, 582, 583, 584, 590.09, 593.20, 792; ICD-10: E10.2, E11.2, E14.2, N03, N05, N11.0, N14, N16, N18-N19, N26.9, Q61.1-Q61.4
Alcoholism-related diseases	ICD-8: 291, 303, 456, 571.09, 571.10, 577.10; ICD-10: F10.1-9, G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1; ATC: N07BB
Cancer	ICD-8: 140-207; ICD-10: C00-C96
Dementia	ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30
Osteoporosis	ICD-8: 723.09; ICD-10: M80-M82
Rheumatoid arthritis or connective tissue disease	ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05-M06, M30–M36, M45
Rheumatoid arthritis	ICD-8: 712; ICD-10: M05-M06
Systemic connective tissue disease	ICD-8: 716, 734, 446, 135.99; ICD-10: M30–M36, M45
Osteoarthritis	ICD-8: 713; ICD-10: M015-19, M47

Table e-2. Characteristics of stroke patients with current NSAID use, according to new and long-term use.

	NSAID use											
	Ischaemic stroke				Intracerebral haemorrhage				Subarachnoid haemorrhage			
	New use		Long-term use		Current use		Former use		Current use		Former use	
	n	%	n	%	n	%	n	%	n	%	n	%
Total number (%)	3289	100.0	5844	100.0	476	100.0	737	100.0	247	100.0	242	100.0
Gender (female)	1606	48.8	3287	56.2	254	53.4	395	53.6	150	60.7	153	63.2
Age, years												
<60	708	21.5	882	15.1	116	24.4	114	15.5	163	66.0	94	38.8
60-69	711	21.6	1220	20.9	93	19.5	151	20.5	45	18.2	60	24.8
70-79	915	27.8	1789	30.6	126	26.5	229	31.1	22	8.9	40	16.5
≥80	955	29.0	1953	33.4	141	29.6	243	33.0	17	6.9	48	19.8
Comorbidity level*												
Low	1520	46.2	2374	40.6	220	46.2	310	42.1	177	71.7	126	52.1
Moderate	1243	37.8	2466	42.2	188	39.5	311	42.2	54	21.9	88	36.4
High	526	16.0	1004	17.2	68	14.3	116	15.7	16	6.5	28	11.6
Individual comorbidities												
Myocardial infarction	251	7.6	471	8.1	29	6.1	35	4.7	3	1.2	9	3.7
Angina pectoris	465	14.1	910	15.6	59	12.4	75	10.2	11	4.5	28	11.6
Atrial fibrillation or flutter	374	11.4	685	11.7	58	12.2	79	10.7	9	3.6	19	7.9
Heart valve disease	132	4.0	225	3.9	13	2.7	16	2.2	9	3.6	3	1.2
Intermittent claudication	108	3.3	187	3.2	14	2.9	16	2.2	1	0.4	4	1.7
Venous thromboembolism	121	3.7	241	4.1	18	3.8	31	4.2	4	1.6	8	3.3
Obesity	158	4.8	392	6.7	22	4.6	44	6.0	8	3.2	13	5.4
Diabetes mellitus	414	12.6	887	15.2	37	7.8	81	11.0	12	4.9	25	10.3
Chronic kidney disease	73	2.2	113	1.9	8	1.7	11	1.5	3	1.2	4	1.7
Hypertension	827	25.1	1617	27.7	87	18.3	184	25.0	36	14.6	45	18.6
COPD	722	22.0	1515	25.9	97	20.4	171	23.2	36	14.6	55	22.7
Alcoholism-related disease	248	7.5	420	7.2	45	9.5	44	6.0	16	6.5	25	10.3

Dementia	74	2.2	162	2.8	17	3.6	32	4.3	.	.	6	2.5
Cancer	535	16.3	898	15.4	94	19.7	128	17.4	18	7.3	31	12.8
Rheumatoid arthritis	53	1.6	251	4.3	11	2.3	32	4.3	9	3.6	11	4.5
Connective tissue disease	93	2.8	225	3.9	12	2.5	27	3.7	6	2.4	10	4.1
Osteoarthritis	676	20.6	1947	33.3	79	16.6	216	29.3	23	9.3	74	30.6
Osteoporosis	170	5.2	395	6.8	28	5.9	57	7.7	6	2.4	23	9.5
Comedications												
ACE or A2R inhibitors	879	26.7	1775	30.4	89	18.7	195	26.5	38	15.4	61	25.2
β-blockers	657	20.0	1270	21.7	69	14.5	111	15.1	18	7.3	29	12.0
Calcium channel blockers	527	16.0	1063	18.2	51	10.7	82	11.1	24	9.7	31	12.8
Diuretics	951	28.9	2083	35.6	117	24.6	194	26.3	31	12.6	60	24.8
Nitrates	61	1.9	152	2.6	4	0.8	12	1.6	.	.	4	1.7
Statins	540	16.4	1068	18.3	59	12.4	113	15.3	19	7.7	37	15.3
Acetylsalicylic acid	782	23.8	1684	28.8	86	18.1	156	21.2	15	6.1	41	16.9
Clopidogrel	63	1.9	93	1.6	1	0.2	8	1.1	1	0.4	4	1.7
Vitamin K antagonists	128	3.9	216	3.7	43	9.0	65	8.8	8	3.2	5	2.1
Systemic glucocorticoids	223	6.8	469	8.0	23	4.8	35	4.7	10	4.0	9	3.7
SSRIs	289	8.8	723	12.4	55	11.6	86	11.7	15	6.1	22	9.1
Bisphosphonates	106	3.2	307	5.3	24	5.0	40	5.4	7	2.8	15	6.2
CT or MRI scan during admission	2906	88.4	5080	86.9	434	91.2	681	92.4	224	90.7	216	89.3
CT scan	2817	85.6	4954	84.8	422	88.7	674	91.5	220	89.1	215	88.8
MRI scan	445	13.5	560	9.6	46	9.7	50	6.8	21	8.5	12	5.0

Abbreviations: ACE, angiotensin-converting enzyme; A2R, angiotensin-2 receptor; NSAIDs, nonsteroidal anti-inflammatory drugs, SSRIs, selective serotonin reuptake inhibitors
*Three levels of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1-2 (moderate), and ≥3 (high).

Table e-3. Characteristics of stroke patients according to preadmission NSAID use in the propensity-score-matched cohorts.

	Ischaemic stroke				Intracerebral haemorrhage				Subarachnoid haemorrhage			
	Current use		No use		Current use		No use		Current use		No use	
	n	%	n	%	n	%	%	n	n	%	n	%
Total number (%)	9133	100.0	9133	100.0	1212	100.0	1212	100.0	485	100.0	485	100.0
Gender (female)	4958	54.3	4893	53.6	647	53.4	649	53.5	311	64.1	302	62.3
Age, years												
<60	1528	16.7	1590	17.4	236	19.5	230	19.0	251	51.8	257	53.0
60-69	1887	20.7	1931	21.1	250	20.6	244	20.1	98	20.2	101	20.8
70-79	2739	30.0	2704	29.6	332	27.4	354	29.2	77	15.9	62	12.8
≥80	2979	32.6	2908	31.8	394	32.5	384	31.7	59	12.2	65	13.4
Comorbidity level*												
Low	3940	43.1	3894	42.6	563	46.5	530	43.7	301	62.1	303	62.5
Moderate	3625	39.7	3709	40.6	454	37.5	499	41.2	146	30.1	142	29.3
High	1568	17.2	1530	16.8	195	16.1	183	15.1	38	7.8	40	8.2
Individual comorbidities												
Myocardial infarction	697	7.6	722	7.9	59	4.9	64	5.3	17	3.5	12	2.5
Angina pectoris	1323	14.5	1375	15.1	118	9.7	134	11.1	35	7.2	38	7.8
Atrial fibrillation or flutter	1023	11.2	1059	11.6	127	10.5	137	11.3	24	4.9	28	5.8
Heart valve disease	345	3.8	357	3.9	39	3.2	29	2.4	9	1.9	12	2.5
Intermittent claudication	235	2.6	295	3.2	31	2.6	30	2.5	10	2.1	5	1.0
Venous thromboembolism	321	3.5	362	4.0	41	3.4	49	4.0	7	1.4	12	2.5
Obesity	494	5.4	550	6.0	51	4.2	66	5.4	21	4.3	18	3.7
Diabetes mellitus	1259	13.8	1301	14.2	133	11.0	118	9.7	35	7.2	34	7.0
Chronic kidney disease	157	1.7	186	2.0	26	2.1	19	1.6	7	1.4	7	1.4
Hypertension	2415	26.4	2444	26.8	281	23.2	271	22.4	81	16.7	79	16.3
COPD	2257	24.7	2237	24.5	270	22.3	267	22.0	95	19.6	88	18.1

Alcoholism-related disease	625	6.8	669	7.3	97	8.0	89	7.3	30	6.2	41	8.5
Dementia	241	2.6	236	2.6	44	3.6	49	4.0	8	1.6	6	1.2
Cancer	1436	15.7	1433	15.7	213	17.6	221	18.2	35	7.2	45	9.3
Rheumatoid arthritis	295	3.2	304	3.3	21	1.7	42	3.5	14	2.9	19	3.9
Connective tissue disease	309	3.4	318	3.5	36	3.0	39	3.2	10	2.1	16	3.3
Osteoarthritis	2618	28.7	2623	28.7	293	24.2	294	24.3	88	18.1	93	19.2
Osteoporosis	591	6.5	565	6.2	77	6.4	85	7.0	22	4.5	29	6.0
Comedications												
ACE or A2R inhibitors	2653	29.0	2654	29.1	271	22.4	284	23.4	93	19.2	97	20.0
β-blockers	1863	20.4	1927	21.1	193	15.9	180	14.9	45	9.3	46	9.5
Calcium channel blockers	1628	17.8	1590	17.4	136	11.2	133	11.0	48	9.9	54	11.1
Diuretics	3098	33.9	3034	33.2	331	27.3	311	25.7	90	18.6	88	18.1
Nitrates	179	2.0	213	2.3	13	1.1	16	1.3	6	1.2	4	0.8
Statins	1522	16.7	1608	17.6	169	13.9	172	14.2	59	12.2	55	11.3
Acetylsalicylic acid	2382	26.1	2466	27.0	266	21.9	241	19.9	51	10.5	55	11.3
Clopidogrel	125	1.4	156	1.7	16	1.3	9	0.7	5	1.0	5	1.0
Vitamin K antagonists	327	3.6	344	3.8	93	7.7	108	8.9	16	3.3	13	2.7
Systemic glucocorticoids	662	7.2	692	7.6	80	6.6	57	4.7	24	4.9	17	3.5
SSRIs	1005	11.0	1012	11.1	163	13.4	141	11.6	48	9.9	36	7.4
Bisphosphonates	397	4.3	413	4.5	58	4.8	63	5.2	20	4.1	21	4.3
CT or MRI scan during admission	8053	88.2	7986	87.4	1101	90.8	1114	91.9	448	92.4	437	90.1
CT scan	7791	85.3	7771	85.1	1079	89.0	1095	90.3	445	91.8	432	89.1
MRI scan	1071	11.7	1005	11.0	96	7.9	96	7.9	34	7.0	33	6.8

Abbreviations: ACE, angiotensin-converting enzyme; A2R, angiotensin-2 receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors
*Three levels of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (low), 1-2 (moderate), and ≥3 (high).

Table e-4. Preadmission use of individual NSAIDs and 30-day mortality rate ratio following haemorrhagic stroke.

	Mortality rate ratio (95% CI)					
	Intracerebral haemorrhage			Subarachnoid haemorrhage		
	Unadjusted	Multivariable-adjusted*	Propensity-score-matched*	Unadjusted	Multivariable-adjusted*	Propensity-score-matched*
No use (of any NSAIDs)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Ibuprofen (current use)	0.90 (0.77-1.04)	0.92 (0.79-1.07)	1.02 (0.83-1.26)	0.83 (0.63-1.09)	0.85 (0.64-1.12)	0.86 (0.60-1.25)
New use	0.83 (0.67-1.02)	0.85 (0.69-1.05)	0.95 (0.73-1.22)	0.64 (0.44-0.94)	0.66 (0.45-0.97)	0.67 (0.42-1.05)
Long-term use	0.98 (0.79-1.21)	1.00 (0.81-1.24)	1.12 (0.87-1.45)	1.19 (0.80-1.75)	1.19 (0.80-1.76)	1.25 (0.79-1.97)
Naproxen (current use)	0.87 (0.50-1.49)	0.92 (0.53-1.60)	1.15 (0.53-2.50)	0.49 (0.07-3.48)	0.67 (0.09-4.77)	0.50 (0.05-5.22)
New use	0.73 (0.33-1.62)	0.91 (0.41-2.03)	0.96 (0.36-2.58)	-	-	-
Long-term use	1.04 (0.49-2.18)	0.94 (0.45-1.98)	1.40 (0.55-3.52)	13.04 (1.83-92.82)	18.54 (2.60-132.3)	10.95 (1.57-76.29)
Etodolac (current use)	0.76 (0.52-1.12)	0.72 (0.49-1.06)	0.74 (0.45-1.22)	1.12 (0.53-2.37)	0.79 (0.37-1.67)	0.99 (0.35-2.79)
New use	0.83 (0.43-1.59)	0.81 (0.42-1.56)	0.81 (0.38-1.69)	0.82 (0.20-3.28)	0.74 (0.18-3.00)	0.73 (0.15-3.48)
Long-term use	0.74 (0.46-1.17)	0.69 (0.43-1.09)	0.71 (0.40-1.25)	1.32 (0.55-3.19)	0.81 (0.33-1.97)	1.17 (0.38-3.57)
Diclofenac (current use)	0.98 (0.80-1.21)	0.97 (0.79-1.20)	0.92 (0.69-1.23)	0.79 (0.53-1.18)	0.84 (0.57-1.26)	0.82 (0.48-1.40)
New use	0.79 (0.56-1.12)	0.79 (0.56-1.12)	0.74 (0.50-1.10)	0.58 (0.32-1.05)	0.66 (0.36-1.19)	0.60 (0.30-1.19)
Long-term use	1.15 (0.88-1.49)	1.12 (0.86-1.45)	1.07 (0.78-1.49)	1.12 (0.66-1.90)	1.09 (0.64-1.86)	1.16 (0.61-2.20)
Celecoxib (current use)	1.38 (0.62-3.08)	1.26 (0.56-2.81)	0.87 (0.29-2.60)	1.26 (0.18-8.93)	1.42 (0.20-10.16)	0.82 (0.08-8.65)
New use	1.55 (0.58-4.12)	1.52 (0.57-4.07)	0.94 (0.29-3.04)	-	-	-
Long-term use	1.15 (0.29-4.57)	0.93 (0.23-3.73)	0.76 (0.17-3.31)	4.27 (0.60-30.37)	3.45 (0.47-25.11)	2.45 (0.38-15.82)
Rofecoxib (current use)	1.09 (0.41-2.90)	1.13 (0.42-3.01)	0.63 (0.18-2.22)	1.85 (0.26-13.17)	0.97 (0.13-7.27)	0.71 (0.08-6.62)
New use	-	-	-	-	-	-
Long-term use	1.42 (0.53-3.79)	1.51 (0.56-4.05)	0.81 (0.23-2.83)	3.86 (0.54-27.44)	2.32 (0.26-20.56)	1.41 (0.21-9.54)

*See description of the multivariable-adjusted and propensity-score-matched models in the text and in the footnote to Table 2.

Table e-5. 30-day mortality following stroke, comparing former and non-use of NSAIDs.

	30 day mortality rate ratio (95% confidence interval)								
	Ischaemic stroke			Intracerebral haemorrhage			Subarachnoid haemorrhage		
	Unadjusted	Multivariable-adjusted*	Propensity-score-matched*	Unadjusted	Multivariable-adjusted*	Propensity-score-matched*	Unadjusted	Multivariable-adjusted*	Propensity-score-matched*
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Any NSAIDs (former use)	0.82 (0.76-0.89)	0.84 (0.78-0.91)	0.86 (0.78-0.96)	0.94 (0.84-1.06)	0.93 (0.82-1.04)	0.97 (0.83-1.14)	0.69 (0.53-0.90)	0.66 (0.51-0.85)	0.63 (0.45-0.86)
Nonselective NSAIDs (former use)	0.82 (0.74-0.91)	0.90 (0.81-1.00)	0.84 (0.74-0.96)	0.89 (0.76-1.04)	0.91 (0.78-1.06)	0.91 (0.75-1.10)	0.67 (0.48-0.94)	0.69 (0.49-0.97)	0.59 (0.39-0.88)
COX-2 inhibitors (former use)	0.89 (0.78-1.02)	0.89 (0.78-1.01)	0.91 (0.78-1.06)	1.16 (0.96-1.41)	1.11 (0.91-1.34)	1.21 (0.96-1.52)	0.72 (0.47-1.11)	0.68 (0.45-1.05)	0.66 (0.41-1.08)
Older types (former use)	0.89 (0.78-1.01)	0.90 (0.78-1.02)	0.90 (0.77-1.06)	1.15 (0.94-1.40)	1.10 (0.90-1.35)	1.18 (0.93-1.49)	0.67 (0.43-1.05)	0.66 (0.42-1.03)	0.57 (0.34-0.96)
Coxibs (former use)	1.04 (0.69-1.57)	0.81 (0.53-1.21)	0.94 (0.54-1.64)	1.31 (0.70-2.44)	1.21 (0.65-2.25)	1.75 (0.89-3.44)	2.33 (0.75-7.23)	1.22 (0.38-3.89)	6.23 (3.11-12.48)

*See description of the multivariable-adjusted and propensity-score-matched models in the text and in the footnote to Table 2.

Table e-6. Preadmission NSAID use and 30-day mortality rate ratio estimates following stroke confirmed by CT or MRI.

	Ischaemic stroke			Intracerebral haemorrhage			Subarachnoid haemorrhage		
	Risk (95% CI)	Mortality rate ratio (95% CI)		Risk (95% CI)	Mortality rate ratio (95% CI)		Risk (95% CI)	Mortality rate ratio (95% CI)	
		Unadjusted	Multivariable-adjusted*		Unadjusted	Multivariable-adjusted*		Unadjusted	Multivariable-adjusted*
No use of any NSAIDs	9.8 (9.5-10.0)	1 (reference)	1 (reference)	35.2 (34.2-36.2)	1 (reference)	1 (reference)	25.0 (23.6-26.5)	1 (reference)	1 (reference)
Any NSAIDs	10.2 (9.5-10.9)	1.04 (0.97-1.12)	1.03 (0.96-1.11)	34.2 (31.5-37.1)	0.96 (0.86-1.07)	0.95 (0.85-1.06)	22.5 (18.9-26.7)	0.88 (0.72-1.09)	0.85 (0.69-1.06)
New use	10.2 (9.2-11.4)	1.05 (0.93-1.18)	1.10 (0.98-1.24)	30.9 (26.8-35.5)	0.85 (0.72-1.02)	0.86 (0.72-1.03)	16.6 (12.3-22.1)	0.62 (0.45-0.86)	0.67 (0.48-0.94)
Long-term use	10.2 (9.4-11.0)	1.04 (0.95-1.14)	0.99 (0.91-1.09)	36.3 (32.8-40.0)	1.03 (0.91-1.17)	1.01 (0.88-1.15)	28.7 (23.2-35.3)	1.18 (0.91-1.53)	1.03 (0.79-1.34)
Nonselective NSAIDs‡	9.8 (9.0-10.8)	1.01 (0.91-1.11)	1.07 (0.97-1.19)	32.5 (28.9-36.4)	0.91 (0.79-1.05)	0.93 (0.80-1.07)	21.7 (17.1-27.2)	0.84 (0.64-1.11)	0.90 (0.68-1.18)
New use	9.2 (8.0-10.6)	0.94 (0.80-1.09)	1.03 (0.89-1.20)	30.1 (25.3-35.5)	0.83 (0.67-1.02)	0.85 (0.69-1.04)	16.2 (11.3-22.9)	0.61 (0.41-0.90)	0.64 (0.43-0.94)
Long-term use	10.4 (9.2-11.8)	1.07 (0.93-1.22)	1.10 (0.96-1.26)	35.0 (29.9-40.7)	0.99 (0.82-1.21)	1.02 (0.84-1.24)	30.7 (22.5-40.8)	1.28 (0.89-1.84)	1.38 (0.95-1.99)
COX-2 inhibitors	11.5 (10.3-12.7)	1.18 (1.05-1.32)	1.16 (1.03-1.30)	33.4 (28.7-38.7)	0.92 (0.76-1.10)	0.91 (0.75-1.09)	22.2 (16.3-29.9)	0.87 (0.61-1.24)	0.84 (0.59-1.20)
New use	12.7 (10.9-14.9)	1.32 (1.11-1.56)	1.34 (1.14-1.59)	29.0 (22.0-37.6)	0.78 (0.57-1.07)	0.79 (0.57-1.09)	16.7 (10.0-27.0)	0.63 (0.36-1.09)	0.69 (0.40-1.20)
Long-term use	10.6 (9.2-12.2)	1.09 (0.94-1.27)	1.04 (0.90-1.21)	36.1 (30.1-42.9)	1.01 (0.80-1.26)	0.98 (0.78-1.22)	28.8 (19.4-41.3)	1.18 (0.75-1.86)	1.00 (0.63-1.59)
Older types	11.5 (10.3-12.8)	1.18 (1.05-1.33)	1.18 (1.05-1.33)	32.5 (27.7-37.9)	0.89 (0.73-1.08)	0.89 (0.73-1.08)	21.6 (15.6-29.4)	0.85 (0.59-1.22)	0.83 (0.57-1.19)
New use	12.5 (10.7-14.6)	1.29 (1.09-1.53)	1.32 (1.12-1.57)	28.5 (21.3-37.3)	0.76 (0.55-1.06)	0.78 (0.56-1.10)	17.3 (10.5-28.0)	0.66 (0.38-1.14)	0.73 (0.42-1.27)
Long-term use	10.8 (9.3-12.4)	1.11 (0.95-1.29)	1.08 (0.93-1.26)	35.0 (28.9-42.0)	0.97 (0.77-1.23)	0.94 (0.75-1.20)	26.6 (17.4-39.2)	1.09 (0.68-1.77)	0.93 (0.57-1.52)
Coxibs	10.8 (6.1-18.6)	1.11 (0.61-2.00)	0.77 (0.42-1.39)	45.8 (28.6-67.3)	1.31 (0.72-2.37)	1.19 (0.65-2.15)	40.0 (11.8-87.4)	1.46 (0.37-5.84)	1.11 (0.27-4.61)
New use	21.9 (11.1-40.5)	2.40 (1.15-5.03)	1.50 (0.71-3.14)	36.4 (15.5-70.3)	0.98 (0.37-2.61)	0.87 (0.32-2.32)	-	-	-
Long-term use	5.7 (2.2-14.5)	0.57 (0.22-1.52)	0.41 (0.16-1.10)	53.9 (30.4-80.8)	1.62 (0.77-3.40)	1.50 (0.71-3.17)	-	-	-

See description of the multivariable-adjusted model and NSAID categories in the text and in the footnote to Table 2.

Table e-7. Sensitivity analysis of the association between preadmission NSAID use and 30-day stroke mortality using a 30-day instead of a 60-day exposure window of NSAID use.

	Ischaemic stroke			Intracerebral haemorrhage			Subarachnoid haemorrhage		
	Risk (95% CI)	Mortality rate ratio (95% CI)		Risk (95% CI)	Mortality rate ratio (95% CI)		Risk (95% CI)	Mortality rate ratio (95% CI)	
		Unadjusted	Multivariable-adjusted*		Unadjusted	Multivariable-adjusted*		Unadjusted	Multivariable-adjusted*
No use of any NSAIDs	10.9 (10.6-11.1)	1 (reference)	1 (reference)	35.1 (34.1-36.0)	1 (reference)	1 (reference)	24.5 (23.1-25.9)	1 (reference)	1 (reference)
Any NSAIDs	11.5 (10.7-12.4)	1.06 (0.98-1.15)	1.04 (0.96-1.13)	35.5 (32.3-38.9)	1.01 (0.89-1.14)	0.98 (0.87-1.11)	20.6 (16.7-25.4)	0.82 (0.64-1.05)	0.81 (0.63-1.04)
New use	11.8 (10.3-13.4)	1.09 (0.95-1.25)	1.16 (1.01-1.33)	30.3 (25.1-36.3)	0.83 (0.66-1.03)	0.85 (0.68-1.06)	11.9 (7.7-18.2)	0.45 (0.28-0.71)	0.50 (0.31-0.80)
Long-term use	11.4 (10.4-12.4)	1.05 (0.95-1.16)	0.99 (0.90-1.10)	38.1 (34.1-42.4)	1.10 (0.96-1.27)	1.06 (0.91-1.22)	28.1 (22.1-35.4)	1.18 (0.89-1.58)	1.04 (0.78-1.39)
Nonselective NSAIDs	11.1 (10.0-12.3)	1.02 (0.91-1.15)	1.11 (0.99-1.25)	32.4 (28.2-37.1)	0.91 (0.76-1.08)	0.93 (0.78-1.10)	20.1 (15.1-26.4)	0.80 (0.58-1.10)	0.86 (0.63-1.19)
New use	11.1 (9.4-13.1)	1.03 (0.86-1.23)	1.18 (0.99-1.41)	28.7 (22.8-35.9)	0.77 (0.59-1.02)	0.83 (0.63-1.09)	11.7 (6.9-19.2)	0.44 (0.26-0.76)	0.49 (0.28-0.85)
Long-term use	11.1 (9.6-12.7)	1.02 (0.88-1.18)	1.07 (0.92-1.24)	35.3 (29.6-41.7)	1.02 (0.82-1.26)	1.01 (0.81-1.25)	31.5 (22.6-42.7)	1.35 (0.92-2.00)	1.37 (0.93-2.03)
COX-2 inhibitors	13.4 (12.0-14.9)	1.27 (1.12-1.43)	1.21 (1.07-1.37)	38.1 (32.4-44.5)	1.09 (0.89-1.34)	1.08 (0.88-1.32)	20.8 (14.2-29.8)	0.85 (0.56-1.30)	0.81 (0.53-1.24)
New use	13.6 (11.3-16.4)	1.29 (1.05-1.58)	1.29 (1.06-1.58)	32.6 (23.9-43.4)	0.91 (0.63-1.30)	0.90 (0.63-1.31)	13.0 (6.4-25.3)	0.51 (0.24-1.07)	0.58 (0.28-1.22)
Long-term use	13.2 (11.5-15.2)	1.25 (1.08-1.46)	1.17 (1.01-1.36)	41.3 (34.0-49.5)	1.20 (0.94-1.54)	1.18 (0.92-1.51)	28.9 (18.5-43.2)	1.25 (0.75-2.08)	1.00 (0.60-1.68)
Older types	13.4 (11.9-14.9)	1.27 (1.12-1.43)	1.23 (1.09-1.39)	37.2 (31.2-43.8)	1.06 (0.85-1.32)	1.06 (0.85-1.32)	20.2 (13.7-29.3)	0.83 (0.54-1.28)	0.80 (0.52-1.24)
New use	13.2 (10.9-15.9)	1.24 (1.01-1.52)	1.25 (1.02-1.53)	31.3 (22.5-42.5)	0.86 (0.58-1.26)	0.88 (0.60-1.29)	13.0 (6.4-25.3)	0.51 (0.24-1.07)	0.58 (0.27-1.22)
Long-term use	13.5 (11.7-15.5)	1.28 (1.10-1.49)	1.22 (1.05-1.42)	40.6 (33.1-49.1)	1.18 (0.91-1.53)	1.17 (0.90-1.51)	28.0 (17.6-42.7)	1.22 (0.72-2.07)	1.00 (0.58-1.70)
Coxibs	13.4 (7.2-24.2)	1.26 (0.66-2.42)	0.84 (0.43-1.61)	50.0 (30.0-74.1)	1.48 (0.77-2.84)	1.23 (0.64-2.37)	-	-	-
New use	29.4 (13.4-56.9)	3.17 (1.32-7.62)	2.09 (0.87-5.04)	44.4 (20.0-80.0)	1.33 (0.50-3.55)	1.11 (0.42-2.97)	-	-	-
Long-term use	8.0 (3.1-19.9)	0.72 (0.27-1.92)	0.48 (0.18-1.27)	55.6 (28.1-86.4)	1.63 (0.68-3.90)	1.35 (0.56-3.25)	-	-	-

*See description of the multivariable-adjusted model and NSAID categories in the text and in the footnote to Table 2.

Table e-8. Preadmission NSAID use and 30-day mortality rate ratio after stroke, stratified analyses.

	Multivariable-adjusted mortality rate ratio (95% CI)*		
	Ischaemic stroke	**Intracerebral haemorrhage**	**Subarachnoid haemorrhage**
Men			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.03 (0.90-1.19)	0.90 (0.73-1.10)	0.98 (0.65-1.48)
New use	1.10 (0.91-1.34)	0.86 (0.64-1.15)	0.61 (0.31-1.19)
Long-term use	0.97 (0.79-1.18)	0.94 (0.72-1.24)	1.48 (0.88-2.49)
COX-2 inhibitors	1.16 (0.99-1.36)	1.00 (0.77-1.30)	0.96 (0.52-1.78)
New use	1.25 (0.99-1.59)	0.89 (0.59-1.35)	0.84 (0.34-2.04)
Long-term use	1.09 (0.89-1.35)	1.09 (0.79-1.51)	1.13 (0.49-2.65)
Women			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.08 (0.96-1.22)	0.96 (0.79-1.17)	0.78 (0.55-1.11)
New use	1.02 (0.85-1.23)	0.88 (0.68-1.15)	0.63 (0.38-1.02)
Long-term use	1.13 (0.97-1.32)	1.06 (0.81-1.39)	1.03 (0.63-1.68)
COX-2 inhibitors	1.13 (1.00-1.29)	0.88 (0.70-1.12)	0.81 (0.53-1.21)
New use	1.34 (1.11-1.63)	0.86 (0.58-1.27)	0.62 (0.32-1.20)
Long-term use	1.01 (0.85-1.20)	0.89 (0.67-1.19)	1.00 (0.60-1.69)
Age < 60 years			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	0.91 (0.64-1.29)	0.64 (0.43-0.94)	0.85 (0.57-1.27)
New use	0.96 (0.61-1.53)	0.59 (0.35-1.00)	0.74 (0.45-1.23)
Long-term use	0.84 (0.51-1.40)	0.69 (0.39-1.21)	1.11 (0.60-2.05)
COX-2 inhibitors	1.26 (0.85-1.86)	0.61 (0.34-1.09)	0.97 (0.58-1.63)
New use	1.72 (1.04-2.84)	0.36 (0.12-1.13)	0.82 (0.42-1.60)
Long-term use	0.91 (0.51-1.64)	0.81 (0.41-1.59)	1.36 (0.60-3.09)
Age 60-69 years			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.01 (0.78-1.31)	0.97 (0.70-1.34)	0.84 (0.45-1.56)
New use	0.95 (0.64-1.41)	0.92 (0.57-1.47)	0.72 (0.29-1.79)
Long-term use	1.05 (0.75-1.46)	1.03 (0.67-1.57)	1.03 (0.44-2.41)
COX-2 inhibitors	1.34 (1.01-1.77)	0.75 (0.46-1.23)	1.01 (0.48-2.13)
New use	1.52 (1.02-2.27)	0.95 (0.49-1.85)	0.33 (0.05-2.39)
Long-term use	1.21 (0.83-1.76)	0.61 (0.30-1.24)	1.54 (0.66-3.58)
Age 70-79 years			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.03 (0.86-1.24)	1.02 (0.80-1.32)	0.68 (0.30-1.55)
New use	0.96 (0.73-1.27)	0.96 (0.67-1.37)	-
Long-term use	1.09 (0.86-1.37)	1.10 (0.78-1.56)	1.62 (0.69-3.81)
COX-2 inhibitors	1.21 (0.99-1.47)	1.01 (0.75-1.36)	0.84 (0.39-1.81)
New use	1.23 (0.91-1.68)	0.84 (0.50-1.41)	0.86 (0.27-2.74)
Long-term use	1.19 (0.92-1.54)	1.12 (0.79-1.61)	0.84 (0.30-2.32)
Age ≥ 80 years			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.10 (0.97-1.25)	0.93 (0.73-1.17)	1.04 (0.60-1.80)
New use	1.15 (0.96-1.38)	0.91 (0.66-1.26)	0.69 (0.27-1.80)
Long-term use	1.07 (0.90-1.27)	0.94 (0.68-1.30)	1.29 (0.66-2.52)

COX-2 inhibitors	1.05 (0.92-1.21)	1.01 (0.78-1.32)	0.53 (0.21-1.35)
New use	1.25 (1.01-1.53)	1.02 (0.67-1.56)	0.55 (0.07-4.09)
Long-term use	0.94 (0.78-1.12)	1.00 (0.72-1.40)	0.52 (0.18-1.49)
Rheumatoid arthritis			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.21 (0.73-2.00)	0.92 (0.34-2.49)	-
New use	1.59 (0.72-3.53)	-	-
Long-term use	1.07 (0.56-2.02)	1.80 (0.64-5.08)	-
COX-2 inhibitors	1.27 (0.74-2.18)	1.61 (0.66-3.93)	-
New use	1.01 (0.24-4.16)	0.77 (0.15-4.11)	-
Long-term use	1.30 (0.73-2.30)	2.35 (0.82-6.71)	-
No rheumatoid arthritis			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.06 (0.96-1.16)	0.94 (0.81-1.08)	0.87 (0.66-1.13)
New use	1.05 (0.91-1.20)	0.90 (0.74-1.09)	0.62 (0.42-0.93)
Long-term use	1.06 (0.94-1.20)	0.98 (0.80-1.19)	1.24 (0.87-1.76)
COX-2 inhibitors	1.14 (1.03-1.26)	0.91 (0.76-1.09)	0.90 (0.64-1.27)
New use	1.32 (1.13-1.53)	0.86 (0.64-1.15)	0.75 (0.44-1.28)
Long-term use	1.03 (0.89-1.18)	0.94 (0.75-1.18)	1.06 (0.67-1.66)
Osteoarthritis			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.07 (0.89-1.28)	0.99 (0.74-1.33)	0.89 (0.45-1.79)
New use	1.22 (0.92-1.61)	1.04 (0.66-1.64)	0.46 (0.11-2.03)
Long-term use	0.99 (0.79-1.24)	0.96 (0.67-1.38)	1.16 (0.53-2.54)
COX-2 inhibitors	1.02 (0.84-1.24)	0.78 (0.55-1.13)	2.53 (1.35-4.75)
New use	1.23 (0.89-1.71)	0.40 (0.18-0.90)	3.83 (1.24-11.79)
Long-term use	0.94 (0.74-1.19)	1.02 (0.68-1.52)	2.24 (1.08-4.65)
No osteoarthritis			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.07 (0.96-1.19)	0.92 (0.78-1.07)	0.84 (0.63-1.13)
New use	1.02 (0.88-1.19)	0.85 (0.68-1.05)	0.63 (0.42-0.96)
Long-term use	1.11 (0.96-1.29)	1.01 (0.80-1.26)	1.23 (0.82-1.84)
COX-2 inhibitors	1.20 (1.07-1.36)	0.99 (0.81-1.21)	0.68 (0.44-1.04)
New use	1.34 (1.13-1.59)	1.04 (0.77-1.41)	0.55 (0.29-1.02)
Long-term use	1.11 (0.94-1.30)	0.95 (0.74-1.24)	0.86 (0.48-1.54)
Myocardial infarction			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.34 (1.04-1.74)	1.13 (0.69-1.87)	0.38 (0.04-3.45)
New use	1.17 (0.79-1.73)	1.54 (0.81-2.92)	0.47 (0.05-4.52)
Long-term use	1.50 (1.07-2.10)	0.81 (0.37-1.76)	-
COX-2 inhibitors	1.12 (0.84-1.51)	1.48 (0.75-2.92)	1.34 (0.18-9.92)
New use	1.41 (0.95-2.11)	2.19 (0.73-6.60)	-
Long-term use	0.92 (0.60-1.40)	1.21 (0.52-2.82)	1.34 (0.18-9.92)
No myocardial infarction			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.03 (0.94-1.14)	0.92 (0.79-1.06)	0.86 (0.66-1.12)
New use	1.05 (0.91-1.21)	0.83 (0.68-1.02)	0.61 (0.41-0.91)
Long-term use	1.02 (0.90-1.17)	1.02 (0.83-1.24)	1.23 (0.86-1.75)
COX-2 inhibitors	1.15 (1.03-1.28)	0.90 (0.75-1.08)	0.87 (0.62-1.23)
New use	1.29 (1.10-1.52)	0.83 (0.62-1.12)	0.71 (0.42-1.20)

Long-term use	1.06 (0.92-1.22)	0.94 (0.75-1.18)	1.06 (0.67-1.67)
Atrial fibrillation			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	0.93 (0.75-1.15)	1.14 (0.79-1.64)	0.65 (0.22-1.90)
New use	0.97 (0.73-1.30)	1.05 (0.65-1.68)	0.32 (0.06-1.76)
Long-term use	0.88 (0.65-1.19)	1.27 (0.74-2.19)	1.20 (0.33-4.36)
COX-2 inhibitors	1.03 (0.82-1.29)	1.24 (0.84-1.85)	1.12 (0.33-3.79)
New use	1.11 (0.78-1.59)	0.78 (0.41-1.48)	21.44 (1.17-394.2)
Long-term use	0.98 (0.73-1.31)	1.89 (1.15-3.12)	0.85 (0.22-3.33)
No atrial fibrillation			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.10 (0.99-1.22)	0.90 (0.78-1.05)	0.88 (0.67-1.17)
New use	1.08 (0.93-1.26)	0.84 (0.68-1.04)	0.64 (0.43-0.96)
Long-term use	1.11 (0.97-1.28)	0.97 (0.79-1.20)	1.25 (0.87-1.82)
COX-2 inhibitors	1.18 (1.05-1.32)	0.88 (0.72-1.06)	0.87 (0.61-1.24)
New use	1.37 (1.16-1.62)	0.87 (0.64-1.20)	0.67 (0.39-1.16)
Long-term use	1.06 (0.91-1.23)	0.88 (0.69-1.12)	1.11 (0.70-1.77)
Hypertension			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.07 (0.91-1.26)	0.92 (0.67-1.25)	0.88 (0.50-1.52)
New use	1.00 (0.79-1.28)	1.02 (0.65-1.59)	0.73 (0.36-1.48)
Long-term use	1.13 (0.92-1.40)	0.84 (0.55-1.28)	1.19 (0.51-2.77)
COX-2 inhibitors	0.99 (0.82-1.21)	0.97 (0.69-1.35)	0.76 (0.28-2.10)
New use	0.95 (0.69-1.30)	1.17 (0.70-1.97)	0.67 (0.09-4.91)
Long-term use	1.02 (0.80-1.31)	0.86 (0.56-1.33)	0.80 (0.25-2.60)
No hypertension			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.06 (0.94-1.18)	0.93 (0.79-1.08)	0.84 (0.61-1.14)
New use	1.08 (0.92-1.27)	0.84 (0.68-1.05)	0.55 (0.34-0.90)
Long-term use	1.04 (0.89-1.21)	1.03 (0.83-1.28)	1.22 (0.82-1.80)
COX-2 inhibitors	1.21 (1.08-1.37)	0.91 (0.74-1.11)	0.96 (0.67-1.37)
New use	1.49 (1.25-1.76)	0.77 (0.55-1.08)	0.74 (0.43-1.29)
Long-term use	1.05 (0.89-1.23)	1.00 (0.78-1.28)	1.22 (0.76-1.96)
Diabetes			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	0.94 (0.75-1.18)	0.89 (0.59-1.34)	0.84 (0.29-2.45)
New use	0.99 (0.71-1.39)	1.08 (0.63-1.87)	0.48 (0.09-2.45)
Long-term use	0.90 (0.67-1.21)	0.72 (0.40-1.30)	0.94 (0.25-3.48)
COX-2 inhibitors	1.12 (0.88-1.42)	0.71 (0.40-1.25)	3.61 (1.18-10.98)
New use	1.17 (0.80-1.71)	0.64 (0.23-1.75)	2.32 (0.50-10.79)
Long-term use	1.10 (0.81-1.49)	0.74 (0.38-1.44)	6.15 (1.40-27.09)
No diabetes			
No use of any NSAIDs	1 (reference)	1 (reference)	1 (reference)
Nonselective NSAIDs	1.09 (0.98-1.21)	0.93 (0.80-1.08)	0.84 (0.63-1.11)
New use	1.07 (0.93-1.24)	0.85 (0.69-1.05)	0.59 (0.39-0.89)
Long-term use	1.10 (0.96-1.27)	1.02 (0.83-1.25)	1.25 (0.87-1.81)
COX-2 inhibitors	1.15 (1.03-1.28)	0.95 (0.79-1.14)	0.81 (0.57-1.17)
New use	1.34 (1.14-1.58)	0.88 (0.65-1.18)	0.64 (0.36-1.13)
Long-term use	1.02 (0.88-1.19)	0.99 (0.79-1.25)	1.01 (0.63-1.60)

*See description of the multivariable-adjusted model and NSAID categories in the text and in the footnote to Table 2.

Paper V

Clinical Epidemiology

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ORIGINAL RESEARCH

Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999–2012

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Background: Due to over-the-counter availability, no consensus exists on whether adequate information on nonsteroidal anti-inflammatory drug (NSAID) use can be obtained from prescription registries.

Objectives: To examine utilization of aspirin and nonaspirin NSAIDs in Denmark between 1999 and 2012 and to quantify the proportion of total sales that was sold on prescription.

Method: Based on nationwide data from the Danish Serum Institute and the Danish National Prescription Registry, we retrieved sales statistics for the Danish primary health care sector to calculate 1-year prevalences of prescription users of aspirin or nonaspirin NSAIDs, and to estimate the corresponding proportions of total sales dispensed on prescription.

Results: Both low-dose aspirin and nonaspirin NSAIDs were commonly used in the Danish population between 1999 and 2012, particularly among elderly individuals. The 1-year prevalence of prescribed low-dose aspirin increased throughout the study period, notably among men. Nonaspirin NSAID use was frequent in all age groups above 15 years and showed a female preponderance. Overall, the prevalence of prescribed nonaspirin NSAIDs decreased moderately after 2004, but substantial variation according to NSAID subtype was observed; ibuprofen use increased, use of all newer selective cyclooxygenase-2 inhibitors nearly ceased after 2004, diclofenac use decreased by nearly 50% after 2008, and naproxen use remained stable. As of 2012, the prescribed proportion of individual-level NSAID sales was 92% for low-dose aspirin, 66% for ibuprofen, and 100% for all other NSAIDs.

Conclusion: The potential for identifying NSAID use from prescription registries in Denmark is high. Low-dose aspirin and nonaspirin NSAID use varied substantially between 1999 and 2012. Notably, use of cyclooxygenase-2 inhibitors nearly ceased, use of diclofenac decreased markedly, and naproxen use remained unaltered.

Keywords: drug utilization, NSAID, registries, over-the-counter

Introduction

In Danish pharmacoepidemiological studies, use of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are typically identified from prescription databases.[1–3] However, there is no consensus on whether adequate information on NSAID use can be obtained from such databases.[4] Stratification by[4] or adjustment for[5,6] aspirin use has been abandoned or dismissed by some authors, who argue that since aspirin is available over the counter (OTC), use of this drug or other NSAIDs cannot be captured reliably in the Danish prescription registries.[4]

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The potential of prescription registries to capture individual-level use of aspirin and other NSAIDs is of interest in several contexts. One is whether these registries can be used to survey utilization of nonaspirin NSAIDs,[7] which are associated with an increased risk of cardiovascular disease.[8,9] The current evidence indicates that all nonaspirin NSAIDs increase the risk of heart failure, whereas the risk of thrombotic events varies according to type of drug.[9] Use of selective cyclooxygenase(COX)-2 inhibitors (coxibs) is associated with the highest vascular risk, whereas naproxen appears to have the least harmful cardiovascular risk profile.[9,10] Moreover, increasing evidence supports that traditional nonaspirin NSAIDs with high COX-2 selectivity, in particular diclofenac, have thrombogenic properties similar to coxibs.[9] Despite these important differences in cardiovascular toxicity, no study has evaluated whether use of naproxen or diclofenac has changed since the concern about cardiovascular toxicity associated with COX-2 inhibiting agents was first raised in 2004.[8]

We examined the utilization of NSAIDs in Denmark from 1999 to 2012, with specific focus on trends in nonaspirin NSAID use and the potential of prescription registries to capture individual-level use of aspirin and nonaspirin NSAIDs.

Methods

We ascertained individual use of low-dose aspirin and nonaspirin NSAIDs using data from the Danish National Prescription Registry, with focus on trends in overall utilization, age and sex distribution, volume, and the proportion of total sales that was sold on prescription.

Setting

The Danish National Health Service provides universal tax-supported health care, guaranteeing free and equal access to general practitioners and hospitals and partial reimbursement for prescribed medications, including NSAIDs.[11] Individual-level linkage of all Danish databases is possible using the unique Danish personal identification number, which is assigned to each Danish citizen at birth and to residents upon immigration.[12]

Pharmacies in Denmark are equipped with electronic accounting systems, which are primarily used to secure reimbursement from the National Health Service.[13,14]

A detailed account of variables registered in the prescription registries has previously been described.[13] Briefly, for each redeemed prescription, the patient's personal identification number, the type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system,[15] pack size (numbers of pills and daily defined doses), and the date of drug dispensing are transferred electronically from the pharmacies to prescription registries.[13,14] Different dose units for the same pharmaceutical entity can also be identified separately in the prescription registries by use of product codes.[13,14]

We used the web facility Medstat (http://www.medstat.dk) to retrieve data on NSAID sales in Denmark.[16] This publicly available webpage from the Danish Serum Institute provides aggregate statistics on the sale of pharmaceutical preparations in Denmark since 1995 based on the data reported to the Danish National Prescription Registry.[14,16] This reporting is mandatory, and Medstat statistics are complete from 1999 onwards. The registration of total drug sales (including OTC sales) facilitates computations of descriptive statistics, including for example the proportion of total sales sold on prescription, and allows for stratification by age, sex, region, and health care sector (primary or secondary).[16]

OTC use in Denmark

OTC NSAIDs include aspirin in all preparations, diclofenac (during the period July 16, 2007 to December 14, 2008), and low-dose ibuprofen (200 mg tablets) since March 27, 1989.[17,18] Regular users of aspirin or nonaspirin NSAIDs have an economic incentive to obtain the drugs by prescription due to the reimbursement through the Danish National Health Service's insurance program.

In an effort to reduce suicide attempts by overdoses of analgesics,[19] the Danish Health Authorities have implemented several restrictions in the dispensing of OTC drugs since 2001.[20–22] First, packages of aspirin and paracetamol containing ≥30 tablets were labeled with red box warnings alerting parents to read the warnings in the package leaflet and to store the drugs in a safe place (October 1, 2004).[20] More recently (March 7, 2011),[21] OTC sales of aspirin, paracetamol, and ibuprofen were restricted to persons aged ≥18 years and at maximum one package per person per day. Just recently (September 20, 2013), each dispensing of OTC analgesics has been restricted to pack sizes containing a maximum of 10 g of aspirin (ie, 20 high-dose tablets), 10 g of paracetamol (ie, 20 tablets), or 4 g of ibuprofen (ie, 20 tablets).[22]

Aspirin

Aspirin (acetylsalicylic acid) has the characteristic analgesic, antipyretic, and anti-inflammatory properties of nonselective NSAIDs.[23,24] In high doses (500 mg), the main indication for aspirin is pain relief (ATC group: N02BA01,

N02BA51). At low doses (75–150 mg), aspirin is not an effective analgesic, but the drug has an antithrombotic effect conferred by inhibition of platelet aggregation by irreversible blockage of the COX-1 enzyme.[23,24] Accordingly, the main indication for low-dose aspirin (ATC group: B01AC06) is prevention and treatment of occlusive vascular events in patients with coronary artery disease or ischemic stroke.[25]

Nonaspirin NSAIDs

The main indications for nonaspirin NSAIDs are inflammatory conditions and pain (ATC group: M01A).[23] We excluded glucosamine (ATC: M01AX05) from the main group (M01A), as this agent does not possess the pharmacodynamic properties of nonaspirin NSAIDs.[26]

We identified all individual drugs from each NSAID class on the Danish market; ie, butylpyrazolidines, acetic acids, enolic acids, proprionic acids, fenamic acids, nonacidics, and coxibs.[17] We furthermore identified the six most frequently used nonaspirin NSAIDs, which, according to their COX-selectivity, could be classified as nonselective NSAIDs (ibuprofen and naproxen), older COX-2 inhibitors (diclofenac and etodolac), and coxibs (celecoxib and rofecoxib). The newer and older COX-2 inhibitors are almost similar in COX-2 selectivity when comparing the concentration of the drugs (IC_{50}) required to inhibit COX-1 and COX-2 activity by 50%.[27] For instance, the COX-1/COX-2 IC_{50} is 29 for diclofenac and 30 for celecoxib.[27]

Statistical analyses

We obtained sales statistics for the entire Danish population (5.6 million inhabitants as of 2012) from January 1, 1999 to December 31, 2012. The retrieval of sales statistics was restricted to the primary health care sector; ie, sales outside the hospital setting. In addition to pharmacies and nonpharmacy outlets, drug sales in the primary health care sector comprised sales from the Danish Serum Institute and in general practices.[16]

First, we calculated and illustrated graphically the 1-year prevalence of low-dose aspirin users and nonaspirin NSAID users, overall and by sex and age groups (15–19 years, 20–39 years, 40–64 years, 65–79 years, and ≥80 years). Age was defined as age at first redeemed prescription each year. Results were calculated for nonaspirin NSAIDs overall as well as separately for each of the six most frequently used types. Secondly, we identified the proportion of all aspirin and nonaspirin NSAID sales that was dispensed on prescription each year in the study period.

Results

Aspirin

Aspirin was prescribed almost exclusively in low doses for cardiovascular prevention. The annual number of low-dose aspirin prescription users increased steadily from 232,213 (4.4%) in 1999 to 408,555 (7.3%) in 2012 (Table 1 and Figure 1). Age- and sex-stratified analyses for prescribed low-dose aspirin showed an equal sex distribution in 1999, but over time slightly more men than women redeemed prescriptions for aspirin (8.0% vs 6.7% in 2012) (Figure 1). Practically no use of low-dose aspirin occurred in individuals younger than 40 years, but the prevalence of use increased to around 5% in those between the ages of 40–64 years, 25% in those aged 65–79 years, and 40% in those aged 80 years or more in 2012 (Figure 2A). The proportion of total low-dose aspirin sales that was prescribed on an individual level increased steadily from 62% in 1999 to 92% in 2012 (Table 2 and Figure 3).

High-dose aspirin was sold alone or in combination with codeine (9.6 mg) or caffeine (50 mg). As a single-compound product, high-dose aspirin was prescribed to 3,233 persons (0.06%) in 1999 and 521 (0.009%) in 2012 (Table 1). As a combination product, high-dose aspirin was prescribed to 6,340 (0.1%) in 1999 and 8,398 (0.2%) in 2012. The vast majority of total sales of high-dose aspirin both alone (90%–93%) or in combination tablets (97%–99%) were sold OTC (Table 2).

Nonaspirin NSAIDs

Each year, around 13%–15% of the total Danish population redeemed at least one prescription of nonaspirin NSAID between 1999 and 2012 (Table 1). From age 10–15 years, the prevalence of use increased markedly with age (Figure 2B). The overall prescription pattern of nonaspirin NSAIDs varied during the study period. Thus, the 1-year prevalence of individuals redeeming at least one prescription increased from 13.6% (n=723,325) in 1999 to 15.5% (n=836,072) in 2004, before declining steadily to 13.1% (n=731,667) in 2012 (Table 1 and Figure 1). A similar pattern was observed among men and women (Figure 1). Individuals aged 80 years or above constituted the most frequent users of prescription nonaspirin NSAIDs until 2003, after which their use decreased to below that of individuals aged 40–79 years (Figure 2B). All nonaspirin NSAIDs were used more frequently among women than among men.

The decrease in nonaspirin NSAID use from 2004 was seen for all three types of nonaspirin NSAIDs; ie, nonselective NSAIDs, older COX-2 inhibitors, and coxibs (Table 1 and

Table 1 Annual prevalence of NSAID use in Denmark, 1999–2012

	Number of prescription users (per thousand Danish inhabitants)													
	1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Aspirin (salicylates)[a]														
Low-dose (B01AC06)	232,213 (43.70)	243,498 (45.68)	273,028 (51.04)	304,778 (56.77)	329,349 (61.18)	349,598 (64.77)	364,775 (67.41)	383,783 (70.71)	400,332 (73.49)	417,175 (76.19)	422,213 (76.61)	424,714 (76.74)	421,641 (75.83)	408,555 (73.21)
High-dose, alone (N02BA01)	3,233 (0.61)	2,441 (0.46)	2,207 (0.41)	2,241 (0.42)	1,954 (0.36)	1,705 (0.32)	1,624 (0.30)	1,464 (0.27)	1,360 (0.25)	1,041 (0.19)	753 (0.14)	611 (0.11)	604 (0.11)	521 (0.09)
High-dose, combinations (N02BA51)	6,340 (1.19)	6,127 (1.15)	9,883 (1.85)	11,538 (2.15)	9,870 (1.83)	9,129 (1.69)	9,318 (1.72)	8,920 (1.64)	8,776 (1.61)	8,645 (1.58)	8,404 (1.52)	8,933 (1.61)	8,782 (1.58)	8,398 (1.50)
Nonaspirin NSAIDs														
Overall (M01A[b])	723,325 (136.13)	741,211 (139.06)	787,337 (147.19)	821,108 (152.95)	824,860 (153.22)	836,072 (154.90)	829,866 (153.35)	824,291 (151.87)	810,211 (148.74)	803,767 (146.79)	775,676 (140.74)	777,592 (140.49)	768,223 (138.15)	731,667 (131.11)
Butylpyrazolidines (M01AA)	1,154 (0.22)	1,146 (0.22)	1,126 (0.21)	1,034 (0.19)	1,022 (0.19)	965 (0.18)	1,043 (0.19)	1,045 (0.19)	945 (0.17)	963 (0.18)	955 (0.17)	984 (0.18)	960 (0.17)	898 (0.16)
Phenylbutazone (M01AA01)	1,154 (0.22)	1,146 (0.22)	1,126 (0.21)	1,034 (0.19)	1,022 (0.19)	965 (0.18)	1,043 (0.19)	1,045 (0.19)	945 (0.17)	963 (0.18)	955 (0.17)	984 (0.18)	960 (0.17)	898 (0.16)
Acetic acids (M01AB)	300,152 (56.49)	291,352 (54.66)	283,354 (52.97)	279,832 (52.13)	276,974 (51.45)	299,663 (55.52)	314,257 (58.07)	307,328 (56.62)	296,884 (54.50)	288,303 (52.65)	212,287 (38.52)	200,008 (36.14)	183,438 (32.99)	147,235 (26.38)
Indometacin (M01AB01)	14,418 (2.71)	12,614 (2.37)	10,700 (2.00)	7,800 (1.45)	6,280 (1.17)	6,203 (1.15)	6,307 (1.17)	6,123 (1.13)	5,313 (0.98)	4,905 (0.90)	4,539 (0.82)	3,663 (0.66)	2,343 (0.42)	1,180 (0.21)
Sulindac (M01AB02)	848 (0.16)	747 (0.14)	668 (0.12)	563 (0.10)	435 (0.08)	330 (0.06)	–	–	–	–	–	–	–	–
Tolmetin (M01AB03)	531 (0.10)	424 (0.08)	132 (0.02)	–	–	–	–	–	–	–	–	–	–	–
Diclofenac (M01AB05)	206,995 (38.96)	207,754 (38.98)	212,664 (39.76)	211,365 (39.37)	210,409 (39.08)	223,989 (41.50)	229,037 (42.32)	225,968 (41.63)	220,895 (40.55)	226,560 (41.37)	155,745 (28.26)	149,876 (27.08)	138,989 (25.00)	110,203 (19.75)
Etodolac (M01AB08)	37,319 (7.02)	38,925 (7.30)	37,356 (6.98)	46,655 (8.69)	49,193 (9.14)	59,981 (11.11)	63,743 (11.78)	53,925 (9.94)	49,881 (9.16)	51,452 (9.40)	45,367 (8.23)	38,040 (6.87)	33,718 (6.06)	28,747 (5.15)
Ketorolac (M01AB15)	14 (0.00)	16 (0.00)	12 (0.00)	9 (0.00)	7 (0.00)	4 (0.00)	6 (0.00)	9 (0.00)	5 (0.00)	8 (0.00)	12 (0.00)	7 (0.00)	9 (0.00)	8 (0.00)
Aceclofenac (M01AB16)	9,208 (1.73)	6,806 (1.28)	5,130 (0.96)	3,573 (0.67)	2,784 (0.52)	2,021 (0.37)	1,319 (0.24)	474 (0.09)	–	–	–	–	–	–
Diclofenac, combinations (M01AB55)	44,752 (8.42)	34,386 (6.45)	24,978 (4.67)	18,406 (3.43)	15,705 (2.92)	16,188 (3.00)	25,648 (4.74)	31,100 (5.73)	30,130 (5.53)	19,419 (3.55)	12,318 (2.23)	13,040 (2.36)	12,367 (2.22)	9,783 (1.75)
Enolic acids (M01AC)	46,180 (8.69)	36,958 (6.93)	30,762 (5.75)	26,414 (4.92)	22,850 (4.24)	21,632 (4.01)	21,835 (4.03)	20,172 (3.72)	16,724 (3.07)	13,932 (2.54)	11,125 (2.02)	8,706 (1.57)	7,989 (1.44)	6,656 (1.19)
Piroxicam (M01AC01)	30,165 (5.68)	25,072 (4.70)	21,095 (3.94)	18,290 (3.41)	15,693 (2.92)	14,554 (2.70)	14,514 (2.68)	13,909 (2.56)	11,064 (2.03)	8,885 (1.62)	6,368 (1.16)	3,962 (0.72)	4,210 (0.76)	3,811 (0.68)

Tenoxicam (M01AC02)	9,474 (1.78)	7,121 (1.34)	5,512 (1.03)	4,175 (0.78)	3,492 (0.65)	3,252 (0.60)	3,118 (0.58)	2,480 (0.46)	2,126 (0.39)	1,767 (0.32)	1,677 (0.30)	1,413 (0.26)	1,183 (0.21)	692 (0.12)
Lornoxicam (M01AC05)	409 (0.08)	1,124 (0.21)	1,311 (0.25)	1,453 (0.27)	1,362 (0.25)	1,437 (0.27)	1,511 (0.28)	1,511 (0.28)	1,419 (0.26)	1,631 (0.30)	1,787 (0.32)	1,872 (0.34)	1,255 (0.23)	909 (0.16)
Meloxicam (M01AC06)	6,598 (1.24)	4,029 (0.76)	2,996 (0.56)	2,600 (0.48)	2,413 (0.45)	2,490 (0.46)	2,801 (0.52)	2,355 (0.43)	2,186 (0.40)	1,726 (0.32)	1,567 (0.28)	1,535 (0.28)	1,371 (0.25)	1,280 (0.23)
Proprionic acids (M01AE)	417,401 (78.55)	414,299 (77.73)	427,744 (79.96)	449,657 (83.76)	466,934 (86.73)	499,718 (92.58)	530,752 (98.08)	534,783 (98.53)	535,047 (98.23)	552,703 (100.94)	589,621 (106.98)	602,457 (108.85)	608,115 (109.36)	605,594 (108.52)
Ibuprofen (M01AE01)	345,864 (65.09)	349,731 (65.62)	370,105 (69.19)	396,325 (73.83)	418,826 (77.80)	450,903 (83.54)	480,615 (88.82)	486,987 (89.73)	487,208 (89.44)	501,768 (91.63)	529,284 (96.03)	547,003 (98.83)	555,753 (99.94)	554,969 (99.45)
Naproxen (M01AE02)	56,007 (10.54)	51,749 (9.71)	46,302 (8.66)	43,422 (8.09)	39,974 (7.43)	38,468 (7.13)	37,030 (6.84)	32,601 (6.01)	30,940 (5.68)	32,901 (6.01)	43,047 (7.81)	37,256 (6.73)	37,856 (6.81)	40,571 (7.27)
Ketoprofen (M01AE03)	15,905 (2.99)	14,144 (2.65)	12,579 (2.35)	11,023 (2.05)	9,881 (1.84)	9,407 (1.74)	8,517 (1.57)	7,988 (1.47)	7,771 (1.43)	7,291 (1.33)	6,504 (1.18)	5,506 (0.99)	3,867 (0.70)	1,050 (0.19)
Fenoprofen (M01AE04)	294 (0.06)	244 (0.05)	208 (0.04)	164 (0.03)	75 (0.01)	–	–	–	–	–	–	–	–	–
Fenbufen (M01AE05)	68 (0.01)	39 (0.01)	–	–	–	–	–	–	–	–	–	–	–	–
Flurbiprofen (M01AE09)	433 (0.08)	298 (0.06)	241 (0.05)	196 (0.04)	177 (0.03)	180 (0.03)	157 (0.03)	143 (0.03)	122 (0.02)	122 (0.02)	108 (0.02)	89 (0.02)	–	–
Tiaprofenic acid (M01AE11)	7,679 (1.45)	5,725 (1.07)	4,612 (0.86)	3,441 (0.64)	2,179 (0.40)	2,201 (0.41)	2,146 (0.40)	1,753 (0.32)	904 (0.17)	809 (0.15)	616 (0.11)	504 (0.09)	510 (0.09)	564 (0.10)
Dexibuprofen (M01AE14)	–	–	938 (0.18)	2,194 (0.41)	2,625 (0.49)	6,214 (1.15)	10,902 (2.01)	13,684 (2.52)	16,548 (3.04)	19,648 (3.59)	22,297 (4.05)	20,676 (3.74)	18,538 (3.33)	17,373 (3.11)
Dexketoprofen (M01AE17)	–	–	–	–	–	–	–	–	–	–	693 (0.13)	3,242 (0.59)	3,169 (0.57)	2,538 (0.45)
Naproxen + esomeprazole (M01AE52)	–	–	–	–	–	–	–	–	–	–	–	–	–	138 (0.02)
Fenamic acids (M01AG)	16,573 (3.12)	16,973 (3.18)	17,419 (3.26)	17,882 (3.33)	18,747 (3.48)	18,884 (3.50)	17,507 (3.24)	16,100 (2.97)	14,686 (2.70)	5,228 (0.95)	6,007 (1.09)	5,736 (1.04)	5,321 (0.96)	5,193 (0.93)
Tolfenamic acid (M01AG02)	16,573 (3.12)	16,973 (3.18)	17,419 (3.26)	17,882 (3.33)	18,747 (3.48)	18,884 (3.50)	17,507 (3.24)	16,100 (2.97)	14,686 (2.70)	5,228 (0.95)	6,007 (1.09)	5,736 (1.04)	5,321 (0.96)	5,193 (0.93)
Nonacidics (M01AX)	8,599 (1.62)	6,086 (1.14)	4,106 (0.77)	3,305 (0.62)	5,653 (1.05)	9,811 (1.82)	12,000 (2.22)	9,645 (1.78)	6,877 (1.26)	6,122 (1.12)	5,221 (0.95)	4,555 (0.82)	3,441 (0.62)	2,999 (0.54)
Nabumetone (M01AX01)	8,599 (1.62)	6,086 (1.14)	4,106 (0.77)	3,305 (0.62)	5,653 (1.05)	9,811 (1.82)	12,000 (2.22)	9,645 (1.78)	6,877 (1.26)	6,122 (1.12)	5,221 (0.95)	4,555 (0.82)	3,441 (0.62)	2,999 (0.54)
Coxibs (M01AH)	1,294 (0.24)	58,086 (10.90)	121,424 (22.70)	143,833 (26.79)	128,462 (23.86)	88,430 (16.38)	10,302 (1.90)	5,551 (1.02)	4,273 (0.78)	3,942 (0.72)	3,642 (0.66)	3,656 (0.66)	4,175 (0.75)	3,729 (0.67)
Celecoxib (M01AH01)	–	13,215 (2.48)	62,346 (11.66)	75,174 (14.00)	64,207 (11.93)	50,435 (9.34)	6,798 (1.26)	3,233 (0.60)	2,318 (0.43)	2,026 (0.37)	2,105 (0.38)	2,295 (0.41)	2,515 (0.45)	2,447 (0.44)

(*Continued*)

Table 1 (*Continued*)

	Number of prescription users (per thousand Danish inhabitants)												
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Rofecoxib (M01AH02)	1,294 (0.24)	47,014 (8.82)	65,828 (12.31)	75,402 (14.05)	61,406 (11.41)	32,582 (6.04)	–	–	–	–	–	–	–	–
Etoricoxib (M01AH05)	–	–	–	–	8,778 (1.63)	13,071 (2.42)	3,578 (0.66)	2,334 (0.43)	1,967 (0.36)	1,924 (0.35)	1,541 (0.28)	1,368 (0.25)	1,663 (0.30)	1,284 (0.23)

Notes: Some nonaspirin NSAID groups have synonyms: Enolic acids = oxicams, fenamic acids = fenamates, nonacidics = naphthyl alkanone, and coxibs = newer COX-2 inhibitors. The sales information is based on data from the Danish National Prescription Registry. [a]Low-dose aspirin (75–150 mg) for cardiovascular prevention and high-dose (500 mg) for pain relief (alone or in combination with 9.6 mg codeine [Kodimagnyl®] or 50 mg caffeine [Treo®]); [b]M01A, except glucosamine (M01AX05).

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

Figure 4). An exception was ibuprofen, for which the 1-year prevalence increased steadily from 6.5% in 1999 to 9.9% in 2012. Among other commonly used nonaspirin agents, use of naproxen decreased slightly from 1999 to 2004 (1.1% in 1999 and 0.7% in 2004) and remained stable thereafter. Diclofenac was consistently prescribed to around 4% of the Danish population until 2008, after which the prevalence decreased and reached 2% in 2012. Etodolac was prescribed to approximately 0.5% throughout the period (0.7% in 1999 and 0.5% in 2012). Celecoxib and rofecoxib comprised almost the entire sale of coxibs. These agents displayed a fairly similar pattern of use, increasing steeply after their introduction (on November 15, 1999 for rofecoxib and on May 15, 2000 for celecoxib) to surpass both naproxen and etodolac (Figure 4). After 2002, the use of coxibs began to decrease; after September 30, 2004, when rofecoxib was withdrawn from the market, celecoxib use decreased sharply, and it was only used by 0.04% of the population in 2012 (Table 1 and Figure 4). Stratified analyses according to age and sex (Table S1) revealed that coxibs and etodolac were used almost entirely among individuals above 40 years, whereas ibuprofen, naproxen, and diclofenac constituted the most frequently used nonaspirin NSAIDs among younger individuals.

The proportion of nonaspirin NSAIDs dispensed on prescription in Denmark decreased from 85% in 1999 to 75% in 2012 (Table 2 and Figure 3). The OTC availability of diclofenac in part of 2007–2008 did not influence the overall prescription/OTC relation materially (Table 2). Thus, low-dose (200 mg) ibuprofen accounted for practically all OTC use of nonaspirin NSAIDs between 1999 and 2012. Specifically, OTC use of low-dose ibuprofen accounted for 30%–35% of total ibuprofen sales and 15%–25% of total nonaspirin NSAID sales between 1999 and 2012 (Figure 3). The overall decrease in the proportion of nonaspirin NSAIDs dispensed by prescription reflected that OTC ibuprofen use increased more than the prescribed use of ibuprofen.

Discussion

Both low-dose aspirin and nonaspirin NSAIDs were commonly used in the Danish population between 1999 and 2012. The proportions of total sales of low-dose aspirin or nonaspirin NSAIDs dispensed by prescription and thus captured in prescription registries were high: as of 2012, 92% for low-dose aspirin, 66% for ibuprofen and 100% for all other nonaspirin NSAIDs. The 1-year prevalence of prescribed low-dose aspirin increased throughout the period, particularly among men. Except for ibuprofen, the 1-year prevalence of nonaspirin NSAID use decreased

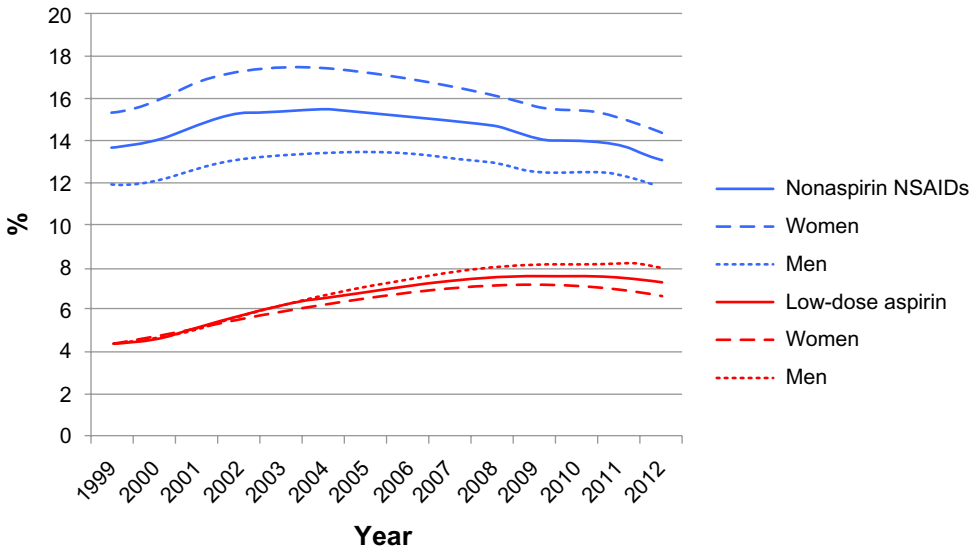

Figure 1 The 1-year prevalence of the Danish population redeeming a prescription for low-dose aspirin or nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) during 1999–2012, overall and by sex.

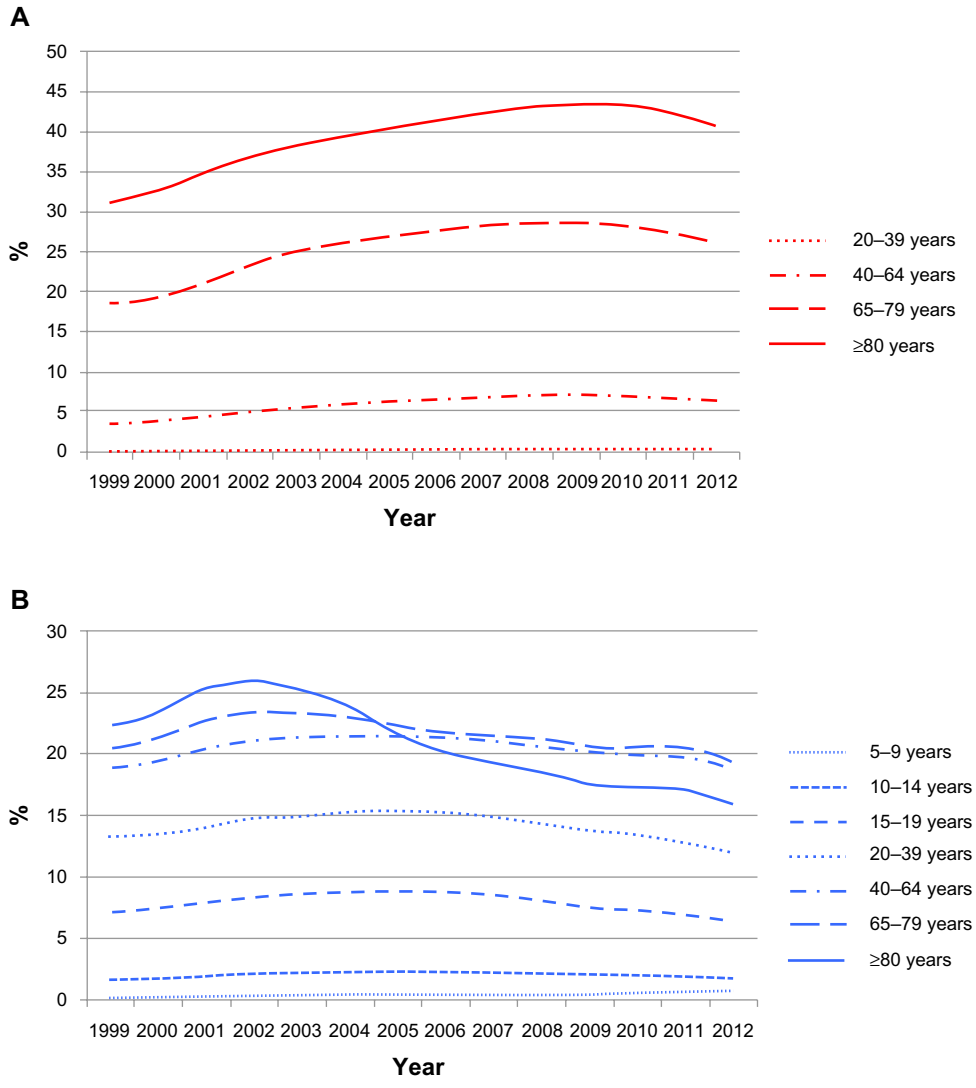

Figure 2 The 1-year prevalence of the Danish population redeeming a prescription for low-dose aspirin (**A**) or nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (**B**) during 1999–2012, by age groups.

Table 2 The percentage of total NSAID sales sold on prescription in Denmark, 1999–2012

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Aspirin (salicylates)[a]														
Low-dose (B01AC06)	62	63	71	77	82	85	87	89	90	90	90	91	91	92
High-dose, alone (N02BA01)	7	7	7	8	8	9	9	9	9	9	10	10	9	10
High-dose, combinations (N02BA51)	1	1	1	2	2	2	2	2	2	2	2	3	3	3
Nonaspirin NSAIDs														
Overall (M01A[b])	85	84	85	85	85	84	83	82	82	81	80	79	77	75
Butylpyrazolidines (M01AA)	97	95	95	96	98	97	99	99	99	>99	99	>99	>99	>99
Phenylbutazone (M01AA01)	97	95	95	96	98	97	99	99	99	>99	99	>99	>99	>99
Acetic acids (M01AB)	99	99	98	98	98	99	99	99	99	98	99	99	99	99
Indometacin (M01AB01)	99	98	99	98	97	99	99	99	99	>99	>99	>99	>99	99
Sulindac (M01AB02)	>99	>99	>99	>99	>99	>99	–	–	–	–	–	–	–	–
Tolmetin (M01AB03)	>99	>99	>99	–	–	–	–	–	–	–	–	–	–	–
Diclofenac (M01AB05)	98	98	98	98	98	98	98	98	98	97	98	99	99	99
Etodolac (M01AB08)	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Ketorolac (M01AB15)	19	35	14	13	37	37	42	33	3	3	5	4	3	2
Aceclofenac (M01AB16)	>99	>99	>99	>99	>99	>99	>99	>99	–	–	–	–	–	–
Diclofenac, combinations (M01AB55)	99	99	99	99	99	99	99	99	99	99	>99	>99	>99	>99
Enolic acids (M01AC)	98	98	98	98	98	97	97	97	98	99	98	99	99	99
Piroxicam (M01AC01)	98	97	97	97	97	97	97	98	99	98	98	99	99	99
Tenoxicam (M01AC02)	>99	>99	>99	>99	>99	>99	>99	99	99	99	99	99	99	>99
Lornoxicam (M01AC05)	96	78	93	90	92	89	72	68	71	92	89	94	96	97
Meloxicam (M01AC06)	>99	>99	99	99	99	99	>99	>99	>99	>99	>99	>99	99	>99
Proprionic acids (M01AE)	76	74	73	72	71	71	72	72	72	72	73	72	70	69
Ibuprofen (M01AE01)	70	68	68	67	67	67	69	69	69	69	69	69	67	66
Naproxen (M01AE02)	99	98	98	99	98	99	99	99	99	99	99	99	99	99
Ketoprofen (M01AE03)	99	99	99	99	99	99	99	99	99	99	99	>99	>99	>99
Fenoprofen (M01AE04)	>99	>99	>99	>99	>99	–	–	–	–	–	–	–	–	–
Fenbufen (M01AE05)	>99	>99	–	–	–	–	–	–	–	–	–	–	–	–
Flurbiprofen (M01AE09)	>99	>99	>99	>99	99	>99	>99	>99	>99	>99	>99	>99	–	–
Tiaprofenic acid (M01AE11)	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Dexibuprofen (M01AE14)	–	–	>99	>99	97	99	>99	>99	99	98	98	99	99	99
Dexketoprofen (M01AE17)	–	–	–	–	–	–	–	–	–	–	97	98	>99	>99
Naproxen and esomeprazole (M01AE52)	–	–	–	–	–	–	–	–	–	–	–	–	–	99
Fenamic acids (M01AG)	99	99	99	99	99	99	99	99	>99	>99	99	99	>99	>99
Tolfenamic acid (M01AG02)	99	99	99	99	99	99	99	99	>99	>99	99	99	>99	>99
Nonacidics (M01AX)	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Nabumetone (M01AX01)	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Coxibs (M01AH)	97	>99	99	99	99	99	98	98	90	94	99	99	99	99
Celecoxib (M01AH01)	–	99	>99	>99	99	>99	97	98	85	92	99	99	99	99
Rofecoxib (M01AH02)	>99	>99	99	99	98	99	–	–	–	–	–	–	–	–
Etoricoxib (M01AH05)	–	–	–	–	>99	>99	>99	>99	>99	>99	99	99	99	99

Notes: Some nonaspirin NSAID groups have synonyms: Enolic acid = oxicams, fenamic acids = fenamates, nonacidics = naphthyl alkanone, and coxibs = newer COX-2 inhibitors. The sales information is based on data from the Danish National Prescription Registry. Even for prescription drugs only, the proportion sold on prescription does not equal exactly 100% because there are small nonperson referable sale for use in general practices, by the Danish Serum Institute, and for medicine stocks at nursing homes and treatment centers. Nonperson referable sale may influence the proportion sold on prescription more when the drug is rarely prescribed (eg, ketorolac). [a]Low-dose aspirin (75–150 mg) for cardiovascular prevention and high dose (500 mg) for pain relief (alone or in combination with 9.6 mg codeine [Kodimagnyl®] or 50 mg caffeine [Treo®]); [b]M01A, except glucosamine (M01AX05).

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

after 2004. The decline was independent of age or sex, but there was a consistently higher prevalence of use in older age groups and among women. Use of coxibs decreased to near null after 2004. Interestingly, the use of diclofenac was reduced by half between 2008 and 2012, but no substantial change occurred in use of naproxen and etodolac.

OTC use of low-dose aspirin and nonaspirin NSAIDs is far less common in Denmark than in many other countries.[28] Therefore, the potential for identification of NSAID use from

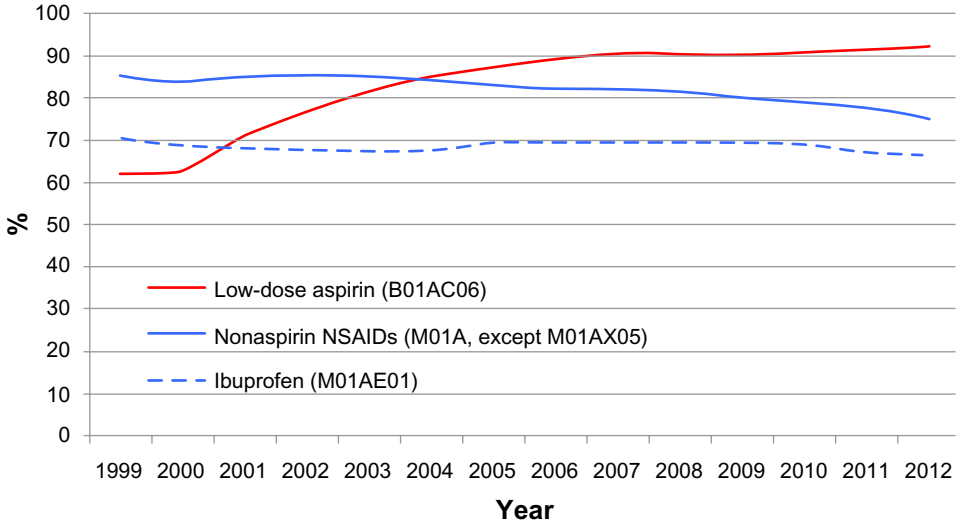

Figure 3 The percentage of total nonsteroidal anti-inflammatory drug (NSAID) sales sold on prescription in Denmark between 1999 and 2012.

prescription registries is high. Indeed, with the most recent restriction on pack sizes of OTC analgesics in Denmark,[22] OTC use of NSAIDs is likely to decrease even further. In this context, it should be noted that while low-dose aspirin is used continuously for prevention of cardiovascular disease and a substantial proportion of high-dose nonaspirin NSAID therapy is also used on a chronic basis, high-dose aspirin and low-dose ibuprofen are mainly used as short-term treatment of transient pain conditions such as headaches, sports injuries, or backaches. Danish prescription registry data are thus reliable data sources for research on the effects of aspirin and nonaspirin NSAID exposure, especially when indicated for chronic use.

Assessment of low-dose aspirin use has the advantage, compared with many other medications, that the daily defined dose equals one pill per day.[17] Thus, the expected number of exposure days from a prescription refill can be modeled from the number of pills per package.[1] Using a more accurate exposure window in this way (rather than a fixed exposure-window) may help to reduce misclassification of aspirin use.

Because the prescription data are prospectively recorded, any misclassification of NSAID use due to nonadherence or OTC use of aspirin or ibuprofen would generally bias measures of associations towards the null. The magnitude of misclassification bias due to OTC use can be illustrated from a hypothetical cohort study examining the effect of drug exposure on a given outcome. Assuming that 15% of the population uses the drug every day, only two-thirds obtain the drug on prescription (as for ibuprofen), and an

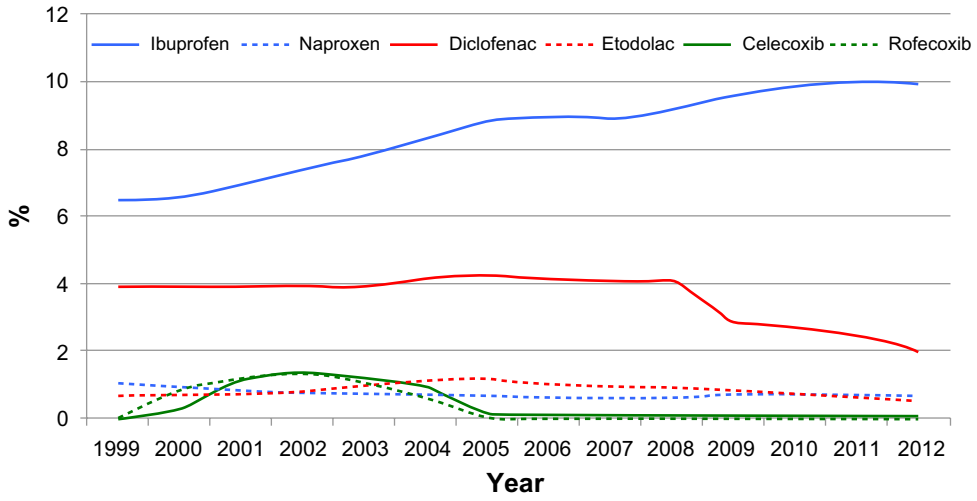

Figure 4 The annual prevalence of the Danish population prescribed the most commonly used nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) (blue), older COX-2 inhibitors (red), and coxibs (green) between 1999 and 2012.
Abbreviation: COX, cyclooxygenase.

equal age distribution among new and long-term users, there will be no misclassification of the apparently exposed and only 5% (nondifferential) misclassification of the apparently nonexposed (as one-third of 15% will be OTC users who are not captured by the prescription registry). Considering another scenario with an exposure prevalence of 10% and prescription coverage of 50%, the misclassification will still be only 5%. Unless the relative risk measure is very high, misclassification of this magnitude has no practical impact on the relative risk estimate, rate difference, or etiologic fraction among the exposed. Only the etiologic fraction in the background population will be substantially underestimated from such misclassification. Moreover, the misclassification would be even less for drugs with a prevalence of use below 10%–15% (which is often the case). Finally, the bias generated by such misclassification would be even smaller if the drug with OTC availability is a confounder drug and not the primary exposure.

The withdrawal of rofecoxib contributed to the subsequent reduction in use of all coxibs following 2004, including celecoxib.[8] The increased focus on the cardiovascular toxicity associated with nonaspirin NSAID use in general, and COX-2 selective NSAIDs in particular, may also have contributed to the overall decrease in prescribed nonaspirin NSAID use from 2004 onwards. The decrease in diclofenac use after 2008 may be a direct consequence of recommendations from the Danish Medicines Agency in 2008[29] and Danish Society for Cardiology in 2009[30] to use diclofenac with caution due to an increased risk of cardiovascular disease. Surprisingly, use of naproxen did not increase during the study period despite several studies pointing to a markedly lower cardiovascular risk profile of naproxen than of other nonaspirin NSAID agents.[9,10] In contrast, both prescribed and OTC use of ibuprofen increased substantially from 1999. These patterns are difficult to explain as a rational response to concerns about cardiovascular toxicity of nonaspirin NSAIDs. Until 2004, however, the dominant discourse on NSAID toxicity concerned gastrointestinal bleeding. Among the traditional NSAIDs, ibuprofen has a well-established low gastrointestinal risk, whereas the gastrointestinal safety is lower for naproxen.[31,32] Although the magnitude of cardiovascular versus gastrointestinal risks for individual NSAIDs is controversial,[33] it is possible that preferences to a large extent still are driven mainly by the perceived gastrointestinal risks.

Whereas low-dose ibuprofen therapy seems safe,[34,35] high-dose ibuprofen has also been associated with adverse cardiovascular events.[9] Even though OTC ibuprofen is only available in 200 mg tablets, it is not possible to monitor the consumed number of pills and hence the daily dose. This is a concern, especially before September 20, 2013,[22] because OTC drugs are often used in higher doses than recommended and with little attention to potential side effects.[28]

Strengths and limitations

Using Medstat, we were able to obtain complete data on prescribed and total sales of all marketed NSAIDs for the entire Danish population during a 14-year period.[14,16] We did not have information on the exact number of OTC users, but we had information on the proportions of total sales of aspirin or nonaspirin NSAID that were dispensed by prescription. The proportion of prescription use of all nonaspirin NSAIDs, except low-dose ibuprofen, equals almost all use in Denmark.

Conclusion

The potential for identification of individual-level use of low-dose aspirin and nonaspirin NSAIDs from prescription registries in Denmark is high. This is of vast importance for analytical studies addressing NSAIDs as either primary or secondary exposures. The pattern of NSAID use in Denmark varied substantially between 1999 and 2012. Use of coxibs nearly ceased and diclofenac use decreased by half since 2008, whereas naproxen use remained stable and did not increase despite its less harmful cardiovascular risk profile.

Research Ethics and Informed Consent

As this study was based solely on register data and did not involve any contact with patients, no approval was required from the Danish Scientific Ethical Committee.

Disclosure

MS has no disclosures. JH has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, and Astellas, with grants paid to the institution where he was employed. JH has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers, Nycomed, Pfizer, Novartis, AstraZeneca, Lundbeck, Menarini, Leo Pharmaceuticals, and Ferring. SF has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers. The authors declare no other conflicts of interest.

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Supplementary materials

Table S1 Annual prevalence of NSAID use in Denmark 1999–2012 stratified by age and sex categories

Age groups	Sex	Number of prescription users in the primary sector per thousand Danish inhabitants							
		1999	2000	2002	2004	2006	2008	2010	2012
Low-dose aspirin (B01AC06)		43.70	45.68	56.77	64.77	70.71	76.19	76.74	73.21
All age groups	Male	43.11	45.27	57.59	66.88	74.04	80.69	82.38	79.63
	Female	44.28	46.08	55.98	62.70	67.45	71.77	71.19	66.90
15–19 years	Male	0.08	0.11	0.09	0.15	0.15	0.27	0.27	0.32
	Female	0.09	0.13	0.17	0.12	0.29	0.34	0.31	0.41
20–39 years	Male	1.07	1.19	1.77	2.27	2.54	2.90	2.74	2.39
	Female	1.07	1.15	1.65	2.04	2.42	2.73	2.54	2.51
40–64 years	Male	42.31	45.10	60.59	72.80	81.14	87.35	85.19	78.14
	Female	26.07	27.86	38.04	45.90	51.25	55.70	53.46	48.28
65–79 years	Male	207.01	214.55	265.49	296.63	314.46	330.21	328.18	306.38
	Female	164.23	169.52	205.96	228.92	240.14	248.21	239.46	218.05
≥80 years	Male	320.86	334.07	385.26	417.39	441.03	461.79	467.92	439.26
	Female	306.59	320.31	359.45	381.51	396.88	414.15	415.74	387.04
Non-aspirin NSAIDs (M01A[a])		136.13	139.06	152.95	154.90	151.87	146.79	140.49	131.11
All age groups	Male	118.80	120.36	132.09	135.03	134.24	130.55	125.66	118.23
	Female	153.04	157.34	173.36	174.34	169.15	162.72	155.07	143.78
15–19 years	Male	45.58	46.94	53.03	56.40	56.75	53.26	48.05	40.06
	Female	98.32	103.15	115.90	120.85	118.96	110.94	99.22	86.49
20–39 years	Male	115.42	116.82	126.40	130.25	130.31	122.95	114.10	102.19
	Female	151.35	154.13	169.26	175.52	174.68	165.02	152.98	136.92
40–64 years	Male	172.02	174.11	190.31	194.91	195.09	189.81	183.10	173.41
	Female	205.55	211.24	231.22	234.55	232.00	224.60	215.77	202.15
65–79 years	Male	189.57	191.77	214.90	214.65	206.36	204.43	200.31	189.51
	Female	219.47	226.68	252.68	244.46	225.27	218.19	212.40	197.93
≥80 years	Male	207.59	212.32	234.05	220.71	192.83	183.30	173.43	159.61
	Female	230.68	242.62	271.39	247.13	203.25	187.75	173.49	158.71
Diclofenac (M01AB05)		38.96	38.98	39.37	41.50	41.63	41.37	27.08	19.75
All age groups	Male	35.26	35.46	35.64	37.11	36.79	35.97	23.61	17.29
	Female	42.56	42.42	43.03	45.80	46.38	46.68	30.49	22.16
15–19 years	Male	14.47	15.31	15.90	15.68	14.82	13.57	7.33	3.97
	Female	27.75	29.01	32.09	33.60	33.51	32.39	19.51	12.36
20–39 years	Male	35.99	36.60	35.55	35.50	33.88	30.73	18.12	12.04
	Female	45.19	46.21	48.45	50.24	49.52	48.24	30.87	21.67
40–64 years	Male	52.16	52.34	53.23	55.43	55.05	53.33	35.62	26.54
	Female	59.66	59.44	60.33	64.16	65.35	65.63	43.06	32.15
65–79 years	Male	50.74	49.77	51.15	56.52	57.75	61.11	42.46	31.86
	Female	54.71	52.05	50.53	56.69	58.35	61.00	40.76	29.68
≥80 years	Male	47.66	45.93	45.13	47.98	47.19	49.98	33.06	24.08
	Female	47.27	44.78	39.10	43.39	44.02	46.21	29.72	20.63
Etodolac (M01AB08)		7.02	7.30	8.69	11.11	9.94	9.40	6.87	5.15
All age groups	Male	5.67	5.95	7.15	8.33	7.29	6.95	5.05	3.78
	Female	8.35	8.62	10.20	13.84	12.53	11.79	8.67	6.50
15–19 years	Male	1.47	1.44	1.60	1.26	1.10	0.95	0.78	0.54
	Female	2.47	2.81	2.93	2.64	2.07	1.84	1.26	1.00
20–39 years	Male	4.67	4.90	5.48	5.15	4.13	3.68	2.49	1.70
	Female	5.71	5.94	6.95	6.99	5.69	5.21	3.44	2.41
40–64 years	Male	8.47	8.80	10.58	12.14	10.43	9.88	7.09	5.30
	Female	11.99	12.49	14.64	19.34	17.38	16.37	11.97	8.87
65–79 years	Male	10.67	11.08	14.45	19.01	17.20	16.56	12.01	9.08
	Female	15.98	16.00	19.64	30.28	28.01	26.13	19.84	14.76
≥80 years	Male	12.77	14.98	17.52	27.24	24.83	23.11	16.65	11.54
	Female	16.47	17.05	20.32	35.86	33.41	30.57	21.86	16.33

(*Continued*)

Table S1 (*Continued*)

Age groups	Sex	Number of prescription users in the primary sector per thousand Danish inhabitants							
		1999	2000	2002	2004	2006	2008	2010	2012
Ibuprofen (M01AE01)		65.09	65.62	73.83	83.54	89.73	91.63	98.83	99.45
All age groups	Male	58.34	58.97	67.22	76.09	82.23	83.86	90.59	91.77
	Female	71.68	72.10	80.29	90.83	97.07	99.27	106.93	107.00
15–19 years	Male	23.15	24.07	30.35	35.41	37.10	36.00	36.93	33.19
	Female	42.72	46.80	58.46	65.28	67.50	65.10	65.75	61.45
20–39 years	Male	61.54	63.47	74.69	83.88	89.09	87.70	90.15	85.52
	Female	77.09	79.32	93.78	104.74	110.58	109.52	112.21	106.19
40–64 years	Male	83.08	84.24	96.45	109.52	119.48	122.56	132.90	135.87
	Female	96.01	97.15	109.36	124.99	135.38	139.59	151.75	153.30
65–79 years	Male	85.51	83.72	89.84	102.84	110.91	116.69	131.80	137.50
	Female	95.33	92.02	93.04	107.24	114.60	121.18	137.26	141.46
≥80 years	Male	92.38	86.26	80.71	88.54	93.88	95.56	106.14	109.38
	Female	99.03	92.92	82.33	91.01	92.41	94.53	103.73	106.82
Naproxen (M01AE02)		10.54	9.71	8.09	7.13	6.01	6.01	6.73	7.27
All age groups	Male	7.98	7.28	6.13	5.40	4.57	4.62	5.44	5.96
	Female	13.04	12.08	10.00	8.82	7.41	7.37	8.00	8.56
15–19 years	Male	3.31	3.36	2.84	3.00	2.55	2.65	2.48	1.94
	Female	19.72	20.32	18.93	17.42	15.52	14.45	13.17	12.13
20–39 years	Male	7.08	6.51	5.31	4.40	3.45	3.32	3.92	3.85
	Female	15.68	14.78	12.50	11.13	9.02	8.56	8.73	8.92
40–64 years	Male	11.68	10.68	8.90	7.55	6.28	6.17	6.99	7.55
	Female	15.28	13.91	11.33	9.68	7.89	8.01	8.93	9.97
65–79 years	Male	13.42	11.98	10.21	8.91	7.65	7.74	9.21	10.62
	Female	13.34	11.83	8.78	7.63	6.38	6.23	7.74	9.02
≥80 years	Male	13.75	11.49	9.73	8.87	6.42	5.95	7.38	9.30
	Female	13.75	11.37	7.75	5.88	4.76	4.93	6.01	6.93
Celecoxib (M01AH01)		–	2.48	14.00	9.34	0.60	0.37	0.41	0.44
All age groups	Male	–	1.55	9.60	6.15	0.38	0.27	0.34	0.38
	Female	–	3.39	18.31	12.47	0.81	0.46	0.49	0.50
15–19 years	Male	–	0.07	0.69	0.40	0.02	0.01	0.01	0.03
	Female	–	0.17	1.71	1.18	0.11	0.04	0.04	0.03
20–39 years	Male	–	0.59	4.02	2.27	0.19	0.12	0.10	0.11
	Female	–	0.99	5.99	3.49	0.44	0.19	0.14	0.09
40–64 years	Male	–	2.28	13.36	8.17	0.53	0.42	0.47	0.46
	Female	–	4.56	23.18	15.23	1.00	0.60	0.60	0.58
65–79 years	Male	–	4.59	27.44	18.10	0.88	0.67	1.12	1.26
	Female	–	8.86	47.53	32.30	1.55	1.05	1.46	1.62
≥80 years	Male	–	6.05	43.72	31.81	1.80	0.83	0.77	0.94
	Female	–	11.27	65.58	50.15	3.13	1.51	1.16	1.14
Rofecoxib (M01AH02)		0.24	8.82	14.05	6.04	–	–	–	–
All age groups	Male	0.15	5.51	9.71	4.10	–	–	–	–
	Female	0.33	12.06	18.28	7.93	–	–	–	–
15–19 years	Male	–	0.27	0.74	0.31	–	–	–	–
	Female	0.01	0.65	1.87	0.90	–	–	–	–
20–39 years	Male	0.03	1.91	4.15	1.69	–	–	–	–
	Female	0.06	3.13	5.71	2.54	–	–	–	–
40–64 years	Male	0.24	7.92	13.14	5.48	–	–	–	–
	Female	0.44	15.73	22.30	9.35	–	–	–	–
65–79 years	Male	0.45	16.73	28.58	11.74	–	–	–	–
	Female	1.01	33.14	48.35	20.76	–	–	–	–
≥80 years	Male	0.76	24.47	44.92	20.01	–	–	–	–
	Female	0.99	41.58	69.97	31.82	–	–	–	–

Notes: The sales information is based on data from the Danish National Prescription Registry. Age group 0–14 are not shown due to the low prevalence of use. [a]M01A, except glucosamine (M01AX05).

Abbreviations: COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug.

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