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Use of opioids prior to hospital admission among the non-surgical critically ill
Studies on risk and prognosis

PhD dissertation

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Dissertation papers

I. Munch T, Christiansen CF, Pedersen L, Sørensen HT. Impact of Preadmission Opioid Treatment on 1-Year Mortality Following Nonsurgical Intensive Care. Crit Care Med. 2018 Jun;46(6):860-868. doi: 10.1097/CCM.0000000000003080. PubMed PMID: 29528945

II. Munch T, Horváth–Puhó E, Adelborg K, Christiansen CF, Pedersen L, Schmidt M, Sørensen HT. Pre-admission opioid use and risk of death following incident myocardial infarction. In preparation

III. Munch T, Christiansen CF, Pedersen L, Stürmer T, Sørensen HT. New use of opioids and risk of a pneumonia-related hospital and intensive care admission: a nationwide new-user active comparator cohort study. In preparation

Contents

Dissertation structure

This dissertation is comprised of three studies (I-III) that shed light on the risk and prognosis associated with prescription opioid use in relation to critical illness, such as intensive care unit (ICU) admission, myocardial infarction (MI), and pneumonia requiring hospital admission. All three studies are nationwide registry-based cohort studies, with studies I and II being studies of prognosis and study III being a study of risk.

The dissertation is divided into eight chapters. The Introduction briefly walks the reader through the history of opioids, their mechanism of action, and their use prior to a literature review and discussion of the current literature in relation to the study populations and outcomes being studied in this dissertation following which the aim of this dissertation is established. The three subsequent chapters present the methodology and results, with a discussion of our findings in relation to the existing literature, the applied methodology, and the clinical and public health impacts.

Concluding this dissertation are an English and Danish summary, references, and Appendix, in which the full versions of studies I-III can be found.

Introduction

Pain is a common symptom that frequently brings patients in contact with the health care system – approximately one-third of all general practice consultations were related to pain.[1] In the Western world, the prevalence of chronic pain in the adult population is estimated to be 20-30%, corresponding to approximately 850 000 in Denmark.[2-4] Alleviating pain has been a central part of clinical medicine's aspiration to preserve and restore health and relieve suffering. However, all potential avenues for pain relief thus far have drawbacks. Opioids have since the dawn of human civilization been a mainstay of pain treatment, with increased use in the past few decades; more than 3% of all adults use opioids regularly, and nearly a third of the American population uses opioids at least once a year.[2,5-8] However, increasing evidence suggests that prescription opioid users may suffer a higher risk of critical illness, such as myocardial infarction (MI)[9-11] and infections requiring hospitalization,[12-19] and may suffer a worse prognosis following such critical illness.[20-22] Thus, the purpose of this dissertation was to examine the association of prescription opioid use with the risk and prognosis of critical illness, such as intensive care unit (ICU) admission, MI, and pneumonia requiring hospital admission.

History of opioids

Crude opium, which is extracted from *Papaver somniferum* and *Papaver album*, was recognized for its ability to alleviate pain and induce euphoria as early as 3000 B.C. in Sumeria, and is one of the oldest known medicinal substances.[23-25] Regardless, it was millennia before a German pharmacist succeeded in isolating one of the active components in the 1800s, naming it morphine after Morpheus, the Greek god of dreams.[23,24,26] It took the invention of the hypodermic needle in 1853 for morphine to find its place in modern medicine and become widely recognized as the class-defining compound to which all other analgesics are compared.[26]

The isolation of morphine led to the isolation and identification of the other opiates in opium (e.g., codeine, papaverine, and thebaine).[26] In the pursuit of a non-addictive and efficacious opioid, which

has thus far failed, a range of semi-synthetic and synthetic opioids was discovered through a combination of careful chemical manipulations of naturally occurring alkaloids and sheer happenstance. [23,26] Historically, this categorization of opioids into naturally occurring (opiates) versus synthesized (opioids) was reflected in the terminology. This classification system has since faded away, and the term *"opioid"* has come to denote any natural, semi-synthetic or synthetic compound that binds to opioid receptors. Strictly speaking, this definition includes all compounds regardless of their action being agonistic, partial agonistic, or antagonistic. However, this definition is not entirely agreed upon, and some include a requirement of the action being "morphine-like" to avoid including antagonists such as naloxone.[27] Throughout this thesis, the term *"opioid"* will be used to refer to opioid analgesics (i.e., agonists and partial agonists).

Indication and considerations for prescribing opioids

Historically, opioids were used primarily for their ability to induce analgesia to treat acute pain in relation to delivery, illness, surgery, and trauma. However, advocacy for their use in other patient groups has expanded their usage to include chronic pain conditions arising from cancer, as well as non-cancer conditions, such as fibromyalgia, low-back pain, and neuropathic pain, including diabetic neuropathy.[28-31] Opioid receptors are found throughout the central nervous system, as well as the gastrointestinal tract, lungs, heart, and reproductive tract, among other organs.[32-34] Opioids exert their actions in diverse systems, including pain modulation, respiratory, cardiovascular, and gastrointestinal regulation.[34] As suggested by the indications, the primary beneficial effects of opioids are to induce analgesia and anesthesia. However, a range of side effects are known to occur. The most common and well established include constipation, nausea, respiratory depression, and cough suppression.[25] Other unwanted side effects on the immune, cardiovascular, and hormonal systems are increasingly recognized. [25] The unwanted side effects will be addressed as they relate to the outcomes of interest in the three studies.

Opioid prescribing also warrants careful evaluation of other clinical concerns owing to their potential for inducing tolerance (i.e., need for escalating dosages to achieve the same effect), which

together with physical and psychological dependence characterizes a substance abuse disorder.[24,25] Tolerance can occur within hours of drug initiation and to a staggering degree – in some cases a prevalent user may ingest dosages that would outright kill an opioid-naïve patient.[24] Physical dependence arises in conjunction with the development of tolerance as the body adapts to the presence of opioids and is the cause of withdrawal symptoms (e.g., hyperthermia, vomiting, diarrhea, anxiety, and hostility) when usage is suddenly discontinued.[24] Psychological dependence denotes a range of changes but is best characterized by cravings for the stimuli in question in an attempt to avoid unpleasantness. Ultimately, the risk of overdose and subsequent death should also be considered when prescribing opioids.

Mechanism of action

Structurally, opioid receptors are G-protein coupled receptors; however, despite extensive research, their mechanism of action remains poorly elucidated.[34] Currently, the existence of four major classes of opioid receptors are accepted (μ/MOP, δ/DOP, κ/KOP opioid receptor-like/NOP), and the existence of multiple subtypes of each has been proposed based on pharmacological studies.[24,26,32,34,35] The cellular response following activation appears to be similar for all classes of opioid receptors, and their effect is dependent on anatomical location.[35] Consequently, the effect of any given opioid compound depends on its affinity towards each receptor class or subtype. Thus, the class and subtype of opioid receptors could be highly clinically important if it was possible to target them specifically. Definite proof in the shape of the genomic make-up of such subtypes has remained elusive, despite successful cloning of each of the major classes of receptors.[32,34,36] Following genetic knockout of the genome of the major classes and subsequent complete absence of an effect following opioid administration, the pharmacological subtypes are a result of either interactions between opioid receptors (dimerization) or alternative splicing.[32,34]

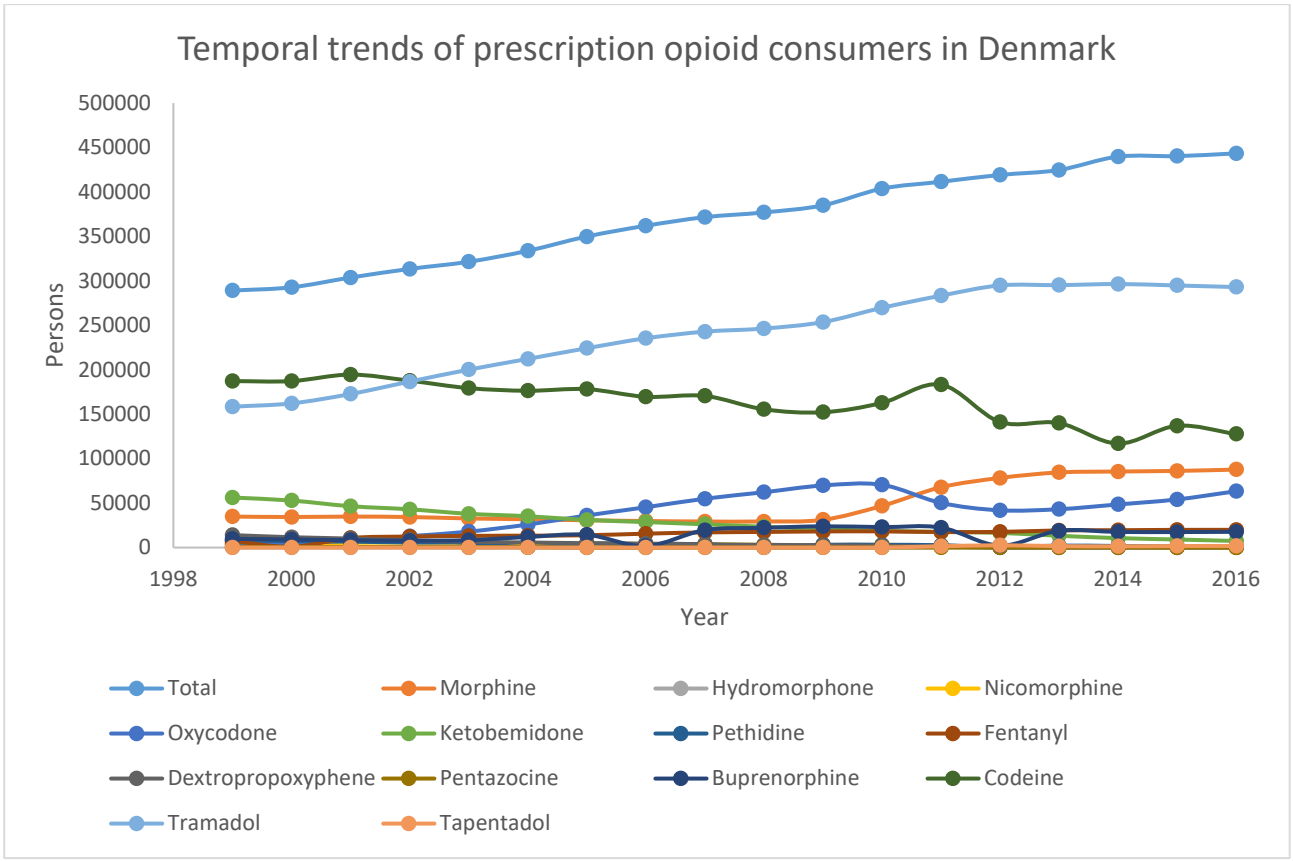
Opioid use in Denmark and internationally

Global opioid consumption has doubled since 1996, but this is primarily due to increased consumption in countries already consuming the majority of opioids;[37] 17% of the world's population consumes 92% of all

morphine produced.[27] This massive increase in opioid usage is largely due to shifts in treatment policies with the acknowledgment of proper pain treatment as a human right.[38-40]

Since the 1980s, Denmark has consistently held a top position in opioid consumption per capita; in 2015, it was surpassed only by the USA, Canada, and Germany. [6,27,41] Approximately 5% of all opioids used in Denmark are in-hospital, with the remaining 95% being prescribed by primary care physicians.[6] Approximately 3% of the Danish adult population uses opioids on a regular basis.[2] Approximately 61% of opioid users suffer from acute pain, 26% from chronic non-cancer pain, and 13% from cancer pain.[6] Mirroring the global increase, Denmark has seen an increase in opioid consumption (specifically tramadol) over the past few decades, with the number of users closing in on half a million in 2016 (Figure 1).[42]

Figure 1. Temporal trends among prescription opioid consumers in Denmark (www.medstat.dk)



Following the global increase in opioid use, an alarming parallel increase in overdose deaths has been observed. This development can only be described as catastrophic in the US, where more than one-third of all adults reported prescription opioid use in 2015.[8] Currently, (unintentional) drug overdose deaths are the leading cause of death among Americans under 50 years of age, comprising more than 100 daily deaths, with opioids constituting at least two-thirds.[43-46] This has been dubbed the "opioid epidemic", which was declared a national emergency by President Donald J. Trump on August 10, 2017.[45]

Literature review

We reviewed the pre-existing literature on the topics of this dissertation by searching Pubmed/Medline using Medical Subject Headings (MeSH) terms combined with AND/OR whilst restricting according to age (≥18 years) and language (English, Danish, Swedish, and Norwegian). Articles were then reviewed based on heading and abstract, and ultimately selected if judged relevant according to the PICO (population, intervention, comparison, outcome) criteria. The reference lists of all identified articles were gleaned for other articles of potential interest that may have been missed in our initial search. Search terms with results are provided in Table 1. A review of the literature as it pertains to the studies (I-III) in this dissertation follows in the subsequent sections.

Table 1. Overview of pre-existing literature

	Study I: Impact of pre-admission opioid treatment on one-year mortality following non-surgical intensive care		
Author, journal, year	Design, setting, period	Population, exposure, comparison groups, outcome	Results, limitations
• Mosher *et al.*[47] • Journal of Hospital Medicine • 2014	• Cohort • United States of America • 2009-2011	• 122 794 hospitalized veterans • Opioid use within 6 months prior to hospitalization • Chronic opioid therapy, occasional opioid use, and non-use • All-cause mortality during hospitalization or within 30 days	• There was no increased risk of all-cause mortality in unadjusted analysis. However, chronic opioid therapy was associated with an increased risk of all-cause mortality during hospitalization or within 30 days in fully adjusted models (aOR 1.19, 95% CI 1.10-1.29) • Did not account for timing of use or new vs. prevalent use
	Study II: Pre-admission opioid use and risk of death following incident myocardial infarction		
Author, journal, year	Design, setting, period	Population, exposure, comparison groups, outcome	Results, limitations
• Meine et al.[20] • American Heart Journal • 2005	• Cohort • United States of America • January 2001-June 2003	• 57 039 patients admitted with non-ST-segment elevation acute coronary syndromes • Intravenous morphine administered within 24 hours of presentation • Morphine vs. no morphine and morphine vs. nitroglycerine • In-hospital death, recurrent myocardial infarction, congestive heart failure, and cardiogenic shock	• Recipients of morphine were at an increased risk of all outcomes compared to those who did not receive morphine, as well as recipients of nitroglycerine. Comparing the risk of all-cause mortality between recipients and non-recipients resulted in an aOR 1.48 (95% CI 1.33-1.64) • Prior opioid use not accounted for, did not include ST-elevation segment myocardial infarction patients
• Puymirat et al.[48] • European Heart Journal • 2015	• Cohort • France (FAST-MI register) • 2010 and 2005	• 2438 ST-elevation myocardial infarction (STEMI) patients • Pre-hospital treatment morphine use • Morphine vs. no morphine • In-hospital mortality and one-year mortality	• Point-estimates suggest lower in-hospital death among pre-hospital morphine recipients (aOR 0.48, 95% CI 0.12-1.85) and lower one-year mortality (aOR 0.69, 95% CI 0.35-1.37) • Few exposed, few suffering the outcome [one-year mortality of 3.3% (morphine recipients) and 8.7% (no morphine)], prior opioid usage unclear
• Iakobishvili et al.[49] • The American Journal of Cardiology	• Cohort • Israel (ACSIS 2008 database)	• 765 STEMI and 993 nSTEMI patients • Pre-hospital and in-hospital intravenous opioid administration	• The point estimate suggests lower 30-day mortality among both STEMI patients (aOR 0.40, 95% CI 0.14-

• 2010	• 2010	• Opioid recipients vs. non-recipients • In-hospital, 30-day mortality, and 30-day death, recurrent infarction, repeat ischemia, stent thrombosis, or cerebrovascular event	1.14) and nSTEMI patients (aOR 0.56, 95% CI 0.11-2.07) • Small study, few recipients of opioids, few suffering the outcome, opioid recipients were more likely to receive care according to guidelines, prior opioid usage was unclear
• de Waha et al.[22] • Clinical Research in Cardiology: Official Journal of the German Cardiac Society • 2015	• Cohort (based on two prior randomized controlled trials) • Germany • August 2006-August 2009	• 276 STEMI patients undergoing primary coronary intervention • Intravenous morphine administration as part of STEMI treatment • Morphine recipients vs. non-recipients • Infarct size, microvascular obstruction, and myocardial salvage index. Clinical endpoint was composite end-point of death and non-fatal myocardial reinfarction	• Morphine recipients had poorer revascularization outcomes than non-recipients. Morphine recipients did not suffer a statistical significant increased risk of the composite end-point at 16 months follow-up • Small study, underpowered for the clinical endpoint, prior medication use uncertain
• Bonin et al.[21] • Journal of the American Heart Association • 2018	• Cohort • International (CIRCUS trial dataset) • April 2011-February 2014	• 967 STEMI patients; 554 received morphine • Intravenous morphine prior to primary percutaneous coronary intervention • Morphine vs. no morphine • Primary outcome was major adverse cardiovascular events within one year. Secondary outcomes included one-year all-cause mortality	• No statistical significant difference was found, but the point estimate for the primary outcome suggested an increased risk for recipients of morphine (HR 1.25 95% CI 0.96-1.62), though this was attenuated in the adjusted analysis [HR 1.04 (0.75-1.45)] • Small study, potentially underpowered, lack of knowledge about prior medication use
	Study III: Opioid initiation and risk of pneumonia requiring hospitalization and subsequent intensive care unit admission		
Author, journal, year	Design, setting, period	Population, exposure, comparison groups, outcome	Results, limitations
• Suzuki et al.[14] • American Journal of Hospice & Palliative Medicine • 2012	• Cohort • Japan • April 2004-December 2010	• 134 cancer pain patients who had been hospitalized • Opioid administration for >10 days and until 30 days after last administration • Morphine vs. oxycodone • Any infection based on either antibiotic administration, clinical diagnosis, blood culture, or biochemistry	• aOR 3.60 (95% CI 1.40-9.26) for suffering an infection during treatment with morphine compared to oxycodone • Small study size, patients in active immunosuppressive treatment, such as radiation or neoplastic therapy, confounding by indication, residual confounding due to severity of cancer,

			different cancer disease, and comorbidity, which were not accounted for
• Shao et al.[13] • Clin J Pain • 2017	• Cohort study • China • Jan 2013-October 2014	• 303 stage IV cancer patients in palliative care • Opioid-consumption >14 days and until 30 days after last administration • Morphine vs. oxycodone vs. fentanyl vs. combination • Any infection defined by a positive microbial culture test, and a clinical diagnosis combined with relevant biochemistry	• No difference according to type of opioid used (morphine 23.5%, oxycodone 24.4%, fentanyl 20.6%; p=0.403), binominal regression using morphine as the reference group found no difference: oxycodone aOR 1.05 (95% CI 0.44-2.51), fentanyl aOR 0.84 (95% CI 0.39-1.82) • Small size, lack of information on comorbidity and other medication, highly select study population, reducing generalizability
• Schwacha et al.[50] • The American Journal of Surgery • 2006	• Nested case-control • United States of America • 1997-2002	• 187 burn patients suffering an infection and 187 length-of-stay-, age-, and burnt total body surface area-matched controls • Cases definition was any complication of infectious etiology during hospitalization • Stratified into either high or low opioid use during administration prior to complication	• Cases generally used higher doses (14.0 vs. 10.0 opiate equivalents) and had a longer period of use (17 days vs. 10 days) of opiates compared with controls. This was modified by total body surface area burnt, with a decreasing relative risk of being in the high-usage group with increasing area • Lack of information on comorbidity and other medication, lack of information on specific opioids used by cases/controls, small size, highly selected study population, reducing generalizability
• Oppeltz et al.[51] • International Journal of Burns and Trauma • 2015	• Cohort study • United States of America (Texas) • 2006-2009	• 180 trauma patients without chronic opioid use • Injury severity score and opioid use • High vs. low opioid usage • Opioid use, length of stay, and infection rates	• In the intermediate injury group, infection rates were higher for patients using high doses of opioids compared to patients receiving low doses among both mechanically ventilated (aOR 1.86) and non-mechanically ventilated patients (aOR 3.96). Conflicting results in mild and severe trauma groups • Lack of information on comorbidity and other medication, lack of information on specific opioids used by cases/controls, small size, highly selected study population, reducing generalizability
• Dublin et al.[12] • Journal of the American Geriatrics Society	• Case-control study	• Community-dwelling adults aged 65-94 years • 1039 cases matched for age, sex, and calendar year with 2022 controls	• Current opioid use was more frequent among cases (13.9%) than controls (8.0%), resulting in increased risk of pneumonia of current users compared to

• 2011	• United States of America (Group Health) • 2000-2003	• Cases definition was pneumonia defined by ICD-9 codes with validation by medical record review • Preceding opioid use was identified and classified as current (5-60 days prior), past use (61-365 days) and non-use (no prescription in prior year)	non-users (aOR 1.38, 95% CI 1.08-1.76). Particularly high risk was observed among new users (aOR 3.24, 95% CI 1.64-6.39) and users of immunosuppressive opioids (aOR 1.88, 95% CI 1.26-2.79) • Low numbers of opioid users, lack of active comparator
• Wiese et al.[16] • Arthritis and Rheumatology • 2016	• Self-controlled case series • United States of America (Tennessee Medicaid) • 1995-2009	• 13 796 eligible rheumatoid arthritis patients yielding 1790 cases with a hospital admission for serious infection • Time-varying opioid exposure (current, recent, or non-use) • Hospitalization due to serious infection defined by discharge code	• More serious infections during periods of current use of opioids (aIRR 1.39, 95% CI 1.19-1.62), new use associated with highest risk (aIRR 2.38, 95% CI 1.65-3.42). In secondary analysis, the point estimate suggested an increased risk of pneumonia, though the confidence interval includes 1.00 • Lack of information on comorbidity and indication for opioid, resulting in a highly selected study population, reducing generalizability
• Wiese et al.[15] • Annals of Internal Medicine • 2018	• Case-control • United States of America (Tennessee Medicaid) • 1995-2014	• TennCare enrollees • 1233 cases matched with 24 399 controls for age, index date, and county of residence • Current, recent, remote, and non-users of opioids • Cases definition was laboratory-confirmed invasive pneumococcal disease	• Current use was associated with an increased risk of invasive pneumococcal disease (aOR 1.62, 95% CI 1.36-1.92). Risk increased with the immunosuppressive potency of opioids, though confidence intervals overlapped. Secondary analysis found a higher risk for new users (aOR 2.44, 95% CI 1.49-4.00) • Low numbers of current (n=311) and new users (n=23) of opioids
• Long et al.[19] • The American Journal of Gastroenterology • 2013	• Case-control • United States of America (IMS Health Inc., LifeLink Health Plan Claims Database) • 1997-2009	• 4856 patients with inflammatory bowel disease were matched for age, gender, geography, and index date to 18 928 controls • Opioid use vs. no use • Cases definition was the ICD-9 code for pneumonia combined with either a prescription for an antibiotic or hospitalization	• Opioid use was independently associated with increased risk of pneumonia (OR 2.28, 95% CI 2.09–2.48) • Restricted to patients <64 years old, no stratification on type of opioid, selected study population, reducing generalizability

• Vozoris et al.[18] • European Respiratory Journal • 2016	• Cohort • Canada (Ontario) • 1 April 2007-31 March 2012	• 130 979 community-dwelling adults suffering from chronic obstructive pulmonary disease (COPD) • Incident opioid use vs. no opioid use • Follow-up was 30 days and outcomes were: outpatient respiratory exacerbation, emergency room visit due to COPD or pneumonia, hospitalization for COPD or pneumonia, ICU admission during hospitalization for pneumonia or COPD, COPD or pneumonia-related mortality, all-cause mortality	• The point-estimate suggested an increased risk of hospitalization due to COPD or pneumonia among incident opioid users (HR 1.08 95% CI 0.97–1.21). There was no increased risk of subsequent ICU admission (HR 0.99 95% CI 0.74–1.33). However, there was increased COPD, pneumonia-related mortality, and all-cause mortality. • Restricted to COPD patients and lack of active comparator
• Won et al.[52] • The Journals of Gerontology. Series A, biological sciences and medical sciences • 2006	• Cohort • United States of America • 1998-2000	• 21 380 nursing home residents aged 65 years or older • Analgesic used through three consecutive quarters • No analgesics compared to no opioids, long-acting opioids, and short-acting opioids • Study looked at a wide range of outcomes, including quality of life and risk of adverse events (including pneumonia)	• Long-term users of opioids did not suffer an increased risk of pneumonia, regardless of whether they were using long-acting opioids (propensity score adjusted OR 0.56, 95% CI 0.12-2.52) or short-acting opioids (OR 0.70, 95% CI 0.32-1.50) • Small number of users, only prevalent users, few patients suffering the outcome

OR=odds ratio, IRR=incidence rate ratio, HR=Hazard ratio, a=adjusted, STEMI=ST-segment elevation myocardial infarction, nSTEMI=non- ST-segment elevation myocardial infarction, ICD=International Classification of Disease

Study I: ("Intensive Care Units"[Mesh] OR "Critical Care"[Mesh]) AND "Prognosis"[Mesh] AND "Analgesics, Opioid"[Mesh] (87 hits, no studies of prognosis, 1 study found through reference lists)

Study II: ("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action]) AND "Myocardial Infarction"[Mesh] (473 hits, 3 studies of prognosis, 2 additional found in reference lists and from own library)

Study III: ("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action]) AND ("Pneumonia"[Mesh] OR "Infection"[Mesh]) (1033 hits, 4 studies of risk, 6 studies found in reference lists and from own library)

Opioid use and intensive care

Intensive care units (ICUs) are highly specialized wards within a hospital designed for the observation, diagnosis, and treatment of critically ill patients with potentially reversible, developing, or manifest failure of one or multiple organs.[53] ICUs are classified into three levels depending on their staffing, equipment, and potential in-hospital collaborators.[53,54] All 43 Danish ICUs are part of the public healthcare system. There are approximately 32,000 ICU admissions each year spread out over 372 beds.[55] With 6.6 ICU-beds per 100,000, the Danish ICU-bed coverage is below the European average of 11.5 beds per 100,000.[56]

Intensive care patients make up a heterogeneous group of patients suffering from many different underlying diseases, with their primary common denominator being admission to an ICU. Admission depends on a clinical evaluation of not only the severity of referral disease, but also of the underlying disease, comorbidity, potential for improvement, and even the capacity of the ICU.[54] Common organ dysfunctions in patients admitted to an ICU include respiratory, cardiovascular, cerebral, and renal dysfunction. As such, the cost of care in this heterogenic group of patients is high, as is mortality, with a 30-day mortality of 11% to 27% depending on comorbidity burden and admission diagnosis. [57-60]

Opioids have remained one of the mainstay analgesics used in ICUs, with more than 80% of all patients receiving an opioid at least once during their stay.[61-63] Opioids have multiple well-established side effects, including respiratory depression, delirium, muscle rigidity, reduced gastrointestinal motility, nausea, and vomiting. [61,62] All of these adversely affect prognosis following ICU admission by increasing length of stay,[64-67] length of mechanical ventilation,[65-67] and mortality.[65-69]

No prior study has examined the mortality associated with prevalent opioid use among patients admitted to an ICU. A single study restricted to hospitalized veterans found an increased risk of all-cause mortality within 30 days of hospitalization in association with chronic opioid therapy [OR 1.19 (1.10-1.29)].[47] In addition, a growing body of evidence outside the ICU setting suggests that prevalent opioid use may increase the risk of myocardial infarction,[9-11,70] stroke,[71-74] and venous thromboembolism,[75,76] suppress

the hypothalamus-pituitary-adrenal hormonal axis with subsequent depression of cortisol levels,[61,77-80] and modulate the immune system.[16,81-84] These effects may adversely affect prognosis following ICU admission.

Opioid use and myocardial infarction

According to the WHO, myocardial infarction (MI) is defined by the presence of myocardial cell necrosis following ischemia, which in combination with one or more clinical signs (ischemia-related symptoms, electrocardiographic changes, or imaging of new ischemic changes) is considered "acute MI".[85,86] MI remains a common disease, with approximately 8000 patients admitted yearly in Denmark despite an overall decreasing incidence since the 1980s.[87] Furthermore, despite a nearly 50% decrease since 1988, 30-day mortality remains high at 15%.[87] MI can be classified into five types according to the mechanism of injury.[86,88] Type 1 is plaque erosion/rupture with thrombus formation, type 2 is an imbalance in oxygen supply/demand to myocardial tissue, and type 3 is sudden unexpected death with symptoms suggestive of MI.[88] Types 4 and 5 are iatrogenic, due to either primary coronary intervention or myocardial surgery.[88]

For initial treatment purposes, MIs are further classified depending on electrocardiographic patterns, as either ST-elevation MI (STEMI) or non-ST-elevation MI (nSTEMI).[86,89,90] Acute phase treatment for STEMI is immediate revascularization with either percutaneous coronary intervention or, if that is not available, fibrinolysis.[89] In contrast, patients suffering from nSTEMI are not offered immediate revascularization, but rather anticoagulants.[91] However, similar to patients suffering STEMI, they will receive treatment with aspirin and platelet inhibitors. Following acute phase treatment, nSTEMI patients will, depending on imaging, be offered either percutaneous coronary intervention with stenting or coronary artery bypass graft.[91] Additional treatment includes rehabilitation, lifestyle changes, and drug therapy, including aspirin and platelet inhibitors, for both types.[89-91]

Cardiovascular risk associated with prescription opioid use has not been well studied. The few prior studies indicate that opioid users may be at increased risk of MI, with the risk increasing with cumulative use. [9-11,70] Two of these studies found that the MI risk associated with opioid use was greater

than that associated with the use of COX-2 inhibitors.[9,70] One study found an increased risk of cardiovascular death (defined as acute death from CHD, stroke, heart failure, sudden death, vascular pathology, and other CVD causes) but only an increased risk among females for coronary heart disease (defined as nonfatal MI or acute death). [11] The underlying cause of this increased risk remains unclear.

As explained above, opioid users may suffer increased risk. In addition, both observational studies and sub-group analyses from randomized clinical trials suggest that treatment with morphine to quell pain during an MI may be associated with worse prognosis.[20-22,92,93] Meine et al. were the first to examine the prognostic implications of opioid administration in relation to nSTEMI; they found opioid administration to be associated with an increased risk of all-cause mortality.[20] Subsequently, the only sub-group in which pre-hospital ticagrelor administration did not improve outcomes in the ATLANTIC trial was in the sub-group of patients who received opioids during acute MI.[92] Bellandi et al. showed that morphine recipients suffer higher residual platelet reactivity and poorer myocardial reperfusion, though morphine use was not an independent risk factor.[93] Similar to Bellandi et al.,[93] de Waha et al. demonstrated that opioid treatment during MI resulted in poorer revascularization, but this apparently did not translate into higher mortality, though the study was underpowered for this endpoint.[22] However, three observational studies found no increased risk associated with opioid administration during acute MI, though these studies suffered from few exposed, few outcomes, differences in the quality of treatment favoring opioid exposure, and/or lack of information on baseline opioid usage.[21,48,49] Multiple plausible pharmacological mechanisms may explain the observed worse prognosis, including opioids' effects on platelet aggregation (observed both *in vitro* and *in vivo*[94,95]), drug interactions with P2Y12-receptor antagonist anticoagulants, which are commonly used as part of initial treatment and secondary prevention,[96-98] or opioid-induced depression of cortisone levels.[99] These findings have already resulted in morphine being downgraded to a class IIb recommendation for managing nSTEMI,[91] and caution has been advised in the guidelines for treating STEMI.[89] The studies thus far have focused on opioid administration during the acute phase of MI, but as prevalent opioid users

would already be exposed at the time of suffering the MI, it is plausible they may constitute an at-risk group suffering a worse prognosis.

Opioid use and pneumonia

Pneumonia is one of the leading causes of morbidity and mortality, with more than 1.5 million hospital contacts annually and 15.9 deaths per 100 000 person-years in the US.[100,101] Severe cases of pneumonia require ICU admission 5-30% of the time,[102,103] and mortality is high in this group of patients, ranging from 20% to 40%.[104-107]

Opioid users may be at increased risk of pneumonia through multiple mechanisms, ranging from associated lifestyle to an opioid-related increase in the risk of aspiration[108,109] and respiratory depression. In addition, select opioids exert an immunomodulatory effect, resulting in decreased natural-killer cell and macrophage activity, impaired migration of neutrophils and macrophages, and decreased cytokine production.[82,84,110-113] Based on current knowledge, opioids can be divided into three groups: opioids with a strong immunosuppressive effect (codeine, morphine, and fentanyl), opioids with a weak immunosuppressive effect (oxycodone, tramadol, buprenorphine, and hydromorphone), and opioids with unknown immunomodulatory effect (ketobemidone, nicomorphine, pethidine, pentazocine, tapentadol, and dextropropoxyphene).[82]

However, the clinical relevance of opioid-induced immunosuppression remains sparsely investigated. Studies in humans have been conducted primarily among injection drug users and opioid abusers, finding an increased risk of viral and bacterial infections.[83,114] However, recent studies examining infections in other groups, such as cancer patients (infections),[14] arthritis patients (severe infections),[16] inflammatory bowel disease patients (pneumonia),[19] burn patients (infections),[50] trauma patients (infections),[51] chronic obstructive pulmonary disease patients (pneumonia),[18] and older adults (pneumonia and invasive pneumococcal disease),[12,15] also revealed an increased risk among opioid users. Notably, the two case-control studies assessing the risk of pneumonia and invasive pneumococcal disease among older

adults found an association between immunosuppressive opioids and the higher risk compared to non-immunosuppressive opioids, though one of them had largely overlapping confidence intervals; thus, the clinical impact of opioids' immunosuppressive potential remains controversial.[12,15] In seeming contrast, two studies found no increased risk of infection associated with opioid use among stage IV cancer patients[13] and nursing home residents.[52] The study by Shao et al. was small and in a highly select patient group suffering from severe disease that may increase the risk of infections, which would make it difficult to detect differences when comparing different opioids.[13] The study by Won et al. required opioid usage for at least 9 months prior to the index date and, thus, only included (non-malignant) long-term users.[52] However, in a study of healthy participants, the immunosuppressive effect was already present within 24 hours of incident opioid administration.[115]

Aims

The overall aim of this thesis was to examine the risk and prognosis of critical illness associated with opioid use. Therefore, in study I we explored the prognosis of current and prior opioid users following ICU admission by comparing them to non-users. In study II, the aim was to examine the impact of current and prior opioid use on all-cause mortality following incident MI. In study III, we investigated the risk of contracting pneumonia requiring hospitalization and the subsequent risk of ICU admission among new users of opioids compared to new users of non-steroidal anti-inflammatory drugs (NSAIDs).

Methods

Setting

All studies were performed in Denmark in the setting of universal tax-paid healthcare. The state provides all Danish citizens with free and unrestricted access to general practitioners and, through these, equal and free access to hospital care. In addition, the system includes partial reimbursement for prescribed drugs to ensure the availability of required medication.[116]

Data sources

Denmark as a cohort

Denmark provides the ideal setting for pharmacoepidemiological research due to a longstanding tradition of prospectively recording administrative and health information on all Danish citizens at an individual level with unambiguous record linkage between registries.[117] The earliest inception of such registries in Denmark dates back to 1645, when data on births, marriages, and deaths were entered into church files. [118,119] Today, a plethora of registries exist, spanning from classical medical registries over clinical databases to registries with comprehensive information on socioeconomic status. Unambiguous cross-linkage of registries is made possible by the civil registration number introduced in 1968 with establishment of the Civil Registration System (CRS). Since then, all Danish residents are designated a unique 10-digit personal civil registration number at birth or following immigration, and it is possible to envision the entire country as a single cohort.[117,118]

Danish Civil Registration System

As mentioned above, the Danish CRS was established in 1968 and records the place and date of birth, civil status, and vital status, including date of death or emigration.[119] The unique 10-digit personal civil registration number allows for individual-level linkage with other registries.

Danish National Prescription Registry

The National Prescription Registry (NPR) was established in 1994 and is considered complete and valid since 1 January 1995.[120] The registry is based on pharmacy reports, capturing all dispensed prescriptions. The NPR allows linkage of prescription redemption on an individual level except for drugs dispensed within hospitals, as hospital pharmacies do not report individual-level information. Information reported by pharmacies includes the dispensing date, package size, strength, form, and Anatomical Therapeutic Chemical (ATC) code of the drug dispensed.[120]

The Danish National Health Service Prescription Database

The Danish National Health Service Prescription Database (DNHSPD) was established in 2004 and contains similar information as the NPR, with the primary difference being that the DNHSPD only captures prescriptions that are part of either the general or individual reimbursement program. In short, the general reimbursement program in Denmark covers most prescriptions in Denmark, including opioids, and is applied for by the pharmaceutical companies when a drug is released to the market. Thus, this reimbursement is automatic for all Danish citizens. The individual reimbursement program covers the prescription of drugs fulfilling certain criteria (e.g., treatment of chronic illness or palliative treatment). The prescribing physician has to apply for the individual reimbursement program on behalf of the patient. In contrast to the NPR, the CPR number is not anonymized and, thus, linkage outside of Statistics Denmark is possible.[121]

Danish National Patient Registry

The Danish National Patient Registry (DNPR) maintains records on more than 99.4% of all discharges from Danish non-psychiatric hospitals since 1977 and on outpatient and emergency room visits since 1995.[118,122,123] Each contact is assigned a primary diagnosis and up to 19 secondary diagnoses coded according to the *International Classification of Diseases, Eighth Revision* until 1994 and *Tenth Revision* since then. Procedure and surgical codes were coded according to a Danish classification system from 1977 until

1995, with adaptation of the Nordic medico-statistical committee classification of surgical procedures thereafter. The discharging physician or surgeon registers the diagnosis codes at time of discharge. Additional data can be "voluntarily" reported to the registry, typically following application by a given medical specialty society in establishing a clinical quality registry (e.g., coding of ICU admission and certain treatments administered during the ICU admission, which was used to establish the Danish Intensive Database).[55] Data reporting for the clinical quality registries is mandated by law and, in some cases, used for economic planning (i.e., not voluntary per se and monetarily incentivized). Data validity varies with specific diagnosis codes.[122,123] The disease codes used to define the cohorts in studies I and II can be found in their respective appendices in the Appendix of this dissertation. For study I, the identification of ICU admissions relied on legally mandated DNPR codes with high positive predictive value according to validation studies.[58,124] Codes used to define myocardial infarction for study II were recently validated and found to have a high positive predictive value (>90%).[125] In one study, hospitalization with pneumonia was validated to have a high positive predictive value (90%, 95% CI 82–95%), with 87% being community-acquired pneumonia.[126] The validity of community-acquired pneumonia, and other lower tract infections, acquiring hospitalization was also shown in another study to be modest, with a sensitivity of 71%, specificity of 92%, PPV of 71%, and NPV of 91%.[127]

Danish Psychiatric Central Research Register

The Danish Psychiatric Central Research Register (DPCRR) was digitized in 1969 and contains information on all psychiatric hospital admissions since that time. Since 1995, outpatient information has also been entered into the register. Diagnoses were classified according to ICD-8 until 1993, and since then according to ICD-10. Data validity varies with specific diagnosis codes. [118,128]

Integrated Database for Labour Market Research

The Integrated Database for Labour Market Research (IDA) has been updated by the end of November each year since 1980. Notably, it contains the employment status, education level, and income of all Danish citizens. Data are gathered from multiple other registries, including the CRS and tax authorities. [118]

Study design

All three studies were performed as nationwide population-based cohort studies. Two studies (I and II) included prior and prevalent opioid users, who were compared to non-users. Both of these studies were studies of prognosis – i.e., studies of the influence of a select risk factor (opioid use) on the course of a disease (ICU admission/myocardial infarction). The third study (III) utilized a new user active comparator design in which the initiators of NSAIDs constituted the comparison cohort. This study was a study of risk (risk of developing pneumonia requiring hospital admission), as well as prognosis (ICU admission following pneumonia requiring hospital admission). A brief overview of the study designs is provided in Table 2.

Table 2. Overview of study designs

	Study I	Study II	Study III
Objective	To examine the impact of opioid use prior to hospitalization on all-cause mortality among non-surgical patients admitted to an ICU	To examine the impact of current and prior opioid use on all-cause mortality following incident MI	To examine the effect of opioids on the risk of community-acquired pneumonia requiring hospitalization and risk of subsequent ICU admission
Design	Population-based cohort	Population-based cohort	Population-based new user, active comparator, cohort study
Data sources	CRS, NPR, DNPR, DPCRR, IDA	CRS, DNHSPD, DNPR	CRS, NPR, DNPR, DPCRR, IDA
Study period	January 2005 to December 2014	January 2006 to December 2012	July 1995 to December 2014
Index event	ICU admission	Incident myocardial infarction	Drug initiation (precipitated by 6-month washout)
Exposure	Opioid exposure prior to admission	Opioid exposure prior to admission	Initiation of opioids or non-steroidal anti-inflammatory drugs
Outcomes	All-cause mortality	All-cause mortality	Hospital admission and ICU admission
Covariates	Age, sex, income, education level, employment status, comedication, somatic and psychiatric comorbidities	Age, sex, civil status, CCI score, any recent surgery, and concurrent medication use	Age, sex, calendar year, civil status, income, education level, employment status, comedication, somatic and psychiatric comorbidities
Statistical method for confounder adjustment	Cox proportional hazards regression	Cox proportional hazards regression	Propensity score-based standardized mortality ratio weighting
Sensitivity analyses	Different exposure windows (15, 30, 45 and 60 days), exclusion of opioid prescriptions within 5 days prior to hospitalization, inclusion of SAPS-II scores into model	Different exposure windows (15, 30, 45 and 60 days)	Different follow-up windows (7, 14, and 30 days), trimming away those treated contrary to prediction
Stratified analyses	Stratification by sex, somatic and psychiatric comorbidity, comedication, and according to admission diagnosis	Stratification by type of MI, size of MI, PCI treatment, cancer, and COPD status	Stratified by deciles of propensity score and age

Study populations

The study population of study I included every Danish citizen with an incident admission to one of the Danish ICUs during the period 2005-2014 (the number of ICUs has varied slightly over time, 43 ICUs existed at the end of the study period).[55] This period was selected because the administrative code for ICU admission was first implemented in 2004 and not completed prior to January 2005.[55] Study II included everyone suffering an incident MI during the period 2006-2012 that was coded as a primary diagnosis. The reasoning for restriction to incident MI was two-fold. First, patients suffering a recurrent MI may differ significantly from patients suffering incident MIs, and their prognosis is worse.[129] Second, recurrent MI is prone to false-positive registration errors (i.e., a follow-up visit after incident MI), though the positive predictive value remains high at 88% (97% for incident MI).[125] Inclusion into study III was based on new use of either an opioid or NSAID. We defined new use as the first redeemed prescription of either drug with a 6-month lookback period; thus, the study period was July 1995 until the end of 2014. By design, we allowed the same subject to enter the cohort multiple times.

Exposure

Prescriptions

Drug use was defined using the NPR and DNHSPD. Opioids are under strict legal regulations and the potential for individual-level identification of users is generally high.[130] However, codeine is also available over-the-counter, specifically in formulations that combine it with acetylsalicylic acid. This over-the-counter sale has been increasingly regulated over the years and, thus, only purchasable by persons 18 years of age or older since 2011 and in small packages with a maximum of 20 pills since 2013. This has led to an increasing percentage of codeine sales moving from over-the-counter to prescription-based (28% since 2014).[42,131] These restrictions were introduced in an attempt to reduce suicide attempts by overdose and ran parallel to the regulations imposed on over-the-counter NSAIDs, which has made it possible to link 80% of all ibuprofen sales and 100% of all other non-aspirin NSAIDs on an individual level as of 2014.[42]

User categories

In studies I and II, we employed similar exposure definitions by classifying patients as current users, recent users, former users, or non-users depending on opioid use prior to the index date (I and II). This categorization was performed with the expectancy that the effect size of opioid use would be related to the recency of use if a true effect of opioids was present. Furthermore, if an effect for current users was observed compared to non-users, we expected former users to revert to a similar effect as non-users. Thus, current users were defined as having redeemed a prescription for opioids within 30 days prior to the index date. Subjects who had redeemed a prescription within 31-365 days prior to the index date were classified as recent users. Former users had no redeemed prescription for opioids within 365 days prior to the index date, but at least one prior record in the prescription database. Subjects with no record of a redeemed prescription for opioids between 1994 and the index date were considered non-users (comparison group). Our underlying assumption of a 30-day exposure window was based on Danish law mandating that the renewal of opioid prescriptions has to be preceded by in-person consultation and opioid prescriptions can only be redeemed once.[132] Notably, we also assumed that opioid users would consume a prescription in 30 days or less regardless of pack size. To check our assumptions, we utilized a data-driven approach by conducting a sensitivity analysis with different exposure windows (14, 30, 45, and 60 days) in both study I and study II.

It is well-established that long-term users are more likely to tolerate a given drug and, thus, their inclusion may lead to underestimating any potential effect.[133] Therefore, in studies I and II, we sub-divided current users into new users (first-ever prescription within 30 days prior to index date) and long-term users (first-ever prescription redeemed more than 30 days before the index date).

Comparisons of dosages and cumulative use in pharmacoepidemiology is generally done by utilizing the defined daily dose (DDD), which the WHO defines as “the assumed average maintenance dose per day for a drug used for its main indication in adults”.[134] As the main indication for opioids varies by specific compound and their potency exhibits similar variation, DDDs are a poor measure of comparison.[135]

Instead, a conversion table (see Appendices I and II) for converting the dose of any given opioid into the oral morphine equivalent (OMEQ) was constructed based on the available literature.[136-151] This conversion table was then used to calculate the OMEQ of the last opioid prescription prior to the index date for current users (studies I and II). Dosage was subsequently categorized as non-use, low (<375 OMEQ or 12.5 mg/daily), intermediate (375-750 OMEQ), high (751-1500 OMEQ), and very high (>1500 OMEQ).[152] Cumulative use was based on the total number of prescriptions redeemed.

The third study was a new user active comparator design[153] utilizing a 6-month washout period. Thus, each new initiation of an opioid or NSAID was counted as a separate observation, allowing each subject to potentially enter multiple times.

Outcomes

Data on all-cause mortality were collected from the CRS (studies I and II). Information concerning hospital admission and ICU admission (coded since 2005) was collected from the DNPR (Study III).

Covariates

Information on covariates was collected to characterize study populations, allow for confounder adjustment, and examine the effect of our exposure on the outcome in subgroups of patients. These covariates included age, sex, and civil status from the CRS, socioeconomic data from the IDA, comorbidities (including those in the Charlson Comorbidity Index [154] and psychiatric comorbidities) from the DNPR and DPCRR, and comedication from the NPR and DNHSPD.

Statistical analysis

Below is a brief summary of the statistical methods used in this thesis. A full description for each study can be found in Appendices I-III.

For each study, we tabulated the distributions of important variables according to exposure status prior to any adjustment. In all studies, we followed subjects from the index date until the outcome of

interest, death, or emigration, whichever came first. Absolute risks of all-cause mortality were estimated using the Kaplan-Meier method (studies I and II). For studies I and II, we used Cox proportional hazard regression analysis to compute measures of relative risk and adjust for important confounders. Estimates were provided as hazard ratios (HRs) with 95% confidence intervals (CIs). Log(-log) plots were used to graphically verify the validity of the assumed proportional hazards. In study III, propensity scores (i.e., the propensity for subjects initiating treatment with an opioid versus an NSAID) were calculated based on important confounders and risk factors using logistic regression. The calculated propensity scores were combined with standardized mortality ratio weighting to estimate the treatment effect among the treated (ATT), comparing the initiation of opioids versus the initiation of NSAIDs.[155,156] An active comparator was chosen in an attempt to ameliorate confounding by indication, as all patients would require pain relief. The rationale for choosing to estimate the ATT rather than the average treatment effect (ATE) utilizing, for example, the inverse-probability of treatment weighting was to estimate the potential effect among opioid users, rather than the potential population-wide effect. Following propensity score estimation and SMR weighting, we compared the distributions of important covariates to check whether balance was achieved.

Confounder selection was based on the plausibility of associations with both exposure and outcome without being an intermediary (i.e., a step on the causal pathway from exposure to outcome). Notably, not all confounders will cause the outcome, but they must affect the outcome under study[157]; for example, socioeconomic status does not directly cause death, but it is a proxy measure for underlying disease, which may. The plausibility of being a confounder was determined based on clinical knowledge and the pre-existing literature.

In all studies, a range of sensitivity analyses were included to ensure that our results were resilient to changes in our underlying assumptions. Thus, in studies I-III, we repeated the main analysis with changes to the exposure or follow-up windows (15, 30, 45, and 60 days in studies I and II; 7, 14, and 30 days in study III) to ensure proper categorization of exposure status. In study III, we repeated the main analysis,

trimming away those treated contrary to prediction to reduce residual unmeasured confounding (i.e., those with high propensity for the treatment with opioids who nonetheless were treated with NSAIDs).[156]

We also conducted a range of stratified analyses to investigate the presence of biological interaction or effect modification –a variation in the effect of exposure depending on the level of another covariate (the effect modifier). We stratified by important comorbidities in studies I and II, specifically by treatment and type of MI in study II, to examine effect modification.

Results

Opioid use and intensive care

We identified 118 388 patients with an incident non-surgical ICU admission during the study period. Fifteen percent of these patients were current users of opioids, with 94% having redeemed multiple opioid prescriptions, making them long-term users. Non-users comprised 40% of the ICU admissions, former users 30%, and recent users 15%. A high absolute risk of mortality was observed across all exposure levels throughout the follow-up period, with current users consistently suffering a much higher absolute risk than non-users (34.8% to 20.6%, respectively, within the first 30 days and 24.2% to 9.8%, respectively, at 365 days) (Table 3).

Within the initial 30-day period, the adjusted HR of all-cause mortality was 1.20 (95% CI 1.15-1.24) when comparing current users of opioids to non-users. Neither recent nor former users were at an elevated risk. Conditional on surviving the initial 30 days, current users remained at an elevated risk during the 31 to 365-day period, but recent users were also at an increased risk compared to non-users (HR 1.20, 95% CI 1.13-1.27). New users of opioids were at highest risk in both periods, but when examining sub-groups of cumulative use, patients having redeemed 2-10 prescriptions suffered the greatest risk (Table 3 in Appendix I). The strength of the last redeemed opioid prescription did not influence risk in the initial 30-day period, but point-estimates suggest a dose-dependent increase in risk during the 31 to 365-day follow-up period (Table 3 in Appendix I).

Estimates were generally stable across strata of comorbidity and comedication. However, during both follow-up periods, we observed effect-measure modification by solid tumor or metastatic solid tumor status, the presence of which greatly increased the magnitude of association between all-cause mortality and current use of opioids (Figures 1 and 2 in Appendix I).

No differences in risk were observed for the initial 30-day period when categorizing users based on opioid potential for immunosuppression (Supplemental Table 4 in Appendix I). During the 31 to 365-day period, the point-estimates suggest that users of opioids with a strong immunosuppressive effect were at a higher risk than users of opioids with a less pronounced effect, but the greatly overlapping confidence intervals should be noted.

Table 3. Association of the timing of use of opioids with all-cause mortality.

	30-day all-cause mortality			31 to 365-day all-cause mortality		
Exposure	Cumulative incidence % (95% CI)	Unadjusted HR (95 %CI)	Adjusted* HR (95% CI)	Cumulative incidence % (95% CI)	Unadjusted HR (95 %CI)	Adjusted* HR (95% CI)
Current users	34.8 (34.1-35.5)	1.84 (1.78 - 1.90)	1.20 (1.15 - 1.24)	24.2 (23.4-25.1)	2.72 (2.59 - 2.86)	1.47 (1.39-1.55)
New users	33.5 (30.7-36.6)	1.80 (1.61 – 2.00)	1.35 (1.21 - 1.51)	20.4 (17.5-23.8)	2.31 (1.94 - 2.74)	1.56 (1.31-1.87)
Long-term users	34.9 (34.1-35.6)	1.84 (1.78 - 1.90)	1.20 (1.16 - 1.25)	24.5 (23.6-25.3)	2.74 (2.61 - 2.88)	1.47 (1.38-1.56)
Recent users	24.4 (24.0-24.9)	1.45 (1.40 - 1.50)	0.98 (0.95 - 1.02)	12.9 (12.5-13.3)	2.00 (1.89 - 2.11)	1.20 (1.13-1.27)
Former users	29.1 (28.4-29.7)	1.21 (1.18 - 1.24)	0.92 (0.90 - 0.95)	19.0 (18.3-19.7)	1.34 (1.28 - 1.40)	0.96 (0.91-1.00)
Non-users	20.6 (20.2-20.9)	1	1	9.8 (9.5-10.1)	1	1

Abbreviations: CI, confidence interval; HR, hazard ratio

*Adjusted for age, sex, socioeconomic status, comorbidities, and concomitant medication use (as listed in Table 1, excluding number of opioid prescriptions and admission diagnosis).

Opioid use and outcome of acute myocardial infarction

A total of 67 742 patients suffered an incident MI during our study period. Non-users constituted 67% of these patients, former users 13%, recent users 10%, and current users 9%. Cumulative mortality was high at 365 days, increasing with the recency of use from 19.4% 95% CI 19.0-19.7 for non-users to 41.9% 95% CI 40.6-43.2 for current users (Table 4). Thus, current use of opioids at time of admission for MI was associated with increased risk of all-cause mortality (unadjusted HR 2.45, 95% CI 2.34-2.56). Risk was persistently increased for current users following adjustment for important confounders, but recent and former users were not at an increased risk. Notably, new users suffered the highest risk (adjusted HR 1.47, 95% CI 1.30-1.65). The greatest attenuation of the strength of association was by adjusting for cancer status. No dose-effect relationship was observed in analyses of cumulative use or prescription strength (Table 3 in Appendix II).

Effect modification by MI type, PCI treatment, and cancer status was observed in stratified analyses, particularly among new users (Table 4 in Appendix II).

Table 4. Association of all-cause mortality and timing of use of opioids prior to incident MI.

	0 to 365-day all-cause mortality		
	Absolute risk estimates	Unadjusted, HR (95% CI)	*Adjusted, HR (95% CI)
Non-users	19.4 (19.0-19.7)	1.00 (ref)	1.00 (ref)
Current users	41.9 (40.6-43.2)	2.45 (2.34-2.56)	1.32 1.26-1.39)
New users	42.8 (39.2-46.6)	2.55 (2.27-2.87)	1.47 (1.30-1.65)
Long-term users	41.8 (40.4-43.2)	2.43 (2.32-2.55)	1.30 (1.23-1.37)
Recent users	29.7 (28.6-30.9)	1.61 (1.53-1.69)	1.02 (0.97-1.08)
Former users	22.8 (21.9-23.7)	1.18 (1.13-1.25)	0.90 (0.86-0.95)

*Adjusted for age, sex, civil status, comorbidity category, any surgery, and concomitant medication use.

Opioid use and risk of pneumonia and subsequent intensive care unit admission

We identified a total of 14 837 124 instances of new use of either NSAIDs (n=11 285 112) or opioids (n=3 552 012) during the study period (Table 5). New users of opioids were generally male, older, married, and had lower income than new users of NSAIDs. Furthermore, new users of opioids generally had a larger comorbidity burden, specifically cancer, chronic obstructive pulmonary disease, prior pneumonia requiring hospitalization, and cardiovascular disease. As a consequence, new users of opioids were also more likely to take concomitant medication. Covariate balance was achieved by SMR-weighting based on propensity scores.

The absolute risk of pneumonia requiring hospital admission was low - 0.04% of NSAID initiators were hospitalized with pneumonia within 7 days compared to 0.23% of opioid initiators, resulting in a 6-fold increased risk associated with opioid initiation. Risk was attenuated following SMR-weighting based on propensity scores, but opioid initiators remained at an elevated risk of pneumonia requiring hospital admission compared to NSAID initiators (aOR 2.38, 95% CI 2.19-2.58). No difference was found in the strength of association observed when stratifying by the immunosuppressive potency of opioids except for the group of opioids whose immunosuppressive potency is yet to be established.

Among hospitalized patients, approximately 5% of NSAID initiators and 3.5% of opioid initiators were subsequently admitted to an ICU (Table 6). Interestingly, SMR-weighting and accounting for death as a competing risk yielded a lower risk of ICU admission for opioid initiators than NSAID initiators (aSHR 0.64, 95% CI 0.50-0.83). No difference was detected when stratifying by the immunosuppressive potency of opioids.

Estimates remained stable across sensitivity analyses, including across deciles of propensity scores, trimming patients treated contrary to prediction, restricting to a primary diagnosis of pneumonia, and restricting to incident admissions. The strength of association decreased with increasing follow-up time

for hospital admission, but even with a 30-day window opioid initiation was associated with an increased risk of hospitalization for pneumonia compared to NSAID initiation (Supplemental Table 3 in Appendix III).

Table 5: Risk of pneumonia requiring hospitalization within 7 days after drug initiation.

	Deaths without hospitalization, n (%)	Hospital admissions, n (%)	Crude OR (95% CI)	Absolute SMRW, n (%)	SMR weighted OR (95% CI)
NSAID, n=11 285 112	1729 (0.02)	4275 (0.04)	ref	11 131 (0.10)	Ref
Opioid, n=3 552 012	27 448 (0.77)	8331 (0.23)	6.20 (5.98-6.44)	8331 (0.23)	2.38 (2.19-2.58)
Strong, n=1 564 586	12 896 (0.83)	3660 (0.23)	6.19 (5.92-6.47)	3660 (0.23)	2.37 (2.18-2.59)
Weak, n=1 627 931	7347 (0.45)	4079 (0.25)	6.63 (6.35-6.92)	4079 (0.25)	2.54 (2.34-2.77)
Other, n=359 495	7205 (2.01)	592 (0.16)	4.35 (3.99-4.74)	592 (0.16)	1.67 (1.49-1.87)

Table 6: Risk of ICU admission within 30 days of hospitalization for pneumonia within 7 days after drug initiation, accounting for death as a competing risk.

	Absolute n (%)	Crude SHR (95% CI)	Absolute SMRW, n (%)	SMR-weighted SHR (95% CI)
NSAID, n=2809	142 (5.1)	ref	147 (5.2)	Ref
Opioid, n=6375	214 (3.4)	0.66 (0.54-0.82)	214 (3.4)	0.64 (0.50-0.83)
Strong, n=2556	79 (3.1)	0.61 (0.47-0.80)	79 (3.1)	0.59 (0.43-0.81)
Weak, n=3467	128 (3.7)	0.73 (0.58-0.92)	128 (3.7)	0.71 (0.53-0.93)
Other, n=352	7 (2.0)	0.39 (0.19-0.83)	7 (2.0)	0.38 (0.18-0.82)

Discussion

Main conclusions

We found that current users of opioids at the time of admission had a higher risk of 30-day and 365-day mortality following ICU admission compared to non-users. Estimates were stable across nearly all subgroups of patients; however, the association was much stronger among cancer patients than non-cancer patients. The immunosuppressive potency of opioids seemed to have little clinical impact. Similarly, we found that current users of opioids at the time of MI suffered a higher risk of death following their MI. New users suffered the highest risk, but long-term users were also at an increased risk compared to non-users. The estimates remained stable regardless of infarct size as estimated by peak troponin T levels. Lastly, we found that initiators of opioids were more likely to contract pneumonia requiring hospitalization within 7 days following initiation than initiators of NSAIDs. Risk was similar regardless of the immunosuppressive potency of opioids. Curiously, opioid initiators had a lower risk of subsequent ICU admission than NSAID initiators.

Methodological considerations

The purpose of all clinical research is to provide accurate, i.e., precise and valid, estimates, including of disease frequency or the risk of a given outcome associated with a given exposure. Randomized clinical trials are generally conducted in healthier patients than those actually receiving drugs in practice due to strict inclusion/exclusion criteria.[158] Thus, randomized clinical trials generally differ from routine clinical day use, especially if a paradigm shift has occurred leading to, for example, increased off-label prescription, as has been the case for opioids increasingly being used to treat chronic non-cancer pain.[158] Advantages of non-randomized studies over randomized studies is that they allow for observation of both the short- and long-term safety of drugs as used routinely in the clinical setting. Additional advantages include associated costs (though establishing a prospective cohort can be expensive, it typically allows for multiple studies), study size, and the possibility of investigating potentially unethical or unfeasible interventions (e.g.,

smoking or prevalent drug use as in studies I and II).[157] However, large valid datasets are required to accurately detect and estimate potential associations and, notably, no study is better than the data upon which it relies. A potential major drawback of registry-based studies is their reliance not only on the pre-existing registries to contain only the information needed, but also on the quality of said information. Without high quality data, it is impossible to attain accurate estimates. Errors threatening accuracy are traditionally classified as either systematic (affects validity) or random (affects precision) error.[159] In the following, we will account for each as it relates to the studies in this thesis.

Precision

Random error relates to the precision of the estimate and can generally be dealt with through increasing statistical efficiency or sample size. Traditionally, it is expressed through confidence interval width, which we have also elected to do in this dissertation. Confidence intervals should be interpreted as an interval in which the true estimate will fall with a frequency equal to the confidence level (traditionally 95%) if a study was repeated an infinite number of times under the assumptions of a correctly specified statistical model, an absence of systematic error, and that the confidence interval is correctly estimated.[160] In addition, the confidence interval contains information on the magnitude of the effect, as points towards the center of the range will be more compatible with the data than points towards the extremes.[160] Thus, interpretation of the confidence intervals should focus on the point estimate (effect size) and width of said interval to determine how compatible the data are with an association rather than, as has erroneously become common practice, as a pseudo-measure of statistical significance.[160,161]

The large number of subjects and outcomes in the three studies (due to the large nationwide registries) resulted in statistically precise estimates of our primary outcomes. Thus, the results of our primary outcome analysis are unlikely to be due to random error.[160] However, not all opioids were equally prescribed and, consequently, precision was poorer in some of the subgroup analyses, e.g., the analysis

risks associated with individual types of opioids in which random error may have a larger impact on our estimates.

Validity

Selection bias

As the name implies, selection bias stems from the selection of subjects compromising the study population in a way that skews the relationship between exposure and outcome compared to the underlying population.[159] Due to the population-based cohort design in which we relied on the combination of nationwide registries and a universal healthcare system guaranteeing free and equal access for all Danish citizens, none of our studies are likely to be susceptible to any major selection bias. However, in study II, patients suffering sudden cardiac death outside of a hospital or who did not receive attempts at resuscitation in the emergency room were not included due to the registration practice of the DNPR. This potential selection bias is unlikely to have differed much across exposure groups. Regarding study III, ibuprofen (200 mg) is sold over-the-counter in Denmark, making linkage on an individual-level impossible. This sale constitutes one-third of all ibuprofen sales; thus, 66% of ibuprofen and 100% of all other NSAID sales are captured by prescription registries in Denmark.[131] Patients using over-the-counter ibuprofen were not included in the analysis, but they are likely less comparable to opioid initiators than prescription NSAID users.

Information bias

Information bias arises from systematic error in the collection or measurement of exposure, covariates, or outcomes from study subjects. Such misclassification can be uniform across other study variables (non-differential) or vary with other study variables (differential). Differential misclassification can potentially magnify or diminish an observed effect depending on the relationship across variables, which can be difficult to predict. On the other hand, non-differential misclassification of an exposure or outcome tends to bias towards the null provided the variable is dichotomous.[159]

Misclassification of exposure

Both opioid use (studies I-III) and NSAID use (study III) was defined using prescription redemption registries. Importantly, these registries did not contain data on in-hospital opioid use, resulting in a potential risk of misclassification of exposure, as patients may have used opioids during an admission prior to the index date. In addition, a risk of misclassification arises from low compliance/non-adherence among those actually prescribed the drugs. However, the risk of patients not adhering to treatment is lessened by the requirement that patients pay out-of-pocket for a portion of prescription costs and an increased vigilance among doctors in their prescription of analgesics, especially opioids, as opioid prescription is monitored by the state. In both study I and study II, there is a risk of misclassification of exposure status concerning recency. In study III, exposure may be misclassified because ibuprofen is available over-the-counter and, thus, theoretically available to all included patients, even during the 6-month wash-out period. Reassuringly, sensitivity analyses with different exposure windows did not substantially alter our findings. Usage during the hospital admission following the index date is not an issue in regards to misclassification of exposure, as exposure status was determined at hospital admission (similar to an intention-to-treat analysis). Opioid initiation during the index hospitalization would bias the estimates towards the null and does not explain any of the associations found in any of the three studies.

Misclassification of outcome

We relied on vital status information from the CRS to identify all-cause mortality. Mortality data are complete in Denmark with daily updates.[119] The identification of ICU admissions relied on legally mandated DNPR codes with high positive predictive value according to validation studies.[58,124] The coding of pneumonia in the Danish National Patient Registry has been validated in two studies, which reported a high positive predictive value (>90%) among both cancer and stroke patients.[162,163] The validity of community-acquired pneumonia, and other lower tract infections, requiring hospitalization has been shown to be modest, with a sensitivity of 71%, specificity of 92%, positive predictive value of 71%, and negative predictive value of 91%.[127] However, it seems unlikely that prior medication use should differentially

influence the validity of hospital coding. In conclusion, misclassification of outcome is unlikely to have majorly affected the estimates in our studies.

Protopathic bias

Protopathic bias is a common issue in pharmacoepidemiological studies and denotes drug initiation due to prodromal or unrecognized symptoms of the disease of interest, which may lead to erroneous inference of reverse causality.[164] In studies I and II, the outcome of interest was all-cause mortality and, thus, the risk of reverse causality was not a concern. In study III, we relied on the study design (new user active comparator) to alleviate, at least in part, the issue of protopathic bias, as theoretically the active comparator should serve as an equal alternative to the exposure of interest at the time of initiation; initiators of either should be equally likely to have initiated due to prodromal or unrecognized symptoms (e.g., in study III due to pleuritis). Such balance was further sought by utilizing propensity scores to weight the cohort based on the propensity of initiating opioids.

Confounding

Confounding can be simplified as a mixing of effects.[159] That is, the estimated effect results from the effect of interest (the effect of the exposure on the outcome) and the effect of an extraneous factor that is imbalanced among those exposed. To act as a confounder, a factor must be associated with both exposure and disease without being affected by either.[159] Unlike selection bias and information bias, confounding can be dealt with during both the design phase and the analytical phase. Observational studies are generally susceptible to the presence of confounding due to imbalances in both measured and unmeasured baseline covariates.[157] Pharmacoepidemiological studies specifically suffer from so-called confounding by indication; the existence of an association between the indication of the drug under investigation and the outcome of interest (e.g., cancer pain) is an indication for opioid treatment but can also be a sign of poor prognosis.[164]

In studies I and II, we utilized regression analysis and stratification to account for potential confounding, and we conducted a range of sensitivity analyses to address confounding by indication (e.g.,

restriction to certain patient groups). In study III, we relied on propensity scores and SMR-weighting to balance covariates at baseline. Confounding by indication was addressed by utilizing the active comparator design, which theoretically improves the comparability of comparison groups. However, NSAIDs are not a perfect active comparator, though currently the clinically most meaningful, for opioids because indications vary; therefore, we utilized propensity scores to weight study participants to improve comparability. In all studies, we lacked data on potentially important confounders, such as frailty, smoking, and physical activity. We attempted to address this unmeasured confounding by including socioeconomic factors (studies I-III), diagnosis of chronic obstructive pulmonary disease (studies I-III), and drugs with paradoxical relationships to mortality as shown by Glynn et al.[165] (study III) as proxy measures. However, we are unable to exclude the potential for residual confounding by unmeasured confounders.

Opioid use and intensive care

This was the first study to directly assess all-cause mortality among opioid users following ICU admission. A single study has examined the risk of all-cause mortality among veterans in chronic opioid therapy following any hospital admission.[47] In agreement with our findings, they found an increased risk of death within the first 30 days following hospital admission (aOR 1.19, 95% CI 1.10–1.29) [47]. Interestingly, Mosher et al. found no increased risk of ICU admission among opioid users compared to non-users.[47]

Multiple theoretically plausible explanations exist for the increased risk of all-cause mortality following both hospitalization and ICU admission. Opioids have several well-established adverse effects, including respiratory depression,[24] increased risk of aspiration,[166,167] and increased risk of delirium,[168,169] which are all associated with poorer outcomes in the ICU setting. In addition, opioids are increasingly scrutinized for their potential to increase infection risk and have repeatedly been associated with an increased risk of infection in diverse patient populations. [12-16,19,50,51] This is in line with our findings that current opioid users are more likely to have a main diagnosis of pneumonia or sepsis than non-users. The prognosis following infection was examined in a newly published study of sepsis patients.[17] Zhang et al.

found that patients treated with opioids during sepsis suffer a substantially worse prognosis than non-recipients of opioids (aOR 6.24, 95% CI 4.41-8.83).[17] This confirms the findings of prior studies in mice.[170-174] Interestingly, we found greatly overlapping confidence intervals when stratifying users by the immunosuppressive potential of the opioid they received. Unfortunately, Zhang et al. did not account for type of opioid used, but compared opioid usage regardless of specific opioid to non-usage.[17] Based on our findings, the direct immunosuppressive potential of an opioid may not be substantial enough to be clinically significant in the setting of the ICU, where other factors may more greatly affect the prognosis of the patient. Furthermore, opioids have been associated with an increased risk of MI[9-11,70] and poorer outcomes following cardiac arrest,[175] which could be an alternate explanation for the poorer prognosis. Lastly, opioids have been associated with endocrinological changes, such as cortisol depression, which may explain, at least in part, our findings of increased all-cause mortality.[78,80] Currently, the degree to which each of the above-proposed mechanisms contribute to the observed increased all-cause mortality is unclear. Future research to elucidate these mechanisms may allow for targeted intervention.

Opioid use and myocardial infarction

No prior study has assessed the association between prevalent opioid use and mortality following MI. However, a few observational studies have investigated the effect of morphine administered as part of treatment for acute coronary syndrome, with conflicting findings.[20-22,48,49] In 2005, Meine et al. evaluated the effect of intravenous morphine administered within 24 hours of presentation with nSTEMI in a cohort of 57 039 patients. They found an increased risk of all-cause mortality for morphine recipients compared to non-recipients (aOR 1.48, 95% CI 1.33-1.64). Following this study, the recommendations for morphine administration in nSTEMI patients was downgraded to IIb by the American Heart Association and, thus, only recommended in the absence of effects of other anti-ischemic medications, such as nitroglycerin.[91] Four smaller studies have been conducted to investigate whether these findings could be expanded to STEMI patients, but conflicting findings have been reported. In a study of 967 STEMI patients, the point estimates suggested that opioid recipients may suffer an increased risk of nearly all cardiovascular complications

within 1 year [HR 1.25 95% CI 0.96-1.62).[21] In another study of 291 STEMI patients, recipients of morphine were not at an increased risk of the composite endpoint of myocardial reinfarction or death within 16 months, despite suffering larger infarcts, microvascular obstruction, and less myocardial salvage following reperfusion.[22] Lastly, two studies found morphine recipients to be at a seemingly reduced risk of 30-day mortality (aOR 0.40, 95% CI 0.14-1.14) [49] and 1-year mortality (aOR 0.69, 95% CI 0.35-1.37)[48] following STEMI. However, both of these studies included few recipients of morphine, and overall survival was remarkably high. One of these studies also included nSTEMI patients, among which they found a seemingly protective effect at 30-day follow-up (aOR 0.56, 95% CI 0.11-2.07).[49]

It is striking how similar the magnitude of the effect estimated by us based on a cohort of mixed nSTEMI and STEMI patients was to that of Meine et al.,[20] especially when restricting the analysis to the new users in our study (HR 1.47, 95% CI 1.30-1.65), which is the most appropriate direct comparison. Interestingly, we found the greatest risk to be among STEMI patients, with new users at the highest risk (aOR 2.39, 95% CI 1.69-3.37). Our findings are supported by compelling evidence that opioids, particularly morphine, interact with the standard of care dual anti-platelet therapy,[176] as well as some evidence that opioids may promote platelet aggregation.[94,95] Following the ATLANTIC trial, in which recipients of morphine were the only sub-group not to experience improved outcomes,[92] multiple studies of drug interactions between morphine and P2Y12 inhibitors have been conducted. Among these studies were the IMPRESSION trial and the study by Parodi et al.,[96] which found a delayed and decreased effect of P2Y12 inhibitors.[97] Furthermore, the PRIVATE-ATLANTIC substudy found that morphine administration appeared to be more important than the timing of ticagrelor administration.[177] Thus far, it is unclear whether this interaction translates into a hard clinical end-point, but caution is certainly warranted based on the current evidence and our findings.

Opioid use and risk of pneumonia

Our findings of an increased risk of pneumonia associated with opioid use adds to an increasingly convincing amount of evidence indicated that opioid users suffer an increased risk of infections in general, [13-16,50,51] as well as pneumonia specifically.[12,15,19]

The magnitude of our association for initiators (aOR 2.38, 95% CI 2.19-2.58) is well in line with other studies of new users among community-dwelling adults (Wiese et al.[15]: aOR 2.44, 95% CI 1.49-4.00; and Dublin et al.[12]: aOR 3.24, 95% CI 1.64-6.39). Our point estimate was slightly lower, though well within the confidence intervals of the other two studies.

It is remarkable that both of these studies including prevalent users found the highest risk to be associated with new use of opioids. Even more interesting, the single study that found no increased risk among community-dwelling adults included prevalent long-term users.[52] This seems to indicate that the risk associated with opioid use in relation to pneumonia wanes over time, whether due to a healthy user bias or due to the development of tolerance. This is in line with the study of healthy volunteers by Yeager et al., who demonstrated that the immunosuppressive effect of certain opioids is present within 24 hours of initiation.[115] However, when stratifying by immunosuppressive effect, we did not find any difference between users of opioids with strong immunosuppressive potency and low immunosuppressive potency. This is in agreement with the findings of Shao et al.,[13] but contrasts the findings of both Dublin et al.[12] and Suzuki et al.[14] The case-control study by Wiese et al. found increased risk, but with overlapping confidence intervals.[15] Though both Shao et al.[13] and Suzuki et al.[14] conducted studies of cancer patients and, thus, may lack comparability to our study, both Wiese et al.[15] and Dublin et al.[12] conducted their studies among community-dwelling adults. These conflicting findings may be due to our usage of an active comparator that plausibly also modulates the course of pneumonia,[178-180] whereas the other studies used non-users as their comparison group.

Mechanisms other than immunosuppression likely play a part in the increased risk of pneumonia associated with opioid use. For example, opioids could reasonably increase the risk of pneumonia via other potential mechanisms, such as reduced ventilation and nausea or reduced gastric motility leading to aspiration. Whether such mechanisms play a substantial role remains to be elucidated. Supporting the hypothesis of aspiration playing a potential role is a single study in which enteral co-administration of an opioid antagonist, such as naloxone, has been shown to reduce the risk of pneumonia among opioid-treated patients.[166] A single study counters reduced ventilation as the sole explanation by demonstrating an association between opioids and an increased risk of hospital-acquired pneumonia among patients with endotracheal intubation (i.e., protected airways).[181] Thus, any conclusion concerning potential mechanisms remains speculative.

Our somewhat puzzling finding that opioid users were less likely to be admitted to an ICU subsequent to pneumonia requiring hospitalization has a couple of potential explanations. One explanation is that doctors may be more likely to hospitalize an opioid user than an NSAID user, though this seems far-fetched. A more likely explanation is residual confounding by, for example, the severity of cancer, which we were unable to acquire data on and unable to balance using propensity score weighting. It is plausible that opioid initiators were more likely to suffer from late-stage cancer and, thus, ICU admission may have been contraindicated. Lastly, as mentioned above, NSAIDs may modulate the natural course of pneumonia, resulting in more complications that could result in a more frequent requirement for ventilation and, thus, ICU admission. [178-180]

Clinical implications

The studies in this dissertation form a compelling argument for caution when prescribing opioids. Study I provides evidence that critically ill opioid users constitute an at-risk population with a poor prognosis following ICU admission. Our finding that former users revert to the same risk as non-users is reassuring, though it needs to be confirmed in another setting. In contrast, the fact that new users suffered the highest

risk warrants special attention, as it may be possible to mitigate the poor prognosis by identifying preventable complications in the clinical course of opioid patients. Though the immunosuppressive potential of opioids has received some scrutiny, our findings suggest that it may have little impact on the prognosis in the ICU setting.

The inhibition of dual-anti-platelet therapy by opioids is well established, but the clinical significance on hard end-points has remained controversial. As the first study among prevalent users, study II lends credence to the other studies finding an association between opioid use and poor outcomes following MI. The findings that neither recent nor former users suffer increased risk warrant special attention on the pharmacological action of opioids and their interactions with other drugs in future studies. Our findings support the recommendation of the current guidelines for nSTEMI treatment, in which morphine should only be administered following the failure of other pain-quelling therapies, such as nitroglycerin.[91] Based on our findings and the pre-existing literature, this recommendation should probably be expanded to the guidelines for STEMI treatment.[89] Though the randomized double-blinded trial design is ideally suited to determine whether opioid administration in the acute phase of MI is safe, it seems unfeasible, if not downright unethical, to confirm our findings of a worse prognosis associated with prevalent opioid use using the randomized double-blinded trial design. Thus, confirmation of our findings will likely have to rely on other well-conducted observational studies.

Study III provides new evidence that new use of opioids is associated with an increased risk of hospitalization with pneumonia within 7 days of drug initiation. By conducting the first new-user active-comparator study utilizing propensity scores, we addressed some of the shortcomings of prior studies examining the risk of infection related to opioid use. Taken together, the current evidence creates a strong argument for caution, though the underlying mechanism remains elusive, as stratification by the immunosuppressive potential of opioids has produced conflicting results. However, in clinical practice, it may be prudent to err on the side of caution and, whenever possible, prescribe opioids with low

immunosuppressive potential until future studies have determined the clinical importance of such immunosuppression in different settings. Furthermore, consideration of preventive measures, such as pneumococcal and influenza vaccination, may be indicated in opioid-treated patients. The effectiveness of such preventive measures should be investigated in a future study.

As untreated pain is ethically unacceptable, opioids are likely here to stay as no good alternative currently exists; thus, it is important to fully elucidate the potential risks associated with treatment to properly assess the expected risk/benefit ratio of opioid treatment prior to instigation.

Perspective

Over the past few years, opioids have come under increased scrutiny from both the medical community and society in general. The current opioid epidemic in the US serves as a warning to the entire world and has highlighted the need for careful consideration in relation to opioid treatment and the importance of limiting the usage of opioids to those who truly need treatment. Multiple laws and guidelines have been and are being introduced in an effort to curb the toll of opioid-related addiction and overdose deaths by both limiting prescriptions and informing of alternatives to opioid treatment, such as neuroleptics, anti-depressants, psychotherapy, and lately, although controversial, medical marijuana. Another avenue worthy of attention which may help limit opioid usage is to strive to prevent (chronic) pain conditions from developing. Such research is already ongoing and advances into our understanding of the pathophysiology, risk factors and prevention of chronic pain has improved over the past decades.[182-184] However, it remains unlikely that pain can be fully prevented or that opioids can fully be replaced by other analgesics or pain-quelling therapies in the near future.

The findings in the three studies that form the basis of this dissertation emphasize the importance of the continued scrutiny of risk and prognosis associated with opioid treatment and the underlying clinical pathways leading to such associations. Considering the continued widespread use of opioids, there is a potential for major public health implications. Future research should focus on

identification of modifiable risk factors or preventable complications in the clinical course of disease among opioid users which may allow for mitigation of the poor prognosis associated with opioid use described in this dissertation. Thus, important questions concerning the underlying mechanisms, such as the clinical importance of immunosuppressive potency, potential for drug interactions, and endocrinological changes, should be investigated in future studies.

Summary

English

Opioid use has substantially increased internationally over the past decades. Well established adverse effects include constipation, respiratory depression, and delirium. A growing body of evidence suggests that other potential deleterious effects may arise owing to an effect on the cardiovascular, endocrine, and immune system. Such deleterious effects are all potentially highly impactful on both risk and prognosis of critical illness. As opioids have largely avoided scrutiny in this context, we conducted three nationwide register-based cohort studies to remedy this.

Study I - *Impact of pre-admission opioid treatment on one-year mortality following non-surgical intensive care*. In this cohort study we identified 118,388 incident non-surgical intensive care patients and compared 0-30 day and 31-365 day all-cause mortality for opioid users with that of non-users. Current use of opioids at time of admission was associated with an increased all-cause mortality both short-term [Hazard Ratio (HR) = 1.20 (1.15 - 1.24)], and long-term [HR 1.47 (1.39-1.55)].

Study II - *Pre-admission opioid use and risk of all-cause mortality following incident myocardial infarction*. This cohort study included all 67,742 patients suffering an incident myocardial infarction from 2006 to 2012. Current use of opioids at time of incident MI was associated with increased one-year all-cause mortality [HR 1.32 (1.26-1.39)] when compared with non-users.

Study III - *Opioid initiation and risk of pneumonia requiring hospitalization and subsequent intensive care admission*. This cohort study included all initiations of opioid (3,552,012) and prescription NSAID use (11,285,112) from 1995 to 2014, resulting in 14,837,124 new drug initiations. New use of opioids was associated with an increased risk of pneumonia requiring hospitalization when compared with NSAID initiation [weighted odds ratio 2.38 (2.19-2.58)]. However, a reduced risk of subsequent ICU admission [sub-distribution hazard ratio 0.64 (0.50-0.83)] was observed for opioid initiators.

In conclusion, this thesis has shed light on the effects of opioid use on both risk and prognosis of critical illness and thus provided information relevant to clinical decision-making as well as in guiding future research into the implications of the worldwide increasing opioid consumption.

Dansk

Det international opioidforbrug er steget voldsomt over de seneste årtier. Velkendte bivirkninger inkluderer forstoppelse, respiratorisk påvirkning og delir. Baseret på en stadig større mængde evidens har opioider sandsynligvis også andre skadelig virkninger grundet deres indvirkning på det kardiovaskulære, endokrine og immunologiske system. Sådanne skadelige virkninger har alle potentiale for at påvirke både risikoen og prognosen i forbindelse med kritisk sygdom. Eftersom disse virkningsmekanismer i høj grad har undgået granskning udførte vi tre nationale register-baserede kohorte studier for at rette op på dette.

Studie I - *Impact of pre-admission opioid treatment on one-year mortality following non-surgical intensive care*. I dette kohorte studie identificerede vi 118,388 patienter der blev indlagt for første gang på en intensivafdeling af ikke-kirurgiske årsager. Vi sammenlignede 0-30 dages og 31-365 dages dødeligheden uanset årsag for opioidbrugere med ikke-brugeres dødelighed. Pågående behandling med opioider på indlæggelsestidspunket var associeret med et forhøjet dødelighed både på kort sigt [Hazard Ratio (HR) = 1.20 (1.15 - 1.24)] og på lang sigt [HR 1.47 (1.39-1.55)].

Studie II - *Pre-admission opioid use and risk of all-cause mortality following incident myocardial infarction*. Dette kohorte studie inkluderede 67,742 patienter som havde haft et førstegangstilfælde af myokardie infarkt fra 2006 til 2012. Pågående behandling med opioider på tidspunktet for myokardie infarktet var associeret med en forhøjet dødelighed uanset årsag sammenlignet med ikke-brugere [HR 1.32 (1.26-1.39)].

Studie III - *Opioid initiation and risk of pneumonia requiring hospitalization and subsequent intensive care admission*. Dette kohorte studie inkluderede alle initierering af opioider (3,552,012) og NSAID på recept (11,285,112) fra 1995 til 2014, hvilket samlet gav 14,837,124 tilfælde af nyt medicinbrug. Opstart af opioider var associeret med en forhøjet risiko for indlæggelseskrævende lungebetændelse sammenlignet med opstart af NSAID [vægtet odds ratio 2.38 (2.19-2.58)]. Derimod observerede vi en reduceret risiko for efterfølgende indlæggelse på en intensivafdeling blandt nye opioidbrugere [sub-distributions hazard ratio 0.64 (0.50-0.83)].

Denne afhandling har belyst effekten af opioidbrug på både risiko og prognose ved kritisk sygdom og har dermed bidraget til at informere den klinisk beslutningstager såvel som guidet den fremadrettede forskning i betydningen af det globalt eskalerende opioid forbrug.

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Appendicies

Paper I

Impact of Preadmission Opioid Treatment on 1-Year Mortality Following Nonsurgical Intensive Care*

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Objectives: Compare all-cause mortality following nonsurgical ICU admission for opioid users with nonusers.

Design: Nationwide register-based cohort study.

Setting: All 43 ICUs in Denmark (7,028,668 citizens cumulatively during the study period). The Danish National Health Service provides universal healthcare, guaranteeing equal access to healthcare along with partial reimbursement for prescribed drugs.

Patients: All 118,388 nonsurgical patients admitted to an ICU from 2005 to 2014.

Intervention: Patients were categorized according to timing of last redeemed opioid prescription before admission: current user (prior 0–30 d), recent user (prior 31–365 d), former user (prior 365+ d), or nonuser (no prescription since 1994).

Measurements: All-cause mortality 0–30 days and 31–365 days following ICU admission was calculated using the Kaplan-Meier method. Crude and adjusted hazard ratios with 95% CIs were computed using Cox regression, comparing users with nonusers. Adjusted models included age, gender, socioeconomic factors, comedications, and comorbidity.

Main Results: Fifteen percent of the patients were current opioid users, 15% recent users, 30% former users, and 40% nonusers. Zero- to 30-day mortality was 35% for current users, 29% for recent users, 24% for former users, and 21% for nonusers. After confounder adjustment, current users remained at elevated risk during the first 30 days following ICU admission (hazard ratio, 1.20; 95% CI, 1.15–1.24). No association remained for recent or former users. A similar pattern was evident for 31–365-day all-cause mortality: 24% for current users, 19% for recent users, 13% for former users, and 10% for nonusers. During 31–365 days of follow-up, both current users and recent users remained at elevated risk of mortality after adjustment (hazard ratio, 1.47; 95% CI, 1.39–1.55 and hazard ratio, 1.20; 95% CI, 1.13–1.27, respectively).

Conclusions: Current opioid users experience increased mortality during the first year following ICU admission. (*Crit Care Med* 2018; 46:860–868)

Key Words: analgesics; intensive care; mortality; opioid

***See also p. 1005.**

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The study was designed by Drs. Munch, Christiansen, and Sørensen. Drs. Pedersen and Munch carried out analysis. Dr. Munch drafted the article, which all authors critically revised and approved before submission. Dr. Munch had full access to all 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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BACKGROUND

Licit opioid use has steadily increased internationally in recent decades (1). A growing body of evidence suggests that adverse effects of opioids may include increased risk of myocardial infarction (2–4), stroke (5–8), venous thromboembolism (9, 10), infection (11–16), and modulation of the immune system (15, 17–20). All potentially worsening the prognosis of ICU patients. Other adverse effects of opioids, such as constipation, sedation, respiratory depression, and delirium, have already proved prognostically detrimental by increasing length of stay (21–24), mechanical ventilation (22–24), and mortality (22–26).

To mitigate the high mortality which characterizes ICU patients, it is of paramount importance to identify patients with poor prognosis. This study aimed to examine the impact

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of opioid use prior to hospitalization on mortality among nonsurgical ICU patients.

METHODS

Setting

This nationwide cohort study included all nonsurgical patients admitted to the 43 Danish ICUs. The Danish National Health Service provides universal healthcare, guaranteeing equal access to health services, along with partial reimbursement for prescribed drugs (27). All ICUs are located in public hospitals with approximately 372 ICU beds or 2.2 ICU beds per 100,000 population (28). A number of national healthcare and administrative registries provided data for this study. Unambiguous record linkage across registries is made possible by the unique central personal register number assigned to each Danish citizen (29).

Study Population

The study population comprised all nonsurgical patients with Danish citizenship 18 years old or older, admitted for the first time to an ICU in Denmark between January 1, 2005, and December 31, 2014. ICU patients were identified in the Danish National Patient Registry (DNPR) (30), corresponding to the data in the Danish Intensive Care Database which relies on mandatory entry of specific intensive care codes into DNPR (31). Data are complete since 2005, and validation has demonstrated a high positive predictive value (32). The DNPR covers 99.4% of all hospital admissions in Denmark since 1977 and outpatient and emergency department visits since 1995 (30). As previously described (33), patients who had a surgical procedure (other than endoscopy or minor surgery) on the day of or 1 day prior to ICU admission were considered surgical and therefore excluded. All patients were followed for 1 year, or until emigration, December 31, 2014, or death.

Opioid Exposure

Opioid users were identified using the Danish National Prescription Registry (data available since 1994) (27), based on prescriptions redeemed since 1994 and prior to the incident ICU admission (for codes, see **Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D359).

We classified patients into four groups depending on preadmission opioid use. Current users had redeemed an opioid prescription within 30 days prior to the hospital admission leading to incident ICU admission. Recent users had redeemed a prescription within 31–365 days prior to admission. Former users had no redeemed prescription for opioids within 365 days prior but at least one previous record in the prescription database. Nonusers had no record of a redeemed prescription for opioids between 1994 and ICU admission.

Current users were disaggregated into new users (first-ever opioid prescription within 30 d prior to admission) and long-term users (redemption of prescription within 30 d prior to admission that was not the first prescription) (34). Current users were also categorized based upon total number of redeemed opioid prescriptions (1, 2–10, 11–50, or > 50 prescriptions) since 1994.

To examine the possibility of a dose-response effect, the total oral morphine equivalents (OMEQs) of the last opioid prescription prior to incident ICU admission was calculated for current users. The underlying idea behind OMEQ is that different drugs, with different potency, may at different dosages provide the same level of analgesia (for conversion rates, see **Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D360). Dosage was categorized as nonuse, low (< 375 OMEQ or 12.5 mg/daily), intermediate (375–750 OMEQ), high (751–1,500 OMEQ), and very high (> 1,500 OMEQ) (35).

To investigate a potential immunosuppressive effect, current users were grouped based on last prescription: nonusers, users of opioids with a strong immunosuppressive effect (codeine, morphine, and fentanyl), users of opioids with a weak immunosuppressive effect (oxycodone, tramadol, buprenorphine, and hydromorphone), and users of other opioids (ketobemidone, nicomorphine, pethidine, pentazocine, tapentadol, and dextropropoxyphene) (18).

Outcomes

Outcomes were all-cause mortality during 0–30 days following ICU admission and (conditional on 30-d survival) during 31–365 days. Information on mortality was obtained from the Danish Civil Registration System, which has recorded all changes in vital status and migration for the Danish population since 1968 (29). Cause of death was obtained from the Danish Register of Cause of Death, which since 1980 has recorded both immediate and underlying causes of death (36).

Covariates

Information on age, sex, and marital status was obtained from the Danish Civil Registration System. Data on nonpsychiatric comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes without end-organ failure, renal disease, diabetes with end-organ failure, any tumor, leukemia, lymphoma, moderate-to-severe liver disease, and metastatic solid tumor) were acquired from the DNPR from 1977 until the date of the hospital admission associated with the incident ICU admission (30). Data on psychiatric comorbidities (opioid abuse, alcohol abuse, schizophrenia spectrum disorder, depression, mania and/or bipolar disorder, anxiety disorders, personality disorder) were acquired from the Danish Psychiatric Central Research Register (data available since 1970) (37). Presence of individual comorbidities were defined dichotomously. Simplified Acute Physiology Score II (SAPS) II was also extracted from the DNPR (recorded since 2010). Information concerning filled prescriptions for concomitant medications within 60 days was acquired from the Danish National Prescription Registry on nonspecific nonsteroidal antiinflammatory drugs, coxibs (nonsteroidal antiinflammatory drugs with high affinity for cyclooxygenase-2 receptors),

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tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, benzodiazepine derivates, and antiepileptics, oral corticosteroids, acetylsalicylic acid (38). Finally, the Integrated Database for Labour Market Research was used to obtain information on the following socioeconomic factors: level of education, income level, and employment status (data available since 1980 based on other government registries) (39).

Statistical Analyses

We tabulated covariates by opioid exposure (**Table 1**) and used the Kaplan-Meier method to compute cumulative incidence as a

TABLE 1. Selected Characteristics of the Study Population

Characteristics	Current Users, *n* = 17,359	Recent Users, *n* = 17,399	Former Users, *n* = 35,931	Nonusers, *n* = 47,699	Total, *n* = 118,388
Age, median (interquartile range)	68.8 (58.6–77.6)	68.7 (56.9–77.6)	66.5 (53.0–76.8)	61.2 (40.9–73.2)	65.3 (50.5–75.8)
Male, *n* (%)	8,231 (47.4)	8,681 (49.9)	19,958 (55.5)	29,223 (61.3)	66,093 (55.8)
Educational level, *n* (%)					
Primary school	8,802 (50.8)	8,464 (48.7)	16,536 (46.0)	20,415 (43.1)	54,217 (45.9)
High school or similar	5,688 (32.8)	5,893 (33.9)	12,799 (35.6)	16,936 (35.7)	41,316 (35.0)
Higher education	1,872 (10.8)	2,073 (11.9)	4,701 (13.1)	7,575 (16.0)	16,221 (13.7)
Employment status, *n* (%)					
Employed	2,203 (12.7)	2,854 (16.4)	8,114 (22.6)	16,465 (34.7)	29,636 (25.1)
Early retirement/ retirement due to illness	517 (3.0)	753 (4.3)	1,572 (4.4)	2,895 (6.1)	5,737 (4.9)
Unemployed/students	4,263 (24.6)	3,637 (20.9)	7,158 (19.9)	8,225 (17.4)	23,283 (19.7)
Retired upon reaching retirement age	8,765 (50.5)	8,483 (48.8)	15,326 (42.7)	16,117 (34.0)	48,691 (41.2)
Income level, Danish kroner[a], *n* (%)					
< 132,002	5,225 (30.1)	4,920 (28.3)	9,369 (26.1)	10,171 (21.4)	29,685 (25.1)
132,002–169,869	4,236 (24.4)	4,407 (25.3)	9,276 (25.8)	11,609 (24.4)	29,528 (25)
169,869–248,127	2,819 (16.3)	3,372 (19.4)	8,668 (24.1)	14,676 (30.9)	29,535 (25)
> 248,127	5,066 (29.2)	4,694 (27)	8,612 (24)	11,079 (23.3)	29,451 (24.9)
Concomitant medication, *n* (%)					
Tricyclic antidepressants	1,108 (6.4)	547 (3.1)	669 (1.9)	425 (0.9)	2,749 (2.3)
Serotonin and norepinephrine reuptake inhibitors	653 (3.8)	498 (2.9)	850 (2.4)	635 (1.3)	2,636 (2.2)
Selective serotonin reuptake inhibitors	2,667 (15.4)	2,002 (11.5)	3,380 (9.4)	2,949 (6.2)	10,998 (9.3)
Benzodiazepine derivates	3,343 (19.3)	2,168 (12.5)	3,125 (8.7)	2,482 (5.2)	11,118 (9.4)
Antiepileptics	2,441 (14.1)	1,605 (9.2)	2,298 (6.4)	1,964 (4.1)	8,308 (7.0)
Acetylsalicylic acid	3,610 (20.8)	3,043 (17.5)	5,935 (16.5)	5,411 (11.3)	17,999 (15.2)
Nonspecific nonsteroid antiinflammatory drugs	2,739 (15.8)	1,639 (9.4)	2,227 (6.2)	1,841 (3.9)	8,446 (7.1)
Cyclooxygenase-2 inhibitors	1,452 (8.4)	838 (4.8)	1,095 (3.0)	906 (1.9)	4,291 (3.6)

(*Continued*)

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TABLE 1. (*Continued*). Selected Characteristics of the Study Population

Characteristics	Current Users, *n* = 17,359	Recent Users, *n* = 17,399	Former Users, *n* = 35,931	Nonusers, *n* = 47,699	Total, *n* = 118,388
Comorbidity, *n* (%)					
Depression	2,235 (12.9)	1,928 (11.1)	3,362 (9.4)	2,746 (5.8)	10,271 (8.7)
Anxiety disorders	2,031 (11.7)	1,714 (9.9)	3,182 (8.9)	2,766 (5.8)	9,693 (8.2)
Myocardial infarction	2,465 (14.2)	2,519 (14.5)	4,736 (13.2)	4,434 (9.3)	14,154 (12.0)
Peripheral vascular disease	3,675 (21.2)	3,291 (18.9)	5,511 (15.3)	4,739 (9.9)	17,216 (14.5)
Cerebrovascular disease	3,876 (22.3)	4,005 (23.0)	8,112 (22.6)	8,547 (17.9)	24,540 (20.7)
Chronic pulmonary disease	5,498 (31.7)	5,298 (30.5)	8,936 (24.9)	7,534 (15.8)	27,266 (23.0)
Ulcer disease	3,218 (18.5)	2,570 (14.8)	3,962 (11.0)	2,776 (5.8)	12,526 (10.6)
Diabetes without end-organ failure	3,298 (19.0)	3,141 (18.1)	5,223 (14.5)	4,418 (9.3)	16,080 (13.6)
Renal disease	2,370 (13.7)	2,378 (13.7)	3,723 (10.4)	3,453 (7.2)	11,924 (10.1)
Diabetes with end-organ failure	2,255 (13.0)	2,067 (11.9)	3,087 (8.6)	2,315 (4.9)	9,724 (8.2)
Any tumor	4,557 (26.3)	3,565 (20.5)	5,747 (16.0)	5,873 (12.3)	19,742 (16.7)
Lymphoma	527 (3.0)	495 (2.8)	576 (1.6)	537 (1.1)	2,135 (1.8)
Metastatic solid tumor	1,240 (7.1)	709 (4.1)	766 (2.1)	813 (1.7)	3,528 (3.0)

[a]Translated to U.S. dollars, the income groups were $18,878 or less, $18,878–$24,294, $24,294–$35,486, $35,486 or more (as of December 14, 2016).

measure of absolute risk of all-cause mortality during 0–30 days and 31–365 days following incident ICU admission. We used Cox proportional hazards regression analysis to compute hazard ratios (HRs) for death with 95% CIs; nonusers were the reference group. The fully adjusted model included age, gender, socioeconomic factors, comedication, and comorbidities individually. Log(-log) plots were used for visual confirmation of the assumption of proportional hazards. Similar Cox models were used to analyze the effect of individual generic opioids, cumulative use, dose-response, hospital admission diagnosis, and immunosuppressive effect. Effect measure modification was examined by stratifying according to comorbidity and concomitant medication status. Last, the ten most frequent immediate and underlying causes of death were tabulated across opioid user groups.

Three sensitivity analyses were conducted. The first excluded patients who redeemed prescriptions within 5 days prior to ICU admission to eliminate potential prothopathic bias. The second used different cutoff points between current and recent use (i.e., prescription redemption within 15, 30, 45, or 60 d prior to admission). The third included SAPS-II score in the fully adjusted models in the subset of the population with this code recorded (n = 18,160).

Approvals

In accordance with Danish law, approval for usage of data was obtained from the Danish Data Protection Agency (record number: 2015-57-0002, AU record number 2016-051-000001/432).

RESULTS

Demographics

During the study period, 202,925 patients were admitted to a Danish ICU. Of these, 84,537 had prior surgery and were excluded leaving 118,388 patients. In the study population, 15% of patients were current opioid users, 15% recent users, 30% former users, and 40% nonusers. Only a minority of current users were new users (6%).

Patients with more recent opioid use were older and tended to be female (for selected characteristics, see Table 1; for full characteristics, see **Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/D361). Further, current users were less educated and less likely to be employed compared with nonusers. Use of comedications, nonpsychiatric comorbidities, depression, alcohol abuse, and number of redeemed prescriptions increased with more recent opioid use.

30-day Mortality

A high absolute risk of 0–30-day all-cause mortality was observed across all categories of users, rising from 20.6% (95% CI, 20.2–20.9) for nonusers to 34.8% (95% CI, 34.1–35.5) for current users (**Table 2**). In adjusted models, only current users remaining at elevated risk (HR, 1.20 [95% CI, 1.15–1.24]). Among current users, new users were at highest risk compared with nonusers, (HR, 1.35 [95% CI, 1.21–1.51]).

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Current users were at an elevated risk across all dose levels of the most recent opioid prescription (**Table 3**). While point estimates revealed increasing risk with higher strength, CIs greatly overlapped. Risk attenuated with number of prescriptions.

Analysis of risk of all-cause mortality comparing current users with nonusers stratified by hospital admission diagnosis revealed that the association was strongest in cancer patients while there was no association in those admitted for gastrointestinal or liver disease and trauma or poisoning (**Supplemental Fig. 1**, Supplemental Digital Content 4, http://links.lww.com/CCM/D362; **legend**, Supplemental Digital Content 12, http://links.lww.com/CCM/D370). The biggest effect measure modification was observed for malignancy-related diagnoses (**Fig. 1**). Generally, stratified estimates differed little from overall estimates.

We found no difference in risks between users of opioids with a strong or weak immunomodulatory effect compared with nonusers, respectively (**Supplemental Table 4**, Supplemental Digital Content 5, http://links.lww.com/CCM/D363).

TABLE 2. Association of Timing of Use of Opioids With All-Cause Mortality

	30-d All-Cause Mortality			31–365-d All-Cause Mortality		
Exposure	Absolute Risk, % (95% CI)	Unadjusted, HR (95 % CI)	Adjusted[a], HR (95% CI)	Absolute Risk, % (95% CI)	Unadjusted, HR (95 %CI)	Adjusted[a], HR (95% CI)
Current users	34.8 (34.1–35.5)	1.84 (1.78–1.90)	1.20 (1.15–1.24)	24.2 (23.4–25.1)	2.72 (2.59–2.86)	1.47 (1.39–1.55)
New users	33.5 (30.7–36.6)	1.80 (1.61–2.00)	1.35 (1.21–1.51)	20.4 (17.5–23.8)	2.31 (1.94–2.74)	1.56 (1.31–1.87)
Long-term users	34.9 (34.1–35.6)	1.84 (1.78–1.90)	1.20 (1.16–1.25)	24.5 (23.6–25.3)	2.74 (2.61–2.88)	1.47 (1.38–1.56)
Recent users	24.4 (24.0–24.9)	1.45 (1.40–1.50)	0.98 (0.95–1.02)	12.9 (12.5–13.3)	2.00 (1.89–2.11)	1.20 (1.13–1.27)
Former users	29.1 (28.4–29.7)	1.21 (1.18–1.24)	0.92 (0.90–0.95)	19.0 (18.3–19.7)	1.34 (1.28–1.40)	0.96 (0.91–1.00)
Nonusers	20.6 (20.2–20.9)	1	1	9.8 (9.5–10.1)	1	1

HR = hazard ratio.

[a]Adjusted for age, sex, socioeconomic status, comorbidities, and concomitant medication use (as listed in Table 1, excluding number of opioid prescriptions and admission diagnosis).

TABLE 3. Association of All-Cause Mortality With Strength of Opioid Prescription and Cumulative Use Among Current Users

	30-d All-Cause Mortality		31–365-d All-Cause Mortality	
Exposure	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Nonusers	1	1	1	1
Strength of opioid				
Low	1.72 (1.64–1.80)	1.19 (1.13–1.26)	2.25 (2.09–2.43)	1.37 (1.26–1.49)
Intermediate	1.79 (1.67–1.92)	1.20 (1.12–1.29)	2.76 (2.50–3.06)	1.58 (1.42–1.76)
High	1.91 (1.82–2.00)	1.22 (1.16–1.28)	2.93 (2.72–3.15)	1.50 (1.39–1.62)
Very high	2.02 (1.90–2.15)	1.25 (1.17–1.33)	3.36 (3.06–3.69)	1.56 (1.41–1.73)
Number of prescriptions				
1	2.50 (2.34–2.67)	1.35 (1.21–1.51)	2.31 (1.94–2.74)	1.56 (1.31–1.86)
2–10	2.05 (1.95–2.15)	1.36 (1.29–1.43)	3.03 (2.80–3.28)	1.72 (1.58–1.87)
11–50	1.88 (1.79–1.97)	1.16 (1.10–1.22)	3.03 (2.82–3.27)	1.51 (1.39–1.63)
> 50	1.68 (1.60–1.76)	1.10 (1.05–1.16)	2.34 (2.18–2.52)	1.21 (1.12–1.32)

HR = hazard ratio.

[a]Adjusted for age, sex, socioeconomic status, comorbidity, and concomitant medication use (as listed in Table 1, excluding number of opioid prescriptions and admission diagnosis).

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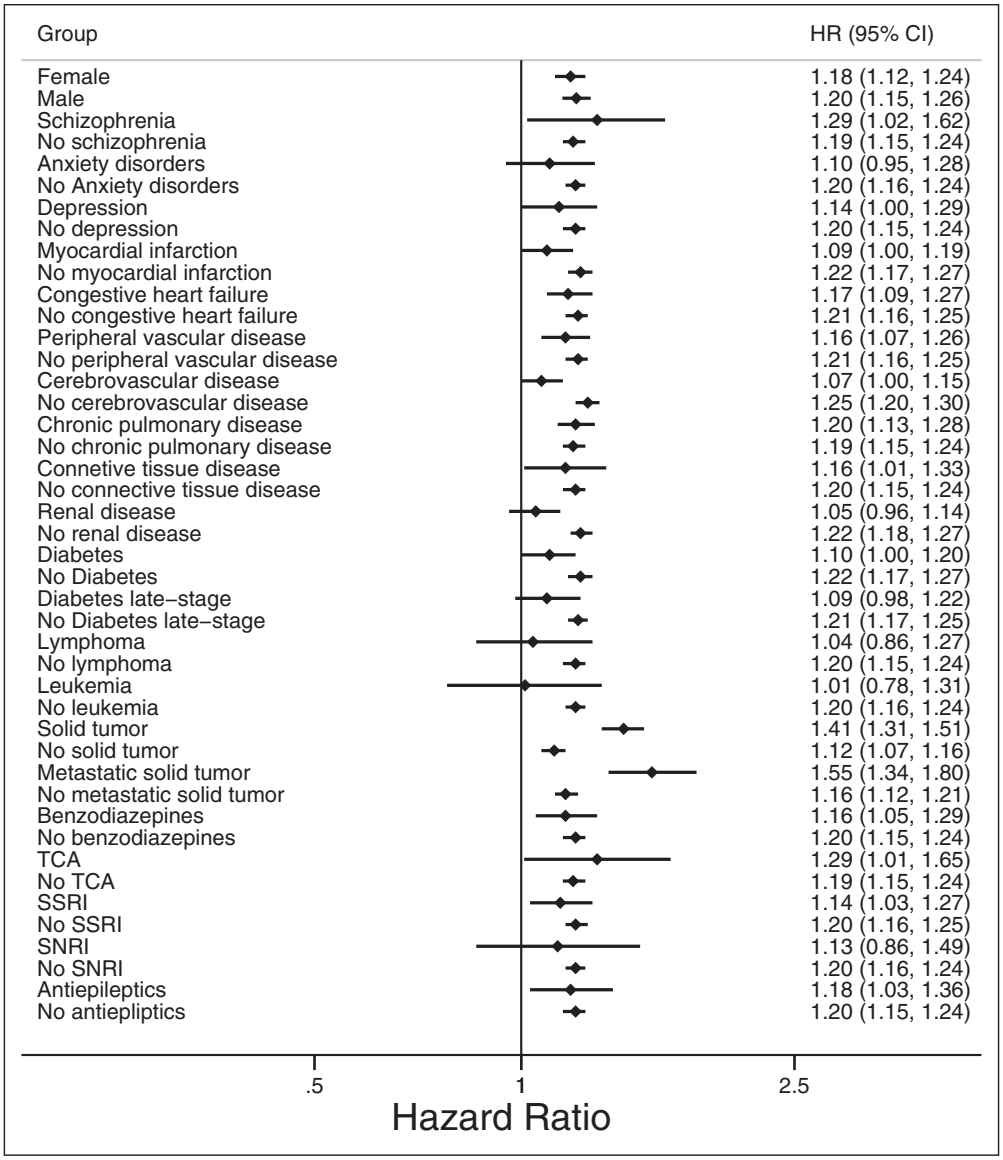

Figure 1. Risk of 30-d all-cause mortality of current users compared with nonusers in fully adjusted models stratified by comorbidity status and concomitant medication use. Adjusted for age, sex, socioeconomic factors, comorbidity, and concomitant medication use. HR = hazard ratio, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Use of nearly all opioids was associated with increased risk except for tapentadol, dextropropoxyphene, nicomorphine, pethidine, and noscapine (**Supplemental Table 5**, Supplemental Digital Content 6, http://links.lww.com/CCM/D364). However, small groups resulted in imprecise estimates.

The primary immediate cause of death across all groups were diseases of the airways (which included pneumonia). The primary underlying cause for current users was malignancy, whereas nonusers primarily died from circulatory diseases (**Supplemental Table 6**, Supplemental Digital Content 7, http://links.lww.com/CCM/D365; and **Supplemental Table 7**, Supplemental Digital Content 8, http://links.lww.com/CCM/D366).

31–365-Day Mortality

Among patients surviving the first month, the absolute risk of mortality remained high for current users (24.2% [95% CI, 23.4–25.1%]) and recent users (19.0% [95% CI, 18.3–19.7%]) (Table 2). In contrast, lower longer term mortality was observed among former and nonusers, both near 10%.

Adjustment attenuated associations. However, recent users (adjusted HR, 1.20 [95% CI, 1.13–1.27]) and current users [adjusted HR, 1.47 [95% CI, 1.39–1.55]) remained at elevated risk of mortality. New users remained at especially high risk (adjusted HR, 1.56 [95% CI, 1.31–1.87]).

A dose-response relation between strength of the last opioid prescription and mortality was observed (Table 3), with risk increasing from an HR of 1.37 (95% CI, 1.26–1.49) for users of low-dose opioids to an HR of 1.56 (95% CI, 1.41–1.73) for users of very high–dose opioids.

Concerning cumulative use patients who had redeemed two to 10 prescriptions were at highest risk of mortality (HR, 1.72 [95% CI, 1.58–1.87]), whereas those who had redeemed greater than 50 prescriptions were at lowest risk (HR, 1.21 [95% CI, 1.12–1.32]) compared with nonusers (Table 3).

Among current users, patients admitted for malignancy or endocrine disease excluding diabetes experienced the highest risk during the 31–365-period in analysis stratified by hospital admission diagnosis (**Supplemental Fig. 2**, Supplemental Digital Content 9, http://links.lww.com/CCM/D367; legend, Supplemental Digital Content 12, http://links.lww.com/CCM/D370). Estimates were otherwise stable regardless of admission diagnosis during the 31–365-day period. Similar to the 0–30-day follow-up period, malignancy-related comorbidity increased the association of opioid use on mortality (**Fig. 2**). Notably, opioid use combined with serotonin and norepinephrine reuptake inhibitors was associated with lower relative risk of all-cause mortality.

Among current users, use of a strongly immunosuppressive opioid was associated with high risk of mortality compared with nonuser (HR, 1.60 [95% CI, 1.48–1.73]). Users of weakly immunosuppressive opioids had a lower (albeit still high) risk (HR, 1.45 [95% CI, 1.36–1.55]) (Supplemental Table 4, Supplemental Digital Content 5, http://links.lww.com/CCM/D363).

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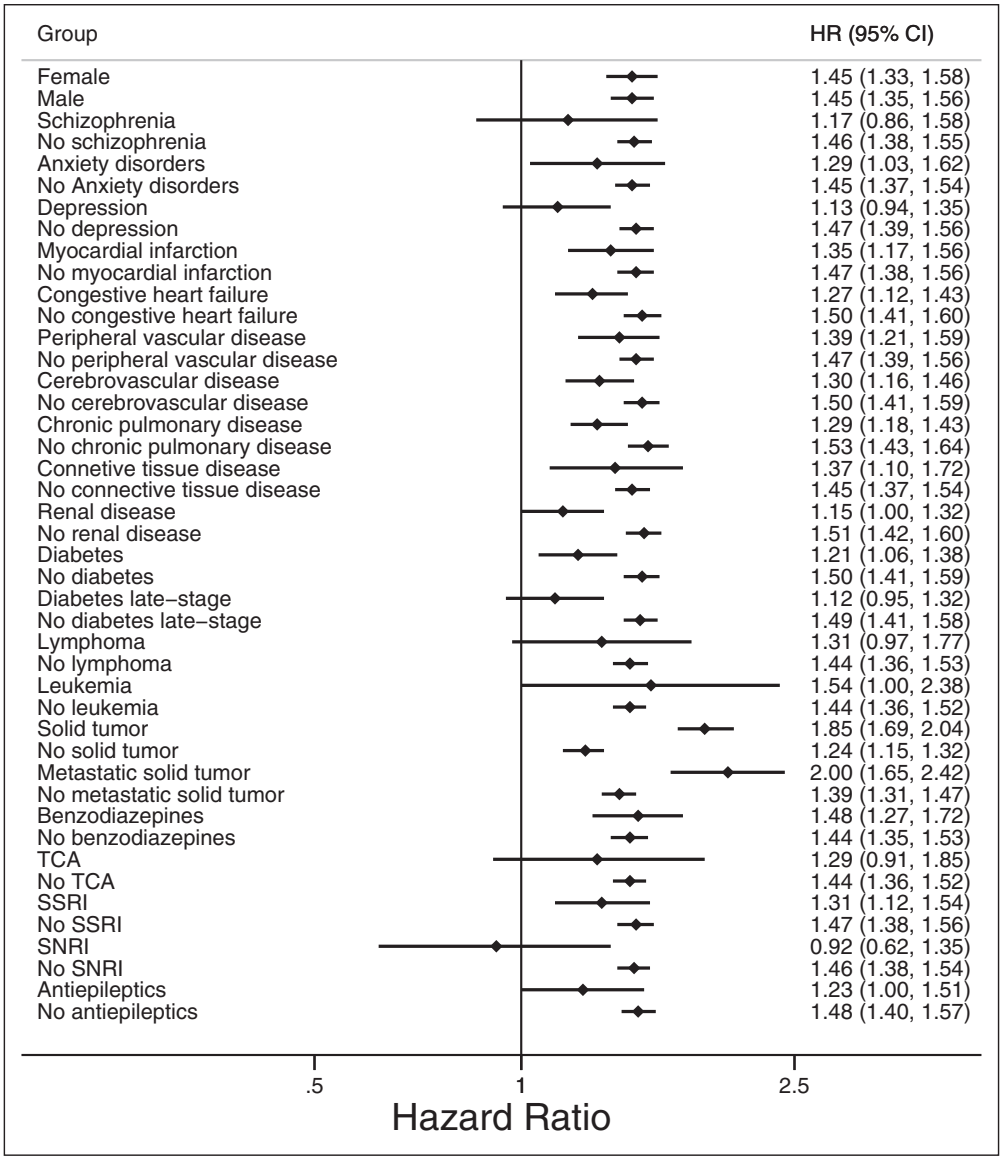

Figure 2. Risk of 31–365-d all-cause mortality of current users compared with nonusers in fully adjusted models stratified by comorbidity status and concomitant medication use. Adjusted for age, sex, socioeconomic factors, comorbidity, and concomitant medication use. HR = hazard ratio.

Nearly, all generic opioids were individually associated with increased risk of all-cause mortality except hydromorphone, dextromethorphan, tapentadol, dextropropoxyphene, nicomorphine, pethidine, and noscapine (Supplemental Table 5, Supplemental Digital Content 6, http://links.lww.com/CCM/D364). Similar to 0–30 days, the immediate cause of death was consistently respiratory disease. Malignancy was more often the underlying cause among current users, whereas respiratory diseases remained the primary cause of death for other groups (**Supplemental Table 8**, Supplemental Digital Content 10, http://links.lww.com/CCM/D368; and **Supplemental Table 9**, Supplemental Digital Content 11, http://links.lww.com/CCM/D369).

Sensitivity Analysis

Excluding those redeeming an opioid prescription within 5 days prior to hospital admission or changing the exposure window did not alter estimates (data not shown). Similarly, adjusting for SAPS II score did not alter estimates within the subpopulation for whom it was recorded (data not shown).

DISCUSSION

This nationwide cohort study of ICU patients showed an increased risk of 0–30-day and 31–365-day all-cause mortality for opioid users following ICU admission compared with nonusers. Among patients who survived the initial 30 days following ICU admission, an elevated risk was observed, after adjustment, for both recent and current users during the following 31–365 days.

New users were at higher risk than long-term users, which might indicate symptomatic treatment of the disease leading to ICU admission. Excluding patients who redeemed an opioid prescription within the 5 days prior to ICU admission produced no change estimate. Potentially supporting a new user phenomenon, or alternatively a healthy user phenomenon, risk seemed to attenuate with increasing number of redeemed prescriptions. However, the dose-response relationship of the strength of last prescription observed during 31–365 days of follow-up in the adjusted analyses contrasts this.

Former users reverted to the same risk as nonusers. This could reflect the difference between long-term versus short-term opioid users. However, more than 60% of former users redeemed multiple prescriptions and mostly differed from current users in terms of cancer burden.

This is the first study to examine prognosis of opioid users following ICU admission. In line with our findings, a study by Mosher et al (40) of veterans in chronic opioid therapy found an increased risk of all-cause mortality within the first 30 days following hospital admission (odds ratio, 1.19 [95% CI, 1.10–1.29]). A Danish study of hip fracture patients found preadmission opioid to be associated with 1-year mortality in unadjusted analysis. Following adjustment, the association failed to reach statistical significance, but study size was small (41). Solomon et al (3) investigated all-cause mortality among older adults with arthritis (excluding cancer patients). They

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found an increased risk of mortality among opioid users compared with nonspecific nonsteroidal antiinflammatory drugs users (HR, 1.87 [95% CI, 1.39–2.53]).

Identification of potential mechanisms that could explain our findings remains speculative. Prior studies have reported an increased risk of infections in other populations (11–16). However, the similarity between our estimates for users of strongly immunosuppressive opioids and users of weakly immunosuppressive opioids suggests that opioids' immunosuppressive effect may have little clinical significance in the ICU. Other potential mechanistic explanations for our findings include increased aspiration risk, adverse respiratory effects, delirium, increased immobility, and sedation. Last, opioid users have been shown to suffer increased risk of cardiovascular disease (2–4), stroke (5–8), and venous thromboembolism (9, 10).

Our study was conducted in a setting of universal healthcare including all nonsurgical ICU patients. Follow-up was complete. Selection bias is therefore unlikely. However, several limitations should be considered (42). Although the Danish National Prescription Registry captures all prescriptions in community pharmacies, it does not include in-hospital drug use. Thus, our findings may be influenced by opioid use after study inclusion similar to an intention-to-treat analysis in a clinical trial. It is also not certain that patients consume opioids as prescribed. However, different exposure windows for current and recent users did not change estimates.

Another limitation is potential confounding by indication. Much of the observed risk was driven by opioid users suffering from cancer and thus potential for residual confounding due to type, severity, and stage remains. Still, even cancer-free opioid users were at elevated risk. Use of opioids for noncancer pain is often due to conditions unlikely to increase all-cause mortality following ICU admission such as back pain or osteoarthritis (43, 44).

Some unmeasured residual confounding, for example, frailty, might have been present in our analyses, but it is unlikely to account fully for the observed negative associations, given the extensive adjustment based on inpatient and outpatient hospital diagnoses, prescription redemptions, and socioeconomic information.

A growing body of evidence suggests that opioid users are a high-risk group for developing critical illnesses. The present study suggests that they also may have a worse prognosis. Considering the current widespread use of opioids, it is important for future studies to investigate the clinical course following ICU admission in order to identify preventable complications in opioid users.

CONCLUSIONS

Opioid users were at increased risk of both 30-day and 31–365-day all-cause mortality following ICU admission. Current users were at especially high risk, and among these patients, new users and cancer patients were at highest risk. It is thus important to identify opioid users at time of ICU admission to potentially mitigate their poor prognosis.

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Supplemental Table 1. Codes used in the study

Inclusion	
Intensive care treatment or observation	NABB, NABE
Exclusion:	
Any surgery	1977-1995 (ICD-8): 0000-9999; 1996-2011 (ICD-10): KA-KZ
Exposure-codes	**ATC codes**
Opioids	MN02A
Opioid, cough-suppressant	MR05DA
Morphine	MN02AA01, MN02AA51
Hydromorphone	MN02AA03
Nicomorphine	MN02AA04
Oxycodone	MN02AA05, MN02AA55
Ketobemidone	MN02AB01, MN02AG02
Pethidine	MN02AB02, MN02AB72
Fentanyl	MN02AB03
Dextroproproxyphen	MN02AC04
Pentazocin	MN02AD01
Buprenorphine	MN02AE01
Tramadol	MN02AX02
Tapentadol	MN02AX06
Codeine	MN02AA59
Comedications	
Acetylsalicylic acid, high-dose	MN02BA01
Acetylsalicylic acid, low-dose	MB01AC06
Oral corticosteroids	MR01AD
Glucosamine	MM01AX05
nsNSAIDs	MM01A excluding codes listed as COX-II inhibitors or glucosamine
COX-II inhibitors	MM01AH, MM01AC06, MM01AC56, MM01AB05, MM01AB55, MM01AB08, MM01AX17
Benzodiazepine-derivates	MN05BA
Tricyclic antidepressants	MN06AA
Selective serotonin reuptake inhibitors	MN06AB
Serotonin and norepinephrine reuptake inhibitors	MN06AX16, MN06AX21, MN06AX23
Antiepileptics	MN03A

Comorbidity codes	**ICD-8**	**ICD-10**
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31,M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease		B18, K70.0-K70.3, K70.9, K71, K73
Diabetes without end-organ damage	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 50.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes with end-organ damage	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8, E11.2-E11.8
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Non-metastatic solid tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic cancer	195-198, 199	C76-C80
Opioid abuse	30409	DF11
Alcohol abuse	303	DF10
Schizophrenia	295	DF20
Depression	29609, 29629, 29809, 30049	DF32, DF33
Mania	29619, 29639, 29819	DF30, DF31
Anxiety	300, excluding 30049	DF40-DF49
Personality disorders	301	DF6-DF69

SAPS-II	ZRRB00-99

Admission diagnoses	**ICD-10**
Pneumonia	J12−J18, A48.1, A70.9
Septicemia	A39.2, A40, A41, A42.7, B37.7, R57.2
Infectious diseases excluding pneumonia and septicemia	A00−B99 (without A39.2, A40, A41, A42.7, A48.1, A70.9, B37.7), G00−G07, I00−I02, I30.1, I32.0, I33, I38, I40.0, J00−J06, J36, J39.0, J10−J11, J20−J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00−L03, L05−L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70−N77
Diabetes	E10−E14, O24 (except O24.4), G63.2, H36.0, N08.3
Endocrinologic diseases excluding diabetes	E00−E90 (without E10−E14)
Cardiovascular diseases	I00−I99 excluding I00−I02, I30.1, I32.0, I33, I38, I40.0
Respiratory diseases	J00−J99 excluding J00−J06, J36, J39.0, J10−J11, J12−J18, J20−J22, J85.1, J86
Gastrointestinal and liver diseases	K00−K99 excluding K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cancer	C00−D89
Trauma and poisoning	S00−T98
Other	all codes not included in other categories

Cause of Death classification	ICD-10
Infections, including parasitic disease	A00-B99
Malignancy	C00-97
Other neoplasms	D00-48
Diseases of the blood and immune system	D50-89
Endocrinological and nutritional diseases	E00-90
Psychiatric disease	F03-99
Diseases of the nervous system	G00-31, G35-H95
Diseases of the heart	I00-25, I27, I30-51
Other vascular diseases	I26, I28, I60-99
Diseases of the airways	J00-99
Diseases of the digestive system	K00-92
Diseases of the skin	L00-99
Diseases of bone, muscle, and connective tissue	M00-99
Disease of the urological or genital system	N00-98
Complications during pregnancy and childbirth	O00-99
Diseases during the perinatal period	P00-96
Congenital diseases	Q00-99
Poorly defined causes	R00-98, R999

Accidents	V01-X59, Y40-69, Y70-86, Y88
Suicide	X60-84, Y870
Murder and assault	Y85-99, Y00-09, Y871
Uncertain circumstances	Y10-34, Y872, Y899
Legal interventions	Y35-36, Y890-891
Death without medical information	R990

Supplemental Table 2. List of opioids, their Anatomical Therapeutic Chemical (ATC) code, defined daily dose (DDD), and equi-analgesic ratios used in the study [1-16].

ATC code	Name	Route	DDD [mg]	Equi-analgesic ratio
N02AA01	Morphine	O	100	1
N02AA01	Morphine	P	30	3
N02AA01	Morphine	R	30	1,5
N02AA03	Hydromorphone	O	20	6
N02AA03	Hydromorphone	P	4	20
N02AA04	Nicomorphine	O	30	1
N02AA04	Nicomorphine	P	30	3
N02AA04	Nicomorphine	R	30	1,5
N02AA05	Oxycodone	O	75	1,5
N02AA05	Oxycodone	P	30	4
N02AB01	Ketobemidone	O	50	1
N02AB01	Ketobemidone	P	50	3
N02AB02	Pethidine	O	400	0,1
N02AB02	Pethidine	P	400	0,4
N02AB02	Pethidine	R	400	0,1
N02AB03	Fentanyl	TD	1.2	100
N02AB03	Fentanyl	N	0.6	50
N02AB03	Fentanyl	SL	0.6	50
N02AC04	Dextropropoxyphene (chloride)	O	200	0,23
N02AC04	Dextropropoxyphene (napsylate)	O	300	0,15
N02AD01	Pentazocine	O	200	0,17
N02AD01	Pentazocine	P	200	0,5
N02AE01	Buprenorphine	P	1.2	100
N02AE01	Buprenorphine	SL	1.2	50
N02AE01	Buprenorphine	TD	1.2	110
N02AX02	Tramadol	O	300	0,2
N02AX02	Tramadol	P	300	0,3
N02AX02	Tramadol	R	300	0,2
N02AX06	Tapentadol	O	400	0,3
N02AA55	Oxycodone, combinations	O	75	1,5
N02AG02	Ketobemidon og antispasmodika	O		2
N02AG02	Ketobemidon og antispasmodika	P		4
N02AA59	Codein, combinations excluding psycholeptics	O/R		0.1

ATC code	Name	Route	DDD [mg]	Equianalgesic ratio
N07BC02	Methadone	O	25	4
N07BC02	Methadone	P	25	8
N07BC01	Buprenorphin	SL	8	50
N07BC06	Diamorphin	P (subcutaneous)		3
N07BC51	Buprenorphin, combinations	SL	8	50
R05DA04	Codeine	O	100	0.1

O=Oral, P = Parenteral, R = Rectal, N = Nasal, SL=Sublingual, TD = Transdermal

Supplemental Table 3. Characteristics of the study population. Data are numbers (percentages).

Characteristics	Current users n=17,359	Recent users n=17,399	Former users n=35,931	Non-users n=47,699	Total n=118,388
Age [median (IQR)]	68.8 (58.6-77.6)	68.7 (56.9-77.6)	66.5 (53.0-76.8)	61.2 (40.9-73.2)	65.3 (50.5-75.8)
Male	8,231 (47.4)	8,681 (49.9)	19,958 (55.5)	29,223 (61.3)	66,093 (55.8)
Educational level					
Primary school	8,802 (50.8)	8,464 (48.7)	16,536 (46.0)	20,415 (43.1)	54,217 (45.9)
High school or similar	5,688 (32.8)	5,893 (33.9)	12,799 (35.6)	16,936 (35.7)	41,316 (35.0)
Higher education	1,872 (10.8)	2,073 (11.9)	4,701 (13.1)	7,575 (16.0)	16,221 (13.7)
Missing	997 (5.7)	969 (5.6)	1,895 (5.3)	2773 (5.8)	6,634 (5.6)
Employment status					
Employed	2,203 (12.7)	2,854 (16.4)	8,114 (22.6)	16,465 (34.7)	29,636 (25.1)
Early retirement/Retirement due to illness	517 (3.0)	753 (4.3)	1,572 (4.4)	2,895 (6.1)	5,737 (4.9)
Unemployed/Students	4,263 (24.6)	3,637 (20.9)	7,158 (19.9)	8,225 (17.4)	23,283 (19.7)
Retired upon reaching retirement age	8,765 (50.5)	8,483 (48.8)	15,326 (42.7)	16,117 (34)	48,691 (41.2)
Missing	1,611 (9.3)	1,672 (9.6)	3,761 (10.5)	3,997 (8,4)	11,041 (9.3)
Income level, DKK[a]					
<132,002	5,225 (30.1)	4,920 (28.3)	9,369 (26.1)	10,171 (21.4)	29,685 (25.1)
132,002-169,869	4,236 (24.4)	4,407 (25.3)	9,276 (25.8)	11,609 (24.4)	29,528 (25)
169,869-248,127	2,819 (16.3)	3,372 (19.4)	8,668 (24.1)	14,676 (30.9)	29,535 (25)

>248,127	5,066 (29.2)	4,694 (27)	8,612 (24)	11,079 (23.3)	29,451 (24.9)
Concomitant medication					
Tricyclic antidepressants	1,108 (6.4)	547 (3.1)	669 (1.9)	425 (0.9)	2749 (2.3)
Serotonin and norepinephrine reuptake inhibitors	653 (3.8)	498 (2.9)	850 (2.4)	635 (1.3)	2636 (2.2)
Selective serotonin reuptake inhibitors	2,667 (15.4)	2,002 (11.5)	3,380 (9.4)	2,949 (6.2)	10,998 (9.3)
Benzodiazepine derivates	3,343 (19.3)	2,168 (12.5)	3,125 (8.7)	2,482 (5.2)	11,118 (9.4)
Antiepileptics	2,441 (14.1)	1,605 (9.2)	2,298 (6.4)	1,964 (4.1)	8,308 (7.0)
Oral corticosteroids	292 (1.7)	275 (1.6)	507 (1.4)	499 (1.0)	1,573 (1.3)
Acetylsalicylic acid	3,610 (20.8)	3,043 (17.5)	5,935 (16.5)	5,411 (11.3)	17,999 (15.2)
nsNSAIDs	2,739 (15.8)	1,639 (9.4)	2,227 (6.2)	1,841 (3.9)	8,446 (7.1)
COX2-inhibitors	1,452 (8.4)	838 (4.8)	1,095 (3.0)	906 (1.9)	4,291 (3.6)
Comorbidity					
Opioid abuse	344 (2.0)	219 (1.3)	486 (1.4)	273 (0.6)	1322 (1.1)
Alcohol abuse	3,102 (17.9)	2,966 (17)	6,051 (16.8)	6,281 (13.2)	18,400 (15.5)
Schizophrenia-spectrum disorder	561 (3.2)	551 (3.2)	1218 (3.4)	1661 (3.5)	3991 (3.4)
Depression	2,235 (12.9)	1,928 (11.1)	3,362 (9.4)	2,746 (5.8)	10,271 (8.7)
Mania and/or bipolar disorder	286 (1.6)	314 (1.8)	587 (1.6)	570 (1.2)	1,757 (1.5)
Anxiety disorders	2,031 (11.7)	1,714 (9.9)	3,182 (8.9)	2,766 (5.8)	9,693 (8.2)
Personality disorder	758 (4.4)	627 (3.6)	1,129 (3.1)	1,119 (2.3)	3,633 (3.1)
Myocardial infarction	2,465 (14.2)	2,519 (14.5)	4,736 (13.2)	4,434 (9.3)	14,154 (12)
Congestive heart failure	3,039 (17.5)	3,098 (17.8)	5,040 (14.0)	4,545 (9.5)	15,722 (13.3)

Peripheral vascular disease	3,675 (21.2)	3,291 (18.9)	5,511 (15.3)	4,739 (9.9)	17,216 (14.5)
Cerebrovascular disease	3,876 (22.3)	4,005 (23)	8,112 (22.6)	8,547 (17.9)	24,540 (20.7)
Dementia	516 (3.0)	540 (3.1)	970 (2.7)	789 (1.7)	2,815 (2.4)
Chronic pulmonary disease	5,498 (31.7)	5,298 (30.5)	8,936 (24.9)	7,534 (15.8)	27,266 (23)
Connective tissue disease	1,678 (9.7)	1,404 (8.1)	2,073 (5.8)	1,189 (2.5)	6,344 (5.4)
Ulcer disease	3,218 (18.5)	2,570 (14.8)	3,962 (11)	2,776 (5.8)	12,526 (10.6)
Mild liver disease	1,151 (6.6)	1,215 (7.0)	2,113 (5.9)	1,720 (3.6)	6,199 (5.2)
Diabetes without end-organ failure	3,298 (19)	3,141 (18.1)	5,223 (14.5)	4,418 (9.3)	16,080 (13.6)
Renal disease	2,370 (13.7)	2,378 (13.7)	3,723 (10.4)	3,453 (7.2)	11,924 (10.1)
Diabetes with end-organ failure	2,255 (13)	2,067 (11.9)	3,087 (8.6)	2,315 (4.9)	9,724 (8.2)
Any tumor	4,557 (26.3)	3,565 (20.5)	5,747 (16)	5,873 (12.3)	19,742 (16.7)
Leukemia	198 (1.1)	240 (1.4)	376 (1.0)	448 (0.9)	1,262 (1.1)
Lymphoma	527 (3.0)	495 (2.8)	576 (1.6)	537 (1.1)	2,135 (1.8)
Moderate to severe liver disease	615 (3.5)	633 (3.6)	1,172 (3.3)	1,163 (2.4)	3,583 (3.0)
Metastatic solid tumor	1,240 (7.1)	709 (4.1)	766 (2.1)	813 (1.7)	3,528 (3.0)
Number of opioid prescriptions					
1	995 (5.7)	2,034 (11.7)	1,2751 (35.5)	n/a	15,780 (22.3)
2-10	4,715 (27.2)	7,536 (43.3)	1,8404 (51.2)	n/a	30,655 (43.4)
11-50	5,182 (29.9)	5,321 (30.6)	3,936 (11)	n/a	14,439 (20.4)
>50	6,467 (37.3)	2,508 (14.4)	840 (2.3)	n/a	9,815 (13.9)
SAPS-II score, [median (IQR)] (n=18,160)	45 (34-58)	44 (34-58)	43 (31-56)	41 (29-55)	42 (31-56)

Main diagnosis at the ICU hospitalization					
Pneumonia	888 (5.1)	721 (4.1)	1439 (4.0)	1532 (3.2)	4580 (3.9)
Septicemia	1367 (7.9)	1038 (6)	1604 (4.5)	1628 (3.4)	5637 (4.8)
Infectious diseases excluding pneumonia and septicemia	794 (4.6)	743 (4.3)	1448 (4.0)	1988 (4.2)	4973 (4.2)
Diabetes	206 (1.2)	205 (1.2)	453 (1.3)	674 (1.4)	1538 (1.3)
Endocrine disorders excluding diabetes	322 (1.9)	316 (1.8)	561 (1.6)	687 (1.4)	1886 (1.6)
Cardiovascular diseases	2886 (16.6)	3438 (19.8)	8103 (22.6)	10677 (22.4)	25104 (21.2)
Respiratory diseases	3011 (17.3)	3011 (17.3)	5629 (15.7)	6018 (12.6)	17669 (14.9)
Gastrointestinal and liver diseases	1826 (10.5)	1468 (8.4)	2620 (7.3)	2655 (5.6)	8569 (7.2)
Cancer	1212 (7.0)	933 (5.4)	1732 (4.8)	2589 (5.4)	6466 (5.5)
Trauma and poisoning	1858 (10.7)	2426 (13.9)	5663 (15.8)	9243 (19.4)	19190 (16.2)
Other	2989 (17.2)	3100 (17.8)	6679 (18.6)	10008 (21.0)	22776 (19.2)

Abbreviations: n, number; IQR, interquartile range; DKK, Danish kroner; nsNSAIDs, non-specific non-steroid anti-inflammatory drugs; COX-2 inhibitors, cyclooxygenase-2-inhibitors; ICU, intensive care unit

[a]Translated to US dollars, the income groups were $18,878 or less, $18,878-$24,294, $24,294-$35,486, $35,486 or more (as of December 14, 2016).

Supplemental Figure 1

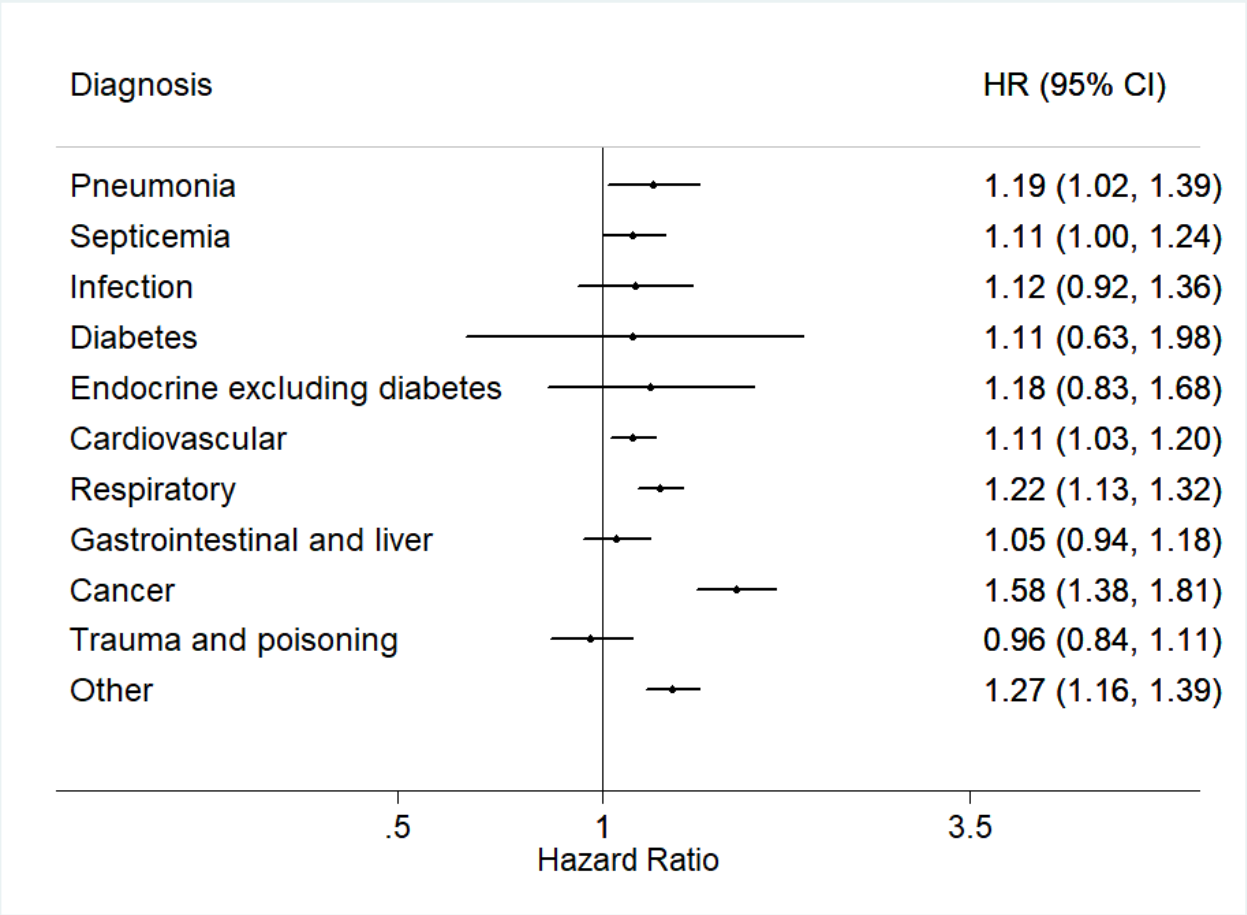

Figure 1 Risk of all-cause mortality of current users compared with non-users following ICU admission by hospital admission diagnosis. Adjusted for age, sex, socioeconomic factors, comorbidity, and concomitant medication use. Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplemental Table 4. All-cause mortality following ICU admission associated with current use of opioids categorized according to immunosuppression. Adjusted for age, sex, socioeconomic factors, comorbidity, and concomitant medication use

Exposure	Cumulative incidence % (95% CI)	30-day mortality, HR (95% CI)	Cumulative incidence % (95% CI)	31-365-day mortality, HR (95% CI)
Non-users	20.6 (20.2-20.9)	1	9.8 (9.5-10.1)	1
Strong immunosuppression	35.0 (33.5-36.6)	1.27 (1.20 - 1.33)	29.7 (27.9-31.7)	1.60 (1.48 - 1.73)
Weak immunosuppression	35.8 (33.9-37.7)	1.21 (1.16 - 1.27)	29.2 (27.0-31.5)	1.45 (1.36 - 1.55)
Other	35.0 (34.1-35.8)	1.13 (1.01 - 1.27)	21.8 (20.9-22.8)	1.49 (1.27 - 1.74)

Abbreviations: CI, confidence interval; HR, hazard ratio

Supplemental Table 5. All-cause mortality following ICU admission associated with type of opioid among current users, adjusted by age, sex, civil status, comorbidity, and concomitant medication use.

Exposure	30-day mortality HR (95% CI)	31-365-day mortality HR (95% CI)
Non-users	1	1
Morphine	1.26 (1.18 - 1.35)	1.86 (1.69 - 2.06)
Hydromorphone	3.24 (1.35 - 7.82)	1.56 (0.22 - 11.11)
Nicomorphine	1.10 (0.68 - 1.81)	1.66 (0.83 - 3.32)
Oxycodone	1.22 (1.13 - 1.31)	1.68 (1.52 - 1.87)
Ketobemidone	1.15 (1.01 - 1.30)	1.61 (1.35 - 1.93)
Pethidine	1.12 (0.75 - 1.70)	1.39 (0.75 - 2.59)
Fentanyl	1.36 (1.22 - 1.52)	2.04 (1.74 - 2.39)
Dextropropoxyphen	1.08 (0.68 - 1.72)	1.65 (0.86 - 3.18)
Buprenorphine	1.31 (1.16 - 1.48)	1.59 (1.30 - 1.94)
Tramadol	1.20 (1.14 - 1.26)	1.36 (1.26 - 1.47)
Tapentadol	1.04 (0.39 - 2.76)	1.57 (0.39 - 6.28)
Noscapine	1.34 (0.64 - 2.81)	1.00 (0.25 - 4.01)
Dextromethrophan	1.54 (1.03 - 2.31)	0.16 (0.02 - 1.16)
Codeine	1.24 (1.16 - 1.33)	1.24 (1.10 - 1.40)

Abbreviations: CI, confidence interval; HR, hazard ratio

Supplemental Table 6. Ten most frequent immediate causes of death 0-30 days following ICU-admission by exposure status.

Immediate cause of death 0-30 day							
Current		Recent		Former		Non-user	
Diseases of the airways	1862 (36.3)	Diseases of the airways	1481 (34.8)	Diseases of the airways	2597 (35.5)	Diseases of the airways	2499 (31.6)
Infectious disease (including parasites)	768 (15.0)	Infectious disease (including parasites)	598 (14.1)	Poorly defined causes	955 (13.1)	Other circulatory diseases	1039 (13.1)
Poorly defined causes	640 (12.5)	Poorly defined causes	533 (12.5)	Heart diseases	867 (11.9)	Heart diseases	1034 (13.1)
Heart diseases	538 (10.5)	Heart diseases	486 (11.4)	Infectious disease (including parasites)	833 (11.4)	Poorly defined causes	922 (11.7)
Other circulatory diseases	324 (6.3)	Other circulatory diseases	359 (8.4)	Other circulatory diseases	762 (10.4)	Infectious disease (including parasites)	893 (11.3)
Diseases of the digestive system	285 (5.6)	Diseases of the digestive system	236 (5.5)	Diseases of the digestive system	385 (5.3)	Disease of the nervous system	414 (5.2)
Malignancy	208 (4.1)	Disease of the nervous system	129 (3.0)	Disease of the nervous system	298 (4.1)	Diseases of the digestive system	408 (5.2)
Disease of the nervous system	117 (2.3)	Malignancy	109 (2.6)	Death without medical information	161 (2.2)	Death without medical information	176 (2.2)
Disease of the urological or genital system	116 (2.3)	Disease of the urological or genital system	109 (2.6)	Disease of the urological or genital system	142 (1.9)	Malignancy	172 (2.2)
Death without medical information	107 (2.1)	Death without medical information	85 (2.0)	Malignancy	129 (1.8)	Disease of the urological or genital system	159 (2.0)

Supplemental Table 7. Ten most frequent underlying causes of death within 0-30 days following ICU-admission by exposure status.

Underlying cause of death 0-30 day							
Current		Recent		Former		Non-user	
Malignancy	1370 (22.5)	Diseases of the airways	1007 (20.3)	Diseases of the airways	1804 (20.6)	Other circulatory diseases	1749 (17.9)
Diseases of the airways	1200 (19.7)	Heart diseases	855 (17.2)	Heart diseases	1516 (17.3)	Heart diseases	1689 (17.3)
Heart diseases	828 (13.6)	Malignancy	744 (15.0)	Other circulatory diseases	1355 (15.5)	Diseases of the airways	1667 (17.1)
Diseases of the digestive system	716 (11.8)	Diseases of the digestive system	599 (12.0)	Diseases of the digestive system	1080 (12.4)	Malignancy	1150 (11.8)
Other circulatory diseases	581 (9.6)	Other circulatory diseases	572 (11.5)	Malignancy	878 (10.0)	Diseases of the digestive system	1094 (11.2)
Infectious disease (including parasites)	248 (4.1)	Accidents	211 (4.2)	Accidents	431 (4.9)	Accidents	544 (5.6)
Endocrinological and nutritional	221 (3.6)	Endocrinological and nutritional	185 (3.7)	Infectious disease (including parasites)	301 (3.4)	Infectious disease (including parasites)	350 (3.6)
Accidents	219 (3.6)	Infectious disease (including parasites)	184 (3.7)	Endocrinological and nutritional	274 (3.1)	Disease of the nervous system	286 (2.9)
Disease of the urological or genital system	131 (2.2)	Disease of the nervous system	113 (2.3)	Disease of the nervous system	234 (2.7)	Endocrinological and nutritional	255 (2.6)
Disease of the nervous system	126 (2.1)	Disease of the urological or genital system	112 (2.3)	Psychiatric disease	181 (2.1)	Psychiatric disease	186 (1.9)

Supplemental Figure 2

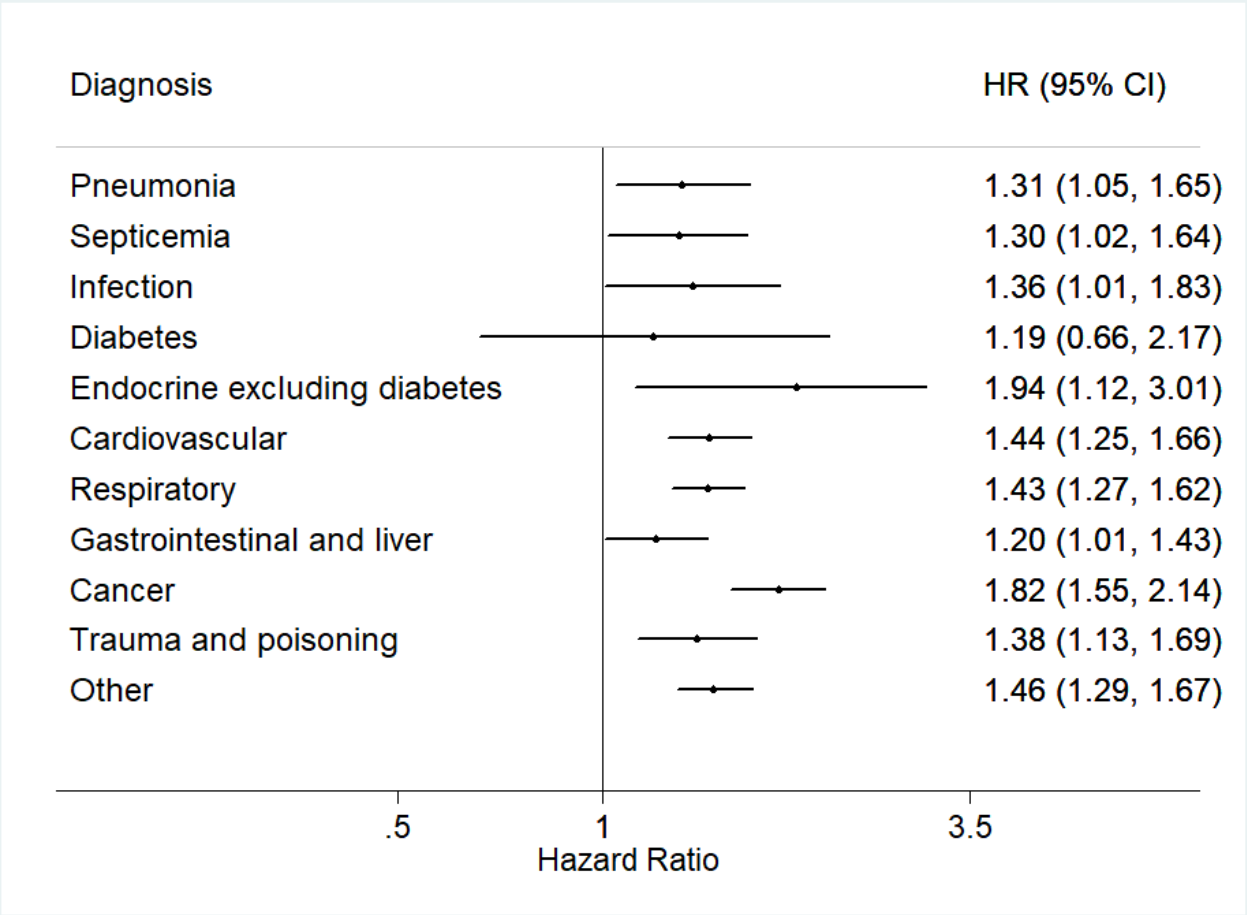

Figure 2 Risk of all-cause mortality of current users compared with non-users following ICU admission by hospital admission diagnosis. Adjusted for age, sex, socioeconomic factors, comorbidity, and concomitant medication use. Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplemental Table 8. Ten most frequent immediate causes of death within 31-365 days following ICU-admission by exposure status.

Immediate cause of death 31-365 day							
Current		Recent		Former		Non-user	
Diseases of the airways	2573 (34.8)	Diseases of the airways	2124 (34.3)	Diseases of the airways	3607 (35.3)	Diseases of the airways	3458 (31.7)
Infectious disease (including parasites)	962 (13.0)	Poorly defined causes	791 (12.8)	Poorly defined causes	1383 (13.5)	Heart diseases	1382 (12.7)
Poorly defined causes	934 (12.6)	Infectious disease (including parasites)	754 (12.2)	Heart diseases	1216 (11.9)	Poorly defined causes	1341 (12.3)
Heart diseases	772 (10.4)	Heart diseases	707 (11.4)	Infectious disease (including parasites)	1056 (10.3)	Other circulatory diseases	1241 (11.4)
Malignancy	621 (8.4)	Other circulatory diseases	473 (7.6)	Other circulatory diseases	932 (9.1)	Infectious disease (including parasites)	1130 (10.4)
Other circulatory diseases	421 (5.7)	Malignancy	361 (5.8)	Diseases of the digestive system	543 (5.3)	Malignancy	565 (5.2)
Diseases of the digestive system	377 (5.1)	Diseases of the digestive system	321 (5.2)	Malignancy	385 (3.8)	Diseases of the digestive system	541 (5.0)
Disease of the urological or genital system	170 (2.3)	Disease of the urological or genital system	175 (2.8)	Disease of the nervous system	353 (3.5)	Disease of the nervous system	470 (4.3)
Death without medical information	163 (2.2)	Disease of the nervous system	156 (2.5)	Disease of the urological or genital system	238 (2.3)	Death without medical information	255 (2.3)
Disease of the nervous system	140 (1.9)	Death without medical information	131 (2.1)	Death without medical information	236 (2.3)	Disease of the urological or genital system	235 (2.2)

Supplemental Table 9. Ten most frequent underlying causes of death within 31-365 days following ICU-admission by exposure status.

Underlying cause of death 31-365 day							
Current		Recent		Former		Non-user	
Malignancy	2365 (27.0)	Diseases of the airways	1462 (20.2)	Diseases of the airways	2474 (20.4)	Diseases of the airways	2268 (17.0)
Diseases of the airways	1629 (18.6)	Malignancy	1371 (19.0)	Heart diseases	2074 (17.1)	Heart diseases	2228 (16.7)
Heart diseases	1140 (13.0)	Heart diseases	1179 (16.3)	Other circulatory diseases	1647 (13.6)	Malignancy	2134 (16.0)
Diseases of the digestive system	912 (10.4)	Diseases of the digestive system	776 (10.7)	Malignancy	1642 (13.5)	Other circulatory diseases	2103 (15.7)
Other circulatory diseases	773 (8.8)	Other circulatory diseases	753 (10.4)	Diseases of the digestive system	1373 (11.3)	Diseases of the digestive system	1374 (10.3)
Endocrinological and nutritional	340 (3.9)	Endocrinological and nutritional	284 (3.9)	Accidents	511 (4.2)	Accidents	633 (4.7)
Infectious disease (including parasites)	312 (3.6)	Accidents	253 (3.5)	Infectious disease (including parasites)	399 (3.3)	Infectious disease (including parasites)	445 (3.3)
Accidents	270 (3.1)	Infectious disease (including parasites)	245 (3.4)	Endocrinological and nutritional	399 (3.3)	Disease of the nervous system	411 (3.1)
Disease of the urological or genital system	178 (2.0)	Disease of the nervous system	157 (2.2)	Disease of the nervous system	325 (2.7)	Endocrinological and nutritional	376 (2.8)
Disease of the nervous system	176 (2.0)	Disease of the urological or genital system	153 (2.1)	Psychiatric disease	278 (2.3)	Psychiatric disease	287 (2.1)

Paper II

Pre-admission opioid use and risk of death following incident myocardial infarction

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Abstract

Background: Opioids may delay onset and attenuate the effects of certain platelet inhibitors, may increase platelet aggregation, and may alter hormonal stress response to an MI thus leading to poor prognosis for recipients of opioids.

Objective: To examine one year all-cause mortality following MI between pre-admission opioid users and non-users.

Methods: This cohort study included all patients hospitalized for incident MI between 2006 and 2012. They were identified using Danish nationwide medical and administrative registries. Patients were categorized by the timing of their last redeemed opioid prescription prior to MI admission, as follows: current users (prior 0-30 days), recent users (prior 31-365 days), former users (prior 365+ days), and non-users. The outcome was one-year all-cause mortality following first-time MI admission. The Kaplan-Meier method was used to compute mortality risk. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox regression. Adjusted models included age, gender, civil status as a proxy for socioeconomic status, comorbidity burden (defined by Charlson Comorbidity Index scores), surgery in the previous six months, and concurrent medication use.

Results: The study included 67,742 MI patients, among whom 9% were current opioid users, 10% were recent users, 13% were former users, and 69% were non-users. Absolute one-year mortality was 42% for current users, 30% for recent users, 23% for former users, and 19% for non-users. Compared with non-users, current users had an elevated risk of one-year all-cause mortality, with an adjusted HR of 1.32 [95% confidence interval (CI) 1.26 - 1.39)]. New users of opioids suffered the highest risk, with an adjusted HR of 1.47 (95% CI 1.30 - 1.65). Following

adjustment, neither recent nor former users were at elevated risk. No dose-response relation was observed in stratified analysis of the strength of the last prescription or cumulative use. Stratification by type of MI indicated potentially higher risk among ST-elevation myocardial infarction patients [HR 1.53 (95% CI 1.31 - 1.79)] than among non-ST-elevation myocardial infarction patients [HR 1.29 (95% CI 1.17 - 1.41)]. Estimates were stable across quartiles of peak Troponin T levels.

Conclusions: Current opioid use was associated with increased one-year mortality following MI.

Key words:

1. Background

Opioids are widely used drugs that act on the nervous system to relieve pain [1]. Danes have since the 1980s been among the top per capita consumers worldwide [2, 3]. However, over the past decades usage has escalated and in 2015 more than one third of all US adults reported prescription opioid use [4]. In parallel with the increased use there has been an alarming increase in unintentional drug overdoses.[5-7] Drug overdoses result in more than 100 daily deaths of which overdose with opioids constitutes two-thirds.[8] Continued use and abuse of opioids is common and opioid usage is thus a major public health problem.

Approximately 8000 patients are admitted each year in Denmark with acute myocardial infarction (MI) [9]. Mortality has decreased with more than 50% since 1983, however mortality remains high with 15% dying within the first 30 days [9]. Recent evidence suggests that treatment with morphine during a MI may be associated with a poor prognosis [10-13], although results are conflicting [14, 15]. The proposed mechanisms through which opioids may adversely affect prognosis include their effect on platelet aggregation, which has been observed both *in vitro* and *in vivo* [16, 17], drug-drug interactions with platelet inhibitors (P2Y12-receptor antagonists in particular) [18-20], and opioid-induced depression of cortisone levels [21].

So far, studies have focused on risk associated with opioids administered as part of MI treatment. No previous study has examined prognosis following incident MI among prevalent opioid users – *i.e*. patients with ongoing opioid treatment at time of their MI. However, as prevalent opioid users are already exposed at time of MI, they may constitute an at-risk group with a poor prognosis. Given the widespread use of opioids, any impact of opioid use on MI

prognosis could have a great public health impact and would potentially identify a large patient subgroup at risk.

We therefore examined the impact of current and prior opioid use on all-cause mortality following incident MI.

2. Methods

2.1 Setting

We conducted this nationwide registry-based cohort study in Denmark, where the National Health Service provides universal healthcare, guaranteeing equal access to general practitioners and hospitals, together with partial reimbursement for prescribed drugs, including opioids [22]. Three Danish registries were used to collect information (see below). The unique central personal register number assigned to each Danish resident at birth or upon immigration allows unambiguous record-linkage among registries[23].

2.2 Study population

All patients with a first-time primary diagnosis of MI between January 2006 and December 2012 were included in the study cohort, based on ICD-10 codes in the Danish National Patient Registry. This Registry has maintained inpatient records from Danish hospitals since 1977 [24]. Only patients admitted to hospital were included in our study, as MI diagnosed in an emergency ward or outpatient clinic may be subject to misclassification. All patients in the study cohort were followed until date of death, emigration, 31 December 2012, or 365 days of follow-up, whichever came first.

2.3 Opioid exposure

Opioid users were identified using Anatomical Therapeutic Chemical codes (see Appendix) for opioids recorded in the Danish National Health Service Prescription Database [22]. This database captures all redeemed prescriptions of drugs since 2004, which are covered by the general or specific drug cost reimbursement plan. The database does not capture opioids used for substitution therapy as these are administered through outpatient clinics.

Patients were classified as current users, recent users, former users, and non-users, based on pre-admission opioid use. Current users were defined as having redeemed a prescription for opioids within 30 days prior to their incident MI. A 30-day window was chosen pragmatically to reduce risk of misclassification. Recent users were defined as having redeemed a prescription within 31-365 days prior to their incident MI. Former users were defined as having redeemed at least one prior prescription for opioids, but none within 365 days of their incident MI. Patients who, according to the prescription database, had never redeemed a prescription for opioids before their incident MI were considered non-users.

Long-term opioid users are less likely to suffer adverse side effects and to some degree adapt to the drug's effects [25]. To investigate a potential development of tolerance, current users were defined either as new users (first-ever opioid prescription within 30 days prior to MI) or long-term users (first prescription redeemed earlier than 30 days prior to MI) [25].

The total oral morphine equivalent (OMEQ) of the last opioid prescription prior to incident MI was calculated for current users (e-Table 2), in order to examine the possible existence of a dose-effect relationship. Use was further categorized as low (<375 OMEQ), intermediate (375-750 OMEQ), high (751-1500 OMEQ), and very high (>1500 OMEQ).

To examine the potential effect of cumulative opioid use on mortality, current users were classified based on their usage in the year prior to their MI as either low users (<4500 mg OMEQ/year), intermittent users (4500-9000 mg OMEQ/year), daily users (9001-18,000 mg OMEQ/year), or patients with persistent therapeutic concentrations of opioids - continuous users (>18,000 mg OMEQ/year) [26].

To examine potential differences between generic opioids, we also stratified exposure according to the generic opioid used in the last prescription redeemed prior to MI.

2.4 Outcomes

The study outcome was all-cause mortality during the first year following hospitalization for MI. Information on all-cause mortality was obtained from the Danish Civil Registration System, which has recorded all changes in vital status and migration for the Danish population since 1968, currently with daily updates [23].

2.5 Concomitant drug use

Concomitant drug use was defined as a redeemed prescription within 90 days (to ensure capture of nearly all drug use) prior to the MI for any of the following drugs: angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers, beta blockers, calcium antagonists, lipid-lowering therapy (statins, fibrates, etc.) diuretics, acetylsalicylic acid, other anti-thrombotic therapy (including P2Y12-receptor inhibitors, vitamin-K antagonists, and direct oral anticoagulants), tricyclic antidepressants, serotonin and norepinephrine reuptake

inhibitors, selective serotonin reuptake inhibitors, benzodiazepine-derivates, antiepileptics, oral corticosteroids, and non-steroidal anti-inflammatory drugs (excluding glucosamine) classified into non-specific NSAIDs and coxibs (non-steroidal anti-inflammatory drugs with high affinity for the COX-II-receptor).

2.6 Covariates

Information on age, sex, and civil status was obtained from the Danish Civil Registration System. Based on civil status at the time of MI, patients were classified as "unmarried", "married/registered partnership", or "divorced/widowed". Data on all surgeries during 6 months prior to incident MI and data on treatment of MI (percutaneous coronary intervention and/or coronary artery bypass graft during hospitalization) were extracted from the Danish National Patient Registry based on procedure codes. We also obtained data on comorbidities, from 1977 up to the date of incident MI, from the Danish National Patient Registry. Severity of comorbidity was categorized using the Charlson Comorbidity Index (CCI), excluding myocardial infarction. CCI scores of 0 were defined as a low comorbidity level, 1 as a moderate comorbidity level, 2 as a severe comorbidity level, and ≥3 as a very severe comorbidity level [27]. Troponin T levels were available for a subset of the study population through the laboratory information systems (LABKA) database. The LABKA database contains information on virtually all laboratory analyses performed in the North and Central Denmark regions in the study period, covering in total 1,901,947 residents [28]. We used the peak troponin T level within 24 hours of admission as a proxy measure for infarct size [29].

2.7 Statistical analysis

We tabulated covariates by opioid exposure groups and used the Kaplan-Meier method to compute one-year all-cause mortality following incident MI.

Cox proportional hazards regression analysis was used to compute hazard ratios with 95% confidence intervals as a measure of the relative risk of all-cause mortality within one year following incident MI. control adjust for possible confounding, models included age, sex, civil status, CCI score, any surgery in the prior 6 months, and concurrent medication use. Proportionality of hazards was tested visually by using log-log plots and found valid. Additional analyses included categorization of current users by strength of their last opioid prescription and by cumulative use, as defined above. Similarly, we grouped users by the opioid compound dispensed in their last prescription prior to incident MI, to examine possible differences associated with choice of opioid type.

To examine any potential effect modification, we conducted a number of subgroup analyses stratified by type of MI (nSTEMI/STEMI), treatment (PCI/no PCI), comorbidity status (cancer and COPD), and quartiles of peak troponin T levels.

In a sensitivity analysis, we re-ran our fully adjusted models with different cutoff points for current and recent use (redeemed prescription for an opioid within 15 days, 30 days, 45 days, or 60 days prior to MI) to test our assumption of an opioid prescription lasting approximately 30 days.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002; AU record number: 2016-051-000001/818).

3.0 Results

3.1 Patient characteristics

We identified 67,742 patients with an incident MI during the study period. The majority [41,590 patients (67%)] were opioid non-users. Current opioid users constituted the smallest group [5679 (9%)], with 697 new users and 4982 long-term users. Current users were generally older, more likely to be female, and more often divorced or widowed than non-users. Current users also were more likely to suffer from comorbid conditions and more likely to take concurrent medications (Table 1).

3.2 One-year all-cause mortality

During the study period, the observed absolute risk of all-cause mortality was highest among current users and decreased with recency of opioid use (Figure 1). At 365 days post-MI, cumulative all-cause mortality among current users was 41.9% [95% confidence interval (CI), 40.6%-43.2%)] (Table 2). In contrast, non-users had an absolute mortality risk of 19.4% (95% CI, 19.0%-19.7%), corresponding to a crude HR of 2.45 (95% CI, 2.34-2.56) for current users compared with non-users. While this association was attenuated in multivariate adjusted models, the relative risk remained elevated for current users [HR 1.32 (95% CI, 1.26-1.39)]. The relative risk appeared higher for new users [HR 1.47 (95% CI 1.30-1.65)] than for long-term users [HR 1.30 (95% CI 1.23-1.37)]. Compared with non-users, neither former nor recent users had an elevated risk of all-cause mortality in adjusted models.

3.3. Additional analyses

No clear dose-response relation was observed when opioid users were grouped according to the strength of their last opioid prescription prior to MI, nor when they were grouped according to cumulative opioid use (Table 3).

In stratified analyses, we observed that mortality estimates varied according to type of MI, treatment, and cancer status, but current users of opioids were at elevated risk across all strata when compared with non-users (Table 4). This was more pronounced among new users than among long-term users. Neither COPD status nor peak troponin T level affected our estimates.

Among current opioid users, all opioids except pethidine and dextropropoxyphen were associated with increased risk of one-year mortality. Users of morphine, nicomorphine, oxycodone, fentanyl, buprenorphine, and tapentadol appeared to be at particularly high risk. However, some groups of opioid users were small, making estimates imprecise (see Supplemental Table 4). Similarly, most opioids were associated with increased risk among recent users of opioids. Notably, however, use of tramadol only slightly increased mortality risk and use of oxycodone and fentanyl did not increase risk.

Estimates were stable across different exposure windows of current and recent users (Supplemental Table 3).

4.0 Discussion

Our study is the first to examine prognosis following MI among prevalent opioid users. However, a few prior studies have examined the impact of morphine used to quell pain

associated with MI. Consistent with our findings, Meine *et al.* found higher in-hospital mortality among recipients of morphine compared with non-recipients [odds ratio 1.41 (95% CI, 1.26–1.57)] [12]. Their large cohort study based on the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) database included 57,039 nSTEMI patients, among whom 17,003 received morphine as part of nSTEMI treatment. These findings led the American Heart Association/American College of Cardiology to update their guidelines to recommend morphine only as pain relief for nSTEMI in the absence of effects from other anti-ischemic medications [30]. A smaller study by Waha *et al.* of 291 STEMI patients found that administration of morphine as part of STEMI treatment was associated with larger infarct size, microvascular obstruction, and less myocardial salvage [13]. Morphine treatment was not associated with increased risk of the composite endpoint of non-fatal myocardial reinfarction or death within 16 months of the index date. However, the study was underpowered for this endpoint.

In contrast, both Puymirat *et al.* and Lakobishvili *et al.* found no association between pre-hospital morphine administration and one-year mortality [14, 15]. Puymirat *et al.*'s study included 2438 STEMI patients, of whom 453 received morphine [14]. Lakobishvili *et al*.'s study included both nSTEMI (n= 993) and STEMI (n=765) patients, with 261 STEMI and 97 nSTEMI patients receiving morphine [15]. Both studies were limited by relatively small numbers of morphine recipients, low number of outcomes, risk of misclassification of exposure status (prevalent opioid users could have been categorized as non-exposed), and by substantial differences between comparison groups regarding infarction size, time-to-needle, administration of dual-antiplatelet therapy, and resolution of ischemia.

Finally, a study by Bonin *et al.* found a slightly higher rate of major adverse cardiovascular events within one year among recipients of morphine for STEMI-associated chest pain, compared with non-recipients [31]. Specifically, recurrent MI and heart failure appeared more common among recipients of morphine. These differences failed to reach statistical significance. However, the study was small and thus suffered from a lack of precision [31].

Any interpretation of our study results regarding underlying causes remains speculative. However, multiple studies (including double-blinded randomized clinical trials) in the wake of the study by Meine *et al.* suggest that opioids attenuate the effect of P2Y12-agonists (with lower plasma levels, delayed onset, and less inhibition of platelet activity). P2Y12-agonists are part of dual anti-platelet therapy, which is considered standard treatment both acutely and for up to one year following MI [18-20, 32-34]. The exact mechanism is unclear, but may be related to delayed gastric emptying. Further, opioids may have a direct effect on the propensity of platelets to aggregate [16, 17]. This could potentially explain the observed increased relative risk experienced by prevalent opioid users, as their anti-platelet therapy may be insufficient.

There are several possible explanations for the stronger association we observed among new opioid users compared to long-term opioid users. Our finding may reflect a mechanistic difference, as the effects of opioids may attenuate with prolonged use. Another explanation could be that opioid initiation occurs because of unrecognized prodromal symptoms of MI, potentially delaying MI diagnosis in the new-user group and leading to larger MI and subsequently worse outcomes. Conversely, the lower risk among long-term opioid users could

indicate the development of tolerance, as long-term opioid users may represent a selected group of particularly resilient patients [25].

A few prior studies of cardiovascular risk add to opioids' relevance as a public health issue beyond that of addiction and risk of overdose. These studies have found that opioid users may be at increased risk of suffering an MI[35-38]. Two studies found that MI risk associated with opioid use was greater than that associated with use of COX-2 inhibitors. [36, 37] One study found no overall increased risk of MI or need for cardiovascular revascularization, but did detect an increased risk among females. [38] The underlying mechanism remains to be fully elucidated, although hormonal changes associated with opioid use have been posited as a potential explanation[35]. As such, opioid users may be the victims of a two-pronged risk: they may not only suffer an increased risk of MI, but, based on our results, also may have a worse prognosis after MI. Thus, the public health implications of increasing opioid use may be more profound than acknowledged thus far.

Limitations

Some limitations should be considered when interpreting our findings. Although the MI diagnosis has recently been validated, showing a high positive predictive value [39], between-group differences regarding severity of MI might exist and could potentially confound our results. However, peak troponin T levels did not substantially differ across exposure groups, nor did size of our estimates change in an analysis stratified by peak troponin T quartile.

Even in this nationwide study which included all hospitalized MI patients diagnosed in the study period, there is a small risk of selection bias: the registers do not capture patients

who suffered an MI but died prior to hospital admission (and were not subsequently brought to the hospitals).

Further, there is a risk of misclassification bias as we utilized a prescription registry and thus cannot be certain that persons who redeemed a prescription for an opioid actually took their medication [40]. However, the risk of patients not adhering to treatment is lessened by the requirement that patients pay out-of-pocket for a portion of prescription costs. It is also reassuring that a sensitivity analysis using a different exposure classification yielded no substantial change in estimates. Such potential misclassification of exposure would bias the estimates towards the null and thus would not explain the positive associations found in the study [41].

The possibility of residual confounding cannot be excluded even in the adjusted models, despite adjustment for factors such as socioeconomic status, comorbidity, and comedication. Residual confounding is especially a concern in the analysis stratified by cancer status, as we were unable to account properly for severity of disease. This likely differed between comparison groups. However, opioid users suffered an increased risk even among non-cancer patients.

5.0 Conclusion

We found that opioid use at time of first-time hospitalization for myocardial infarction was associated with increased one-year all-cause mortality. While new users of opioids appeared to be at particularly elevated risk, the risk was also increased among long-term users. These associations were stable regardless of infarction size as estimated by peak troponin T levels.

Conflict of interests

None of the authors report conflict of interests. However, 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 these studies has any relation to the present study.

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Tables and figures

Table 1. Characteristics of the study population. Data are provided as numbers (%) except for age and Troponin T, which are provided as medians (25^{th} percentile-75^{th} percentile).

	Total 61,742 (100 %)	Non-users 41,590 (67.4%)	Former opioid users 8,208 (13.3 %)	Recent opioid users 6,265 (10.1 %)	Current opioid users 5,679 (9.2 %)
Age	71.1 (60.5-81.0)	69.2 (59.2-79.6)	72.8 (61.5-82.2)	75.2 (64.3-83.4)	76.3 (66.3-84.2)
18-49	5,427 (8.8)	4,097 (9.9)	687 (8.4)	395 (6.3)	248 (4.4)
50-59	9,437 (15.3)	7,042 (16.9)	1,139 (13.9)	719 (11.5)	537 (9.5)
60-69	14,413 (23.3)	10,471 (25.2)	1,713 (20.9)	1,181 (18.9)	1,048 (18.5)
70-79	15,475 (25.1)	9,951 (23.9)	2,162 (26.3)	1,737 (27.7)	1,625 (28.6)
≥80	16,990 (27.5)	10,029 (24.1)	2,507 (30.5)	2,233 (35.6)	2,221 (39.1)
Gender (male)	37,931 (61.4)	27,561 (66.3)	4,663 (56.8)	3147 (50.2)	2560 (45.1)
Civil status					
Single	5,813 (9.4)	4,277 (10.3)	654 (8.0)	447 (7.1)	435 (7.7)
Married/Registered partnership	32,372 (52.4)	23,062 (55.5)	4,149 (50.5)	2,863 (45.7)	2,298 (40.5)
Divorced/widowed	23,557 (38.2)	14,251 (34.3)	3,405 (41.5)	2,955 (47.2)	2,946 (51.9)
Concomitant medication					

ACE-i/ARB	16,216 (26.3)	9,943 (23.9)	2,486 (30.3)	1,955 (31.2)	1,832 (32.3)
β-blockers	10,943 (17.7)	6,538 (15.7)	1,658 (20.2)	1,429 (22.8)	1,318 (23.2)
Calcium antagonists	10,459 (16.9)	6,232 (15.0)	1,593 (19.4)	1,340 (21.4)	1,294 (22.8)
Statins	11,462 (18.6)	6,828 (16.4)	1,836 (22.4)	1,440 (23.0)	1,358 (23.9)
Diuretics	16,503 (26.7)	9,137 (22.0)	2,471 (30.1)	2,355 (37.6)	2,540 (44.7)
Anti-thrombotics	6,443 (10.4)	3,481 (8.4)	1,091 (13.3)	941 (15.0)	930 (16.4)
Tricyclic antidepressants	1,120 (1.8)	416 (1.0)	166 (2.0)	183 (2.9)	355 (6.5)
Serotonin and norepinephrine reuptake inhibitors	743 (1.2)	348 (0.8)	130 (1.6)	110 (1.8)	155 (2.7)
Selective serotonin reuptake inhibitors	4,940 (8.0)	2,380 (5.7)	769 (9.4)	757 (12.1)	1,034 (18.2)
Benzodiazepine derivates	177 (0.5)	61 (0.1)	19 (0.2)	24 (0.4)	73 (1.3)
Antiepileptics	1,934 (3.1)	745 (1.8)	315 (3.8)	356 (5.7)	518 (9.1)
Oral corticosteroids	1,056 (1.7)	694 (1.7)	152 (1.9)	108 (1.7)	102 (1.8)
Acetylsalicylic acid, high	1,858 (3.0)	1,160 (2.8)	217 (2.6)	227 (3.6)	254 (4.5)
Acetylsalicylic acid, low	12,390 (20.1)	7,223 (17.4)	1,939 (23.6)	1,607 (25.7)	1,621 (28.5)
nsNSAIDs	4,841 (7.8)	2,445 (5.9)	717 (8.7)	810 (12.9)	869 (15.3)
COX2-inhibitors	2,715 (4.4)	1,349 (3.2)	357 (4.3)	461 (7.4)	548 (9.6)

Any surgery	11,223 (18.2)	5,666 (13.6)	1,649 (20.1)	1,952 (31.2)	1,956 (34.4)
Comorbidity					
Congestive heart failure	4,622 (7.5)	2,273 (5.5)	768 (9.4)	802 (12.8)	779 (13.7)
Peripheral vascular disease	6,300 (10.2)	2,855 (6.9)	1,103 (13.4)	1,113 (17.8)	1,229 (21.6)
Cerebrovascular disease	5,720 (9.3)	3,062 (7.4)	968 (11.8)	826 (13.2)	864 (15.2)
Dementia	1,168 (1.9)	613 (1.5)	182 (2.2)	165 (2.6)	208 (3.7)
Chronic pulmonary disease	7,153 (11.6)	3,452 (8.3)	1,175 (14.3)	1,222 (19.5)	1,304 (23.0)
Connective tissue disease	2,853 (4.6)	1,209 (2.9)	563 (6.9)	535 (8.5)	546 (9.6)
Ulcer disease	3,916 (6.3)	1,785 (4.3)	656 (8.0)	658 (10.5)	817 (14.4)
Mild liver disease	716 (1.2)	350 (0.8)	124 (1.5)	115 (1.8)	127 (2.2)
Diabetes	6,089 (9.9)	3,168 (7.6)	1,060 (12.9)	941 (15.0)	920 (16.2)
Renal disease	2,369 (3.8)	1,067 (2.6)	432 (5.3)	474 (7.6)	396 (7.0)
Any tumor	7,159 (11.6)	3,887 (9.3)	1,140 (13.9)	1,024 (16.3)	1,108 (19.5)
Leukemia	225 (0.4)	102 (0.2)	39 (0.5)	35 (0.6)	49 (0.9)
Lymphoma	465 (0.8)	238 (0.6)	75 (0.9)	71 (1.1)	81 (1.4)
Metastatic solid tumor	635 (1.0)	255 (0.6)	84 (1.0)	128 (2.0)	168 (3.0)
Comorbidity category[†]					

Low	32,647 (52.9)	25,621 (61.6)	3,537 (43.1)	2,046 (32.7)	1,443 (25.4)
Moderate	11,112 (18.0)	6,881 (16.5)	1,651 (20.1)	1,359 (21.7)	1,221 (21.5)
Severe	8,596 (13.9)	5,008 (12.0)	1,331 (16.2)	1,120 (17.9)	1,137 (20.0)
Very severe	9,387 (15.2)	4,080 (9.8)	1,689 (20.6)	1,740 (27.8)	1,878 (33.1)
Sub-type of myocardial infarction					
nSTEMI	23,388 (37.9)	15,248 (36.7)	3,358 (40.9)	2,610 (41.7)	2,172 (38.2)
STEMI	12,283 (19.9)	8,954 (21.5)	1,660 (20.2)	938 (15.0)	731 (12.9)
Unspecified	26,071 (42.2)	17,388 (41.8)	3,190 (38.9)	2,717 (43.4)	2,776 (48.9)
Treatment					
PCI, unspecified	24,657 (39.9)	18,223 (43.8)	3,207 (39.1)	1,954 (31.2)	1,273 (22.4)
PCI with stent	22,600 (36.6)	16,766 (40.3)	2,936 (35.8)	1,765 (28.2)	1,133 (20.0)
CABG	752 (1.2)	566 (1.4)	103 (1.3)	53 (0.8)	30 (0.5)
Infarction-size*					
Troponin T, n=12,021	1090 (306-3760)	1,320 (370-4,361)	819 (242-3,020)	744 (240-2,560)	700 (218-2,170)

Abbreviations: n, number; ACE-i/ARB, Angiotensin-converting enzyme-inhibitors/Angiotensin-II receptor blockers; nsNSAIDs, non-specific non-steroid anti-inflammatory drugs; COX-2 inhibitors, Cyclooxygenase-2-inhibitors; nSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, Coronary artery bypass graft

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

* Data was available for 12,021 patients (19% of total population). Proportions of exposure-groups were similar to the overall distribution (current: 8%, recent: 10%, former: 15%, non-users: 66%).

Figure 1. Cumulative one-year all-cause mortality following first-time hospital admission for myocardial infarction.

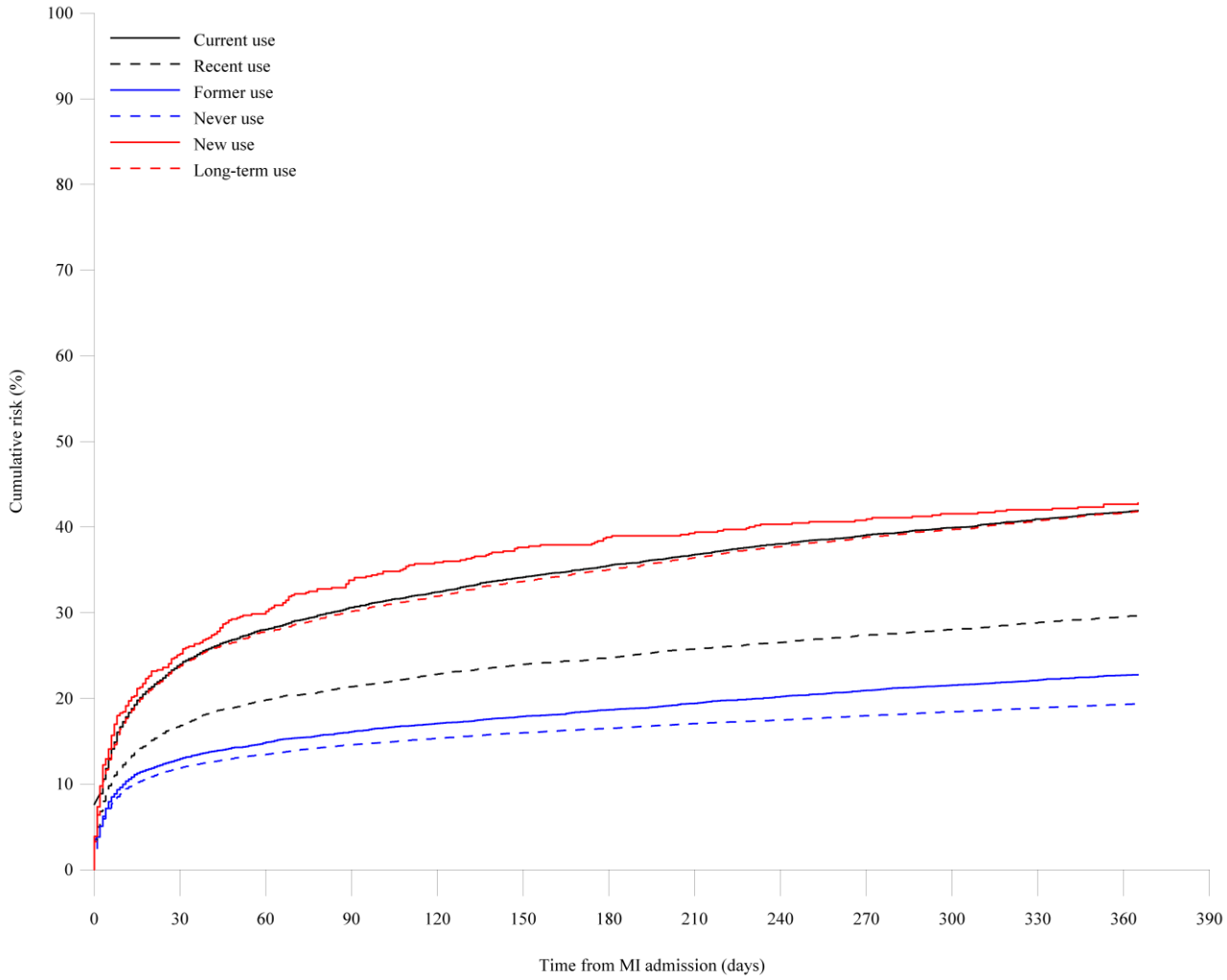

Table 2. Pre-admission opioid use and one year all-cause mortality.

	One-year all-cause mortality		
	Risk, % [95% CI]	Unadjusted, HR [95 %CI]	*Adjusted, HR [95% CI]
Non-users	19.4 (19.0-19.7)	1.00 (ref)	1.00 (ref)
Current users	41.9 (40.6-43.2)	2.45 (2.34-2.56)	1.32 (1.26-1.39)
New users	42.8 (39.2-46.6)	2.55 (2.27-2.87)	1.47 (1.30-1.65)
Long-term users	41.8 (40.4-43.2)	2.43 (2.32-2.55)	1.30 (1.23-1.37)
Recent users	29.7 (28.6-30.9)	1.61 (1.53-1.69)	1.02 (0.97-1.08)
Former users	22.8 (21.9-23.7)	1.18 (1.13-1.25)	0.90 (0.86-0.95)

*Adjusted for age, sex, civil status, comorbidity category, any surgery, and concomitant medication use.

Table 3. Association of all-cause mortality with strength of opioid prescription and cumulative use among current opioid users.

		One-year all-cause mortality		
		Absolute risk estimates	Unadjusted, HR [95 % CI]	*Adjusted, HR [95% CI]
	Non-users		1	1
Strength of last prescription	Low	43.51 (40.65 - 46.47)	2.55 (2.32-2.79)	1.34 (1.22-1.47)
	Intermediate	41.09 (38.23 - 44.09)	2.38 (2.16-2.61)	1.27 (1.15-1.40)
	High	39.16 (37.05 - 41.35)	2.23 (2.08-2.40)	1.27 (1.17-1.37)
	Very high	45.43 (42.79 - 48.17)	2.76 (2.54-3.00)	1.43 (1.31-1.55)
Cumulative use	Short-term	41.83 (39.73 - 43.99)	2.44 (2.28-2.62)	1.40 (1.30-1.51)
	Intermittent	41.61 (38.48 - 44.90)	2.42 (2.18-2.68)	1.26 (1.13-1.40)
	Daily	38.54 (35.74 - 41.48)	2.21 (2.00-2.43)	1.20 (1.09-1.33)
	Continuous	44.87 (42.33 - 47.48)	2.67 (2.46-2.89)	1.35 (1.24-1.46)

*Adjusted for age, sex, civil status, comorbidity category, any surgery, and concomitant medication use.

Table 4. Stratified analysis of one-year all-cause mortality associated with pre-admission opioid use.

	Current users, HR (95% CI)	New users, HR (95% CI)	Long-term users, HR (95% CI)	Recent users, HR (95% CI)	Former use, HR (95% CI)
One-year mortality*					
Overall	1.32 (1.26-1.39)	1.47 (1.30-1.65)	1.30 (1.23-1.37)	1.02 (0.97-1.08)	0.90 (0.86-0.95)
nSTEMI	1.29 (1.17-1.41)	1.32 (1.05-1.67)	1.28 (1.16-1.40)	1.07 (0.98-1.17)	0.90 (0.82-0.98)
STEMI	1.53 (1.31-1.79)	2.39 (1.69-3.37)	1.43 (1.21-1.70)	0.85 (0.71-1.01)	0.90 (0.78-1.04)
No PCI	1.27 (1.20-1.34)	1.34 (1.19-1.53)	1.25 (1.18-1.33)	1.02 (0.97-1.08)	0.91 (0.86-0.96)
PCI	1.46 (1.25-1.71)	2.50 (1.76-3.54)	1.36 (1.14-1.61)	0.87 (0.74-1.03)	0.90 (0.78-1.03)
No cancer	1.16 (1.09-1.23)	1.30 (1.13-1.50)	1.14 (1.07-1.21)	0.97 (0.91-1.03)	0.87 (0.82-0.93)
Cancer	1.84 (1.67-2.04)	1.97 (1.59-2.45)	1.81 (1.62-2.01)	1.10 (0.98-1.23)	0.96 (0.86-1.08)
No COPD	1.33 (1.25-1.40)	1.46 (1.28-1.67)	1.30 (1.22-1.38)	1.00 (0.94-1.07)	0.90 (0.85-0.96)
COPD	1.29 (1.16-1.44)	1.51 (1.14-2.00)	1.27 (1.13-1.42)	1.01 (0.90-1.14)	0.85 (0.76-0.96)
Troponin T 1st quartile	1.44 (1.13-1.85)	1.03 (0.47-2.25)	1.51 (1.17-1.95)	0.98 (0.75-1.27)	0.92 (0.73-1.17)
Troponin T 2nd quartile	1.31 (1.02-1.68)	1.93 (1.10-3.39)	1.26 (0.96-1.64)	1.05 (0.82-1.35)	0.88 (0.70-1.12)

Troponin T 3rd quartile	1.43 (1.08-1.89)	3.13 (1.66-5.91)	1.29 (0.96-1.74)	1.05 (0.77-1.41)	1.05 (0.81-1.35)
Troponin T 4th quartile	1.53 (1.11-2.11)	0.61 (0.14-2.61)	1.62 (1.17-2.25)	0.95 (0.68-1.33)	0.90 (0.68-1.19)

*Adjusted for age, sex, civil status, comorbidity category, surgery, and concomitant medication use.

Appendix

Supplemental Table 1. Codes used in the study

Inclusion		**ICD-10**
Myocardial infarction		I21, I23
Exclusion:	**ICD-8**	**ICD-10**
Myocardial infarction, prior to study period	410	I21, I22, I23
Exposure codes	**ATC codes**	
Opioids	MN02A	
Opioid, cough-suppressant	MR05DA	
Morphine	MN02AA01, MN02AA51	
Hydromorphone	MN02AA03	
Nicomorphine	MN02AA04	
Oxycodone	MN02AA05, MN02AA55	
Ketobemidone	MN02AB01, MN02AG02	

Pethidine	MN02AB02, MN02AB72
Fentanyl	MN02AB03
Dextroproproxyphen	MN02AC04
Pentazocin	MN02AD01
Buprenorphine	MN02AE01
Tramadol	MN02AX02
Tapentadol	MN02AX06
Codeine	MN02AA59
Comedications	
Acetylsalicylic acid, high-dose	MN02BA01
Acetylsalicylic acid, low-dose	MB01AC06
Oral corticosteroids	MR01AD
Glucosamine	MM01AX05
nsNSAIDs	MM01A excluding codes listed as COX-II inhibitors or glucosamine
COX-II inhibitors	MM01AH, MM01AC06, MM01AC56, MM01AB05, MM01AB55, MM01AB08, MM01AX17
Benzodiazepine-derivates	MN05BA
Tricyclic antidepressants	MN06AA
Selective serotonin reuptake inhibitors	MN06AB
Serotonin and norepinephrine reuptake inhibitors	MN06AX16, MN06AX21, MN06AX23
Antiepileptics	MN03A
ACE-I / angiotensin-2 receptor blockers	MC09
β-blockers	MC07
Calcium antagonists	MC08
Statins	MC10
Diuretics	MC03
Anti-thrombotics	MB01A

Comorbidity	**ICD-8**	**ICD-10**
Any surgery	0000-9999-1996-2011	KA-KZ
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31,M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease		B18, K70.0-K70.3, K70.9, K71, K73
Diabetes without end-organ damage	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 50.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes with end-organ damage	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8, E11.2-E11.8
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Non-metastatic solid tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Metastatic cancer	195-198, 199	C76-C80
Opioid abuse	30409	DF11
Alcohol abuse	303	DF10
Schizophrenia	295	DF20

Depression	29609, 29629, 29809, 30049	DF32, DF33
Mania	29619, 29639, 29819	DF30, DF31
Anxiety	300, excluding 30049	DF40-DF49
Personality disorders	301	DF6-DF69
Myocardial infarction		
STEMI		I211B, I210B, I213
nSTEMI		I211A, I210A, I214
PCI		KFNG, KFNF
PCI with stent		KFNG05
CABG		KFNA-KFNB-KFNC-KFND-KFNE-KFNH20
LABKA	NPU-code	
Troponin T	NPU19924, NPU27501	

Supplemental table 2. List of opioids, their Anatomical Therapeutic Chemical (ATC) codes, defined daily dose (DDD), and equi-analgesic ratios used in the study.

ATC-code	Name	Route	DDD [mg]	Equianalgesic ratio
N02AA01	Morphine	O	100	1
N02AA01	Morphine	P	30	3
N02AA01	Morphine	R	30	1.5
N02AA03	Hydromorphone	O	20	6
N02AA03	Hydromorphone	P	4	20
N02AA04	Nicomorphine	O	30	1
N02AA04	Nicomorphine	P	30	3
N02AA04	Nicomorphine	R	30	1.5
N02AA05	Oxycodone	O	75	1.5
N02AA05	Oxycodone	P	30	4
N02AB01	Ketobemidone	O	50	1
N02AB01	Ketobemidone	P	50	3
N02AB02	Pethidine	O	400	0.1
N02AB02	Pethidine	P	400	0.4
N02AB02	Pethidine	R	400	0.1
N02AB03	Fentanyl	TD	1.2	100
N02AB03	Fentanyl	N	0.6	50
N02AB03	Fentanyl	SL	0.6	50
N02AC04	Dextropropoxyphene (chloride)	O	200	0.23
N02AC04	Dextropropoxyphene (napsylate)	O	300	0.15
N02AD01	Pentazocine	O	200	0.17
N02AD01	Pentazocine	P	200	0.5
N02AE01	Buprenorphine	P	1.2	100

N02AE01	Buprenorphine	SL	1.2	50
N02AE01	Buprenorphine	TD	1.2	110
N02AX02	Tramadol	O	300	0.2
N02AX02	Tramadol	P	300	0.3
N02AX02	Tramadol	R	300	0.2
N02AX06	Tapentadol	O	400	0.3
N02AA55	Oxycodone, combinations	O	75	1.5
N02AG01	Morphin og antispasmodika			(No sale)
N02AG02	Ketobemidon og antispasmodika	O		2
N02AG02	Ketobemidon og antispasmodika	P		4
N02AB72	Pethidine, combinations including psycholeptics			No sale
N02AA59	Codein, combinations excluding psycholeptics	O/R		0.1
N07BC02	Methadone	O	25	4
N07BC02	Methadone	P	25	8
N07BC01	Buprenorphin	SL	8	50
N07BC03	Levacetylmethadol			(No sale)
N07BC06	Diamorphin	P (subcutaneous)		3
N07BC51	Buprenorphin, combinations	SL	8	50
R05DA04	Codeine	O	100	0.1

O=Oral

P = Parenteral

R = Rectal

N = Nasal

SL=Sublingual

TD = Transdermal

Supplemental table 3. Sensitivity analysis examining the impact of time since last prescription on the adjusted hazard ratio (HR) of all-cause mortality.

	Exposure category*			
	15 Days	30 Days	45 Days	60 days
	95% CI	95% CI	95% CI	95% CI
One-year mortality †				
Nonusers, HR [95% CI]	1	1	1	1
Current users, HR [95% CI]	1.33 (1.26-1.41)	1.32 (1.26-1.39)	1.29 (1.23-1.35)	1.28 (1.22-1.34)
Recent users, HR [95% CI]	1.08 (1.03-1.13)	1.02 (0.97-1.08)	1.00 (0.94-1.06)	0.97 (0.91-1.03)

*Number of days between last opioid prescription and incident myocardial infarction.

† Adjusted for age, sex, civil status, comorbidity category, surgery, and concomitant medication use.

Supplemental table 4. Mortality associated with type of opioid adjusted for age, sex, civil status, comorbidity category, surgery, and concomitant medication use.

	Current users	Recent users	Former users
	One-year mortality, HR [95% CI]	One-year mortality, HR [95% CI]	One-year mortality, HR [95% CI]
Morphine	1.52 (1.37-1.69)	1.24 (1.11-1.39)	0.95 (0.85-1.07)
Hydromorphone	1.37 (0.44-4.25)	1.18 (0.49-2.86)	0.86 (0.28-2.69)
Nicomorphine	1.83 (1.14-2.96)	1.61 (1.09-2.36)	1.01 (0.72-1.42)
Oxycodone	1.46 (1.33-1.61)	1.08 (0.97-1.20)	0.91 (0.83-0.99)
Ketobemidone	1.38 (1.17-1.62)	1.34 (1.17-1.53)	0.99 (0.88-1.10)
Pethidine	1.02 (0.60-1.73)	0.88 (0.54-1.45)	0.83 (0.58-1.17)
Fentanyl	1.58 (1.39-1.79)	1.01 (0.86-1.20)	1.17 (1.00-1.38)
Dextropropoxyphen	0.86 (0.36-2.07)	0.30 (0.07-1.20)	1.30 (0.70-2.41)
Pentazocin	-	-	-
Buprenorphine	1.45 (1.26-1.67)	1.17 (1.03-1.33)	0.86 (0.76-0.98)
Tramadol	1.20 (1.12-1.28)	1.10 (1.04-1.16)	0.94 (0.89-0.98)
Tapentadol	2.97 (0.74;11.94)	2.72 (0.87-8.45)	-
Codeine	1.23 (0.46-3.30)	1.43 (0.86-2.40)	1.16 (0.81-1.68)

Paper III

New use of opioids and risk of a pneumonia-related hospital and intensive care admission: a nationwide new-user active comparator cohort study

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Abstract

Background: Opioids may increase risk of pneumonia due to side effects such as respiratory depression, sedation, reduced gastric motility, and immunosuppression.

Objective: To assess risk of pneumonia requiring hospitalization and risk of subsequent admission to an intensive care unit associated with initiation of opioids.

Methods: We conducted a nationwide new-user active comparator registry-based cohort study comparing new users of opioids with new users of non-steroidal anti-inflammatory drugs (NSAIDs) during 2005-2014. We defined new use as a first prescription after a 6-month period without opioid or NSAID prescription and allowed patients to be included multiple times. Follow-up was 7 days for hospitalization and 30 days for ICU admission. Propensity score-based standardized mortality ratio (SMR) weights were used to control for confounding. Potential important confounders included socioeconomic status, comorbidity, and comedication use. We used logistic regression to calculate absolute risks for hospitalization, as well as crude and weighted odds ratios (wORs) with 95% confidence intervals (CIs). For ICU admission, we accounted for death as a competing risk and reported the sub-distribution hazard ratio (SHR) with 95% confidence intervals.

Results: We identified a total of 14,837,124 drug initiations (11,285,112 NSAID initiations and 3,552,012 opioid initiations) by 4,021,186 patients. The absolute 7-day risk of hospital admission with pneumonia was low in both groups, although higher among opioid initiators (opioid initiators: 0.23%; NSAID initiators: 0.04%). Opioid initiation was thus associated with a high relative risk of hospitalization with pneumonia [OR 6.20 (95% CI: 5.98-6.44)]. Following SMR weighting, the relative risk was attenuated, although it remained elevated [wOR 2.38 (95% CI 2.19-2.58)]. When hospitalization occurred, new use of opioids was associated with reduced risk of a subsequent ICU

admission [SHR 0.64 (95% CI: 0.50-0.83)] compared with NSAID initiation. Stratification by the immunosuppressive effect of selected opioids did not alter estimates.

Conclusions: Opioid initiation was associated with increased risk of hospital admission, but not subsequent ICU admission. Observed associations were independent of the immunosuppressive effect of opioids.

Introduction

Licit opioid use has increased internationally, at a steady pace, in recent decades[1]. In parallel, safety concerns have become prominent as a veritable opioid epidemic has unfolded in the United States of America which has been declared a national emergency [2]. Thus, opioids have recently received increased scrutiny due to their possible adverse effects on infectious diseases [3-8].

Well-established side effects of opioids that can increase risk of infection include sedation, respiratory depression, and aspiration due to reduced gastric motility [9]. An increasing amount of recent evidence also has raised the concern that opioids may have a direct immunosuppressive effect by disrupting both the innate and the adaptive immune systems [5-7]. Several animal studies have established an association between opioid use (both during active treatment and in models of withdrawal) and susceptibility to infections[10-13]. The degree of immunosuppression appears to depend largely on choice of opioid.

Morphine is one of the more potent immunosuppressive and thus far most investigated opioids [7,8]. Recent studies have reported an increased risk of infection among opioid users in diverse patient populations, including hospitalized patients suffering from cancer[14,15], burns[16], or trauma[17], outpatient groups of older adults[18], arthritis patients[19], chronic obstructive pulmonary disease patients[20], inflammatory bowel disease patients[21], nursing home residents[22], and Medicaid enrollees [23]. These studies were limited by small numbers of opioid-exposed patients (particularly new users), comparison of opioid users to non-users or lack of active comparators, and highly selected populations (e.g. patients in palliative care due to cancer) where underlying disease severity may also influence infection risk. Further, these studies either focused on prevalent users or excluded the initial 3-7 days following drug initiation to account for protopathic bias (drug initation due to prodromal symptoms of outcome of interest, here

infectious disease), as none utilized an active comparator. It is important to note that in a study of healthy volunteers, the immunosuppressive effect of morphine already was observed within 24 hours of initiation [24].

Pneumonia is a common cause of hospitalization and an admission for this indication is associated with high mortality (5%-30%) [25-27]. Given its potential immunosuppressive effect, with acute onset, opioid initiation potentially could be a modifiable risk factor for pneumonia severe enough to require hospitalization. The public health implications are considerable, given the widespread use of opioids.

This study's objectives were to assess the risk of pneumonia requiring hospitalization following initiation of opioid treatment, as well as the risk of subsequent ICU admission. It utilized a new-user active comparator design comparing opioid initiators to NSAID initiators.

Methods

Setting

This nationwide new-user cohort study was nested in the Danish population [28,29]. The Danish National Health Service (NHS) provides universal tax-supported healthcare ensuring free and unfettered access to general practitioners and hospital care, and thus allowing equal access to needed treatment. The NHS also provides partial reimbursement for prescribed drugs.[30] A number of national healthcare and administrative registries provided data for this study [30-37]. Unambiguous record linkage among registries is possible via the unique central personal register (CPR) number assigned to each Danish resident at birth or at time of immigration. [36]

Study population and exposure definition

A new user active comparator design was adopted to eliminate or at least minimize the risks of confounding by indication and "healthy user" bias [29]. New use of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) was identified from Anatomical Therapeutic Chemical (ATC) codes in the Danish National Prescription Registry, which was established in 1995 (see Supplemental Table 1 for ATC codes).[30] We chose NSAIDs as our active comparator due to its clinical relevance as the closest potential substitute for opioids. A 6-month prescription history was ascertained for each patient to ensure new use, which we defined as "no consumption of either drug in the prior six months". Every patient with new opioid and NSAID use from July 1995 on was included in the study, allowing the same patient to initiate use multiple times.

Outcomes

Primary outcomes were (1) hospitalization with pneumonia as either the primary or secondary diagnosis within 7 days following drug initiation, and (2) admission to an intensive care unit (ICU) during this hospitalization as a marker of severity. Outcomes were examined during the period January 1, 2005 to December 31, 2014.

Pneumonia requiring hospitalization was identified from the Danish National Patient Registry (DNPR).[33] The DNPR contains records for all hospital admissions in Denmark since 1977 and for outpatient and emergency room visits since 1995 [33,35]. Diagnoses have been coded according to the *International Classification of Diseases, Eighth Revision* until 1994 and *Tenth Revision* since then.

ICU admission within 30 days of hospital admission during the hospitalization for pneumonia since 2005 was determined based on the intensive care codes utilized by the Danish Intensive Care Database.[31] This clinical database relies on the legally mandated entry of specific

intensive care codes into the DNPR. The Danish Intensive Care Database contains complete data since 2005 and has been validated, demonstrating a high positive predictive value.[31]

Covariates

Information on age (continuous) and sex was obtained from the Danish Civil Registration System.[36] Non-psychiatric comorbidities were ascertained from the DNPR up to 10 years prior to drug initiation. These comorbidities included prior pneumonia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes without end-organ failure, renal disease, diabetes with end-organ failure, any tumor, leukemia, lymphoma, moderate to severe liver disease, metastatic solid tumor, and HIV with or without AIDS (see Supplemental Table 1 for codes used to identify comorbidities).[35] Psychiatric comorbidities (opioid abuse, alcoholism, depression, anxiety, schizophrenia spectrum disorder, and mania/bipolar disorder) up to 10 years prior to drug initiation were ascertained from the Danish Psychiatric Central Research Register (data available since 1970).[34] Individual comorbidities were included in the model as present/absent within 6 months prior, 7 months to 1 year prior, 1-5 years prior, 5-10 years prior to drug initiation exposure [38]. Information concerning concomitant medications (oral glucocorticoids, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, benzodiazepine derivates, antiepileptics, lipotropics, anti-glaucoma drugs, beta blockers, calcium channel blockers, thiazides, vasodilators, insulin, potassium replacements, anti-arrhythmics, digitalis, and loop diuretics) was acquired from the Danish National Prescription Registry and defined as use/non-use[32]. A patient was considered to be a user of a concomitant medication if a prescription was redeemed within 60 days prior to initiation of an opioid or NSAID. Finally, the Integrated Database for Labour Market Research (IDA) was used to obtain information

on socioeconomic factors (data available since 1980)[37], including educational level (low, medium, or high), income level (quartiles), employment status (employed, unemployed, retired, or other), and marital status (never married, married/registered partnership, or divorced/widowed).

Statistical Analysis

We first tabulated the frequency and proportion of covariates according to new use of opioids and NSAIDs. We computed propensity scores using a logistic regression model that included the covariates defined above. We subsequently employed standardized mortality rate (SMR) weighting to balance important covariates across comparison groups [39]. Absolute risk of pneumonia requiring hospitalization was computed without accounting for the competing risk of death. Odds ratios (ORs) were estimated using logistic regression, accounting for SMR weights as a measure of relative risk, comparing new users of opioids with new users of NSAIDs. Results are presented as ORs [with 95% confidence intervals (CIs)]. Among patients hospitalized with pneumonia, we calculated the absolute as well as relative risk (expressed by the sub-distribution hazard ratio) of ICU admission, comparing opioid-exposed to NSAID-exposed patients, while accounting for death as a competing risk.

We repeated the main analysis stratifying exposure to opioids according to their immunosuppressive effects, as described in the current literature: opioids with a strong immunosuppressive effect (codeine, morphine, and fentanyl), opioids with a weak immunosuppressive effect (oxycodone, tramadol, buprenorphine, and hydromorphone), and other opioids (ketobemidone, nicomorphine, pethidine, pentazocine, tapentadol, and dextropropoxyphene)[7].

We further conducted a range of sensitivity analyses to check whether or assumptions were valid. Thus, we repeated analysis of hospitalization with pneumonia with different follow-up periods starting from drug initiation (hospitalization within 7, 14, and 30 days). Because propensity scores are merely an estimation of likelihood to initiate a given treatment this prediction will sometimes fail – i.e. someone with a high propensity for initiating opioids may instead have initiated NSAIDs for unknown reasons (treated contrary to prediction) which may be due to unmeasured confounding [40]. To check for the presence of such unmeasured confounding we trimmed away a proportion of those potentially treated contrary to prediction by propensity scores in two analysis (the 1% and 5% opioid initiators with the lowest propensity for initiating opioid treatment and the 1% and 5% initiators of NSAIDs with the highest propensity for initiating opioid treatment) [40]. Further, we redid our analysis but restricted to incident drug initiation. We also conducted stratified analysis to detect potential heterogeneous effects and thus stratified by deciles of propensity scores,[40] and by age. We also repeated the main analysis using three scenarios for patients who died within 7 days of drug initiation without hospitalization.

Approvals

In accordance with Danish law, approval for use of the data for research was obtained from the Danish Data Protection Agency (record number: 2015-57-0002, AU record number 2016-051-000001/432).

Results

Study population

During the period 1995-2014 we identified 11,285,112 instances of new use of NSAIDs by 3,628,747 patients, and 3,552,012 instances of new use of opioids by 1,898,372 patients. This totaled 14,837,124 total drug initiations by 4,021,186 patients as there was an overlap between opioid initiators and NSAID initiators. Of these, patients in 12,606 instances (0.08%) were admitted

with pneumonia within 7 days of their drug initiation (8,331 or 0.23% among opioid initiators; 4,275 or 0.04% among NSAID initiators). From 2005 on, 356 instances of patients admitted within 7 days for pneumonia subsequently were followed by an ICU admission within 30 days (214 opioids; 142 NSAIDs).

New users of opioids were more likely to be male, older, retired, married, and with lower income than new users of NSAIDs (Table 1). Further, new users of opioids generally had a larger comorbidity burden – notably cancer, COPD, ulcers, prior pneumonia requiring hospitalization, and cardiovascular disease. Consequently, they were also more likely to take concomitant medications. Following SMR weighting, covariate balance was achieved (Table 1).

Hospital admission

Absolute risk of pneumonia requiring hospitalization within 7 days of drug initiation was low among both new users of NSAIDs (0.04%) and new users of opioids (0.23%) (Table 2). Relative risk, however, was high when comparing new use of opioids with new use of NSAIDs [OR 6.20 (95% CI: 5.98-6.44)]. Following SMR weighting, the relative risk was OR 2.38 (95% CI: 2.19-2.58).

In the analysis stratifying opioid exposure according to immunosuppressive potency, no difference was observed between opioids with assumed strong versus assumed weak immunosuppressive effects (Table 2). The group of initiators using "other" opioids, *i.e.*, opioids whose immunosuppressive effects have yet to be established, were at markedly lower relative risk [SMR-weighted OR = 1.67 (95% CI: 1.49-1.87)].

ICU admission

Approximately 3% of opioid users and 4% of NSAID users were admitted to an ICU during their hospitalization for pneumonia (Table 3). In contrast to the risk of hospital admission, we found

that opioid users were at lower risk of subsequent ICU admission than NSAID users [crude OR = 0.70 (95% CI: 0.57-0.85)]. This association persisted following SMR weighting [OR = 0.64 (95% CI: 0.50-0.82)]. No differences were detected among opioids stratified by immunosuppressive effect.

Sensitivity analyses

In sensitivity analyses in which the follow-up window was expanded to 14 and 30 days, respectively, the association between new use of opioids and hospitalization for pneumonia attenuated with increasing follow-up time. However, even after 30 days, the relative risk was markedly elevated for opioid users [OR 1.71 (95% CI: 1.61-1.81)] (Supplemental Table 3). Trimming away those treated contrary to prediction resulted in a slight increase in relative risk as more patients were trimmed away (Supplemental Table 3). Restricting the analysis to incident drug initiation or hospitalization with pneumonia coded as the primary diagnosis did not substantially change estimates (Supplemental Table 3). Estimates also were stable across deciles of the propensity score (Supplemental Table 4).

Neither expanding the follow-up window to 14 or 30 days, nor trimming patients who were not treated according to prediction, yielded substantially different estimates for risk of ICU admission (Supplemental Table 5). Estimates were stable across all deciles of the propensity score (Supplemental Table 6).

Discussion

In this nationwide new-user active comparator propensity-score SMR-weighted study, we found a low absolute risk of pneumonia requiring hospitalization within 7 days following drug initiation for both new users of NSAIDs and opioids. However, opioid initiation was associated with a high relative risk of pneumonia requiring hospitalization within 7 days following drug initiation

compared to new use of NSAIDs. The varying immunosuppressive effect of different opioids did not seem to influence this association. Once admitted to the hospital, opioid initiators were at lower risk than NSAID initiators of subsequent ICU admission.

Our findings corroborate the findings of the majority of prior studies that examined opioid use and risk of infections in general,[14,16,17,19,23] as well as studies focusing on pneumonia[18-21,23]. One study found no increased risk of pneumonia associated with opioid use, but it was restricted to prevalent users[22]. Within 30 days of opioid initiation among chronic obstructive pulmonary disease patients, Vozoris *et al.* found only a marginally increased risk of pneumonia severe enough to require hospitalization [HR 1.08 (95% CI: 0.97–1.21)] [20]. However, they also reported an increased risk of pneumonia-related deaths among opioid initiators in this patient group[20]. Similarly, Wiese *et al.* (2016) found that the point estimate itself suggested increased risk of pneumonia among rheumatoid arthritis patients who were taking opioids although the 95% confidence interval did include 1.00 [19]. The finding in these studies that risk of hospitalization with pneumonia was only marginally increased may be related to the underlying disease defining the two cohorts, *i.e*., the risks associated with the diseases themselves in part may have overshadowed the risk associated with opioid initiation observed in our study. Interestingly, a later study by Wiese *et al.* (2018) found an increased risk of all invasive pneumococcal diseases, as well as of pneumonia, among patients who were current opioid users [23]. In line with our findings, both Wiese (2018) *et al.* and Dublin *et al.* found that new users were at highest risk of pneumonia [18,23]. It is noteworthy that Dublin *et al.* observed the highest risk during the initial 14 days of use [18]. Yeager *et al.'s* study documented that an immunosuppressive effect occurs within 24 hours. The attenuation of estimates observed in our sensitivity analysis might indicate that the effect of opioids wanes over time with consistent use, as patients develop tolerance. Such a mechanism

remains speculative. Still, Won *et al.'s* work lends credence to this possibility, as they did not find that opioid use during a 6-month period was associated with increased risk of pneumonia [22].

Our study results were unaffected when we stratified by immunosuppressive potency. In contrast, Dublin *et al.* reported that users of highly immunosuppressive opioids had the highest risk of serious infection [18]. Wiese *et al.* also found this group of users were at highest risk, although confidence intervals overlapped with those using opioids with low immunosuppressive potency [23]. A third study found no differences when comparing risk of infections associated with morphine use, oxycodone use, and fentanyl use [15]. However, the latter study was limited by a small sample size and limited to stage IV cancer patients in palliative care. In a similarly small group of cancer patients, Suzuki *et al.* found a higher risk of infections among patients treated with morphine compared with those treated with oxycodone [14].

Based on animal studies [10-12,41], one would expect the risk of pneumonia to increase among users of opioids with greater immunosuppressive potency. However, NSAIDs, which we used as a comparator, have inherent anti-inflammatory properties. This may have made it difficult for us to detect subtle differences in immunosuppression across opioid groups. Further, it is possible that other mechanisms have a greater impact on development of pneumonia severe enough to require hospitalization. Well-established side-effects of opioid use include respiratory depression and reduced gastric motility. Reduced gastric motility could potentially lead to aspiration. In this light, a study of 84 ICU patients found that enteral naloxone reduced gastric tube reflux and frequency of pneumonia.[42] However, opioids also have been associated with increased risk of hospital-acquired pneumonia among patients with endotracheal intubation[43], rendering any conclusions concerning mechanism speculative.

It is intriguing that the risk of subsequent ICU admission was lower among new users of opioids compared to new users of NSAIDs. As discussed above, possible explanations include residual confounding by e.g. severity of illness or confounding by indication in spite of our use of an active comparator and propensity score-based SMR weighting. Additionally, ICU admission is decided at the discretion of the attending physician and is influenced by disease severity, comorbidity, potential for patient improvement, and availability of ICU beds. It is thus plausible that some new users of opioids begin treatment for severe illness or as part of end-of-life palliative care, which would exclude care in an ICU. Another explanation may be differences in treatment during hospitalization due to modulation of the disease trajectory, such as the reported adverse effect of NSAIDs on pneumonia. Several studies that investigated prognosis following NSAID use during early stages of pneumonia found an increased risk of pleural complications[44-46]. Finally, it is possible that different infectious organisms cause pneumonia in new users of opioids compared with new users of NSAIDs. However, no nationwide laboratory data were available to examine this theory at time of study.

Several strengths and limitations should be considered when interpreting our results. Since this nationwide cohort study relied on Danish registry data, it is unlikely that selection bias substantially influenced its findings [47]. The coding of pneumonia in the Danish National Patient Registry has been validated in two studies, which reported a high positive predictive value (>90%) among both cancer and stroke patients [48,49]. A third study restricted to community-acquired pneumonia found a lower positive predictive value (71%) [50]. A concern is that some patients contracted pneumonia during hospitalization for another disease. However, our results remained stable in analyses restricted to patients with a primary diagnosis of pneumonia and it is unlikely that treatment with an opioid versus an NSAID would differentially influence coding validity.

Because our study was not randomized, residual confounding is possible. However, we addressed potential important confounders such as socioeconomics, comorbidity, and comedication in several ways, including use of an active comparator (to counter confounding by indication and protopathic bias), use of a new-user design (to counter healthy user bias), and use of propensity score-based SMR weighting (to counter confounding by indication). However, we were unable to account fully for disease severity (e.g. cancer stage at time of drug initiation), which may influence drug initiation. Thus some residual confounding may have persisted. Further, the potential for protopathic bias (*i.e.*, drug initiation due to unrecognized symptoms of pneumonia) remains. However, use of an active comparator group minimized its potential impact, as symptoms were likely to be present in both groups. In addition, our estimates remained stable in a sensitivity analysis that lengthened follow-up time, making it unlikely for protopathic bias to account fully for our findings. Finally, we lacked data on in-hospital drug use and thus cannot exclude crossover during the hospital stay preceding ICU admission. While this may have influenced our findings relating to ICU admission, it would not have influenced our findings relating to pneumonia requiring hospitalization.

Our study adds to the increasingly compelling evidence that opioid use is associated with increased risk of pneumonia severe enough to require hospitalization. As pneumonia is a common disease with high mortality, clinicians should give careful consideration to alternative therapies and/or pneumococcal vaccination prior to initiation of opioid therapy. Although we did not detect an increased risk when we stratified our analysis by the immunosuppressive potency of given opioids, it appears preferable - based on the studies by Dublin *et al.* and Wiese *et al.* - to prescribe opioids with low immunosuppressive potency when possible.

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Tables

Table 1. Frequency and proportion of NSAID and opioid initiations across covariates

	NSAIDs, n=11,285,112 (76.1%)		Opioids, n=3,552,012 (23.9%)
	Original cohort	SMRW-weighted,	
	n (%)	n (%)	n %
Age [median (IQR)]	47.5 (34.6-60.3)	55.1 (39.9-68.9)	54.2 (39.2-69.0)
Male	6,228,920 (55.2)	6,573,573 (58.2)	2,084,091 (58.7)
Marital status			
Never married	3,302,712 (29.3)	2,702,927 (24.0)	838,325 (23.6)
Married/Registered partnership	1,946,503 (17.2)	2,740,124 (24.3)	902,098 (25.4)
Divorced/widowed	6,035,897 (53.5)	5,842,060 (51.8)	1,811,589 (51.0)
Educational level			
Low	3,773,020 (33.4)	4,070,111 (36.1)	1,302,507 (36.7)
Medium	4,416,318 (39.1)	3,975,973 (35.2)	1,228,386 (34.6)
High	2,024,147 (17.9)	1,781,180 (15.8)	566,143 (15.9)
Missing	1,071,627 (9.5)	1,457,848 (12.9)	454,976 (12.8)
Employment status			

Employed	6,511,751 (57.7)	4,584,633 (40.6)	1,462,234 (41.2)
Unemployed/student	1,558,680 (13.8)	1,351,270 (12.0)	431,060 (12.1)
Retired	2,859,920 (25.3)	4,905,290 (43.5)	1,522,309 (42.9)
Other	354,761 (3.1)	443,919 (3.9)	136,409 (3.8)
Income level, DKK[a]			
0-25th percentile	2,668,883 (23.6)	3,229,156 (28.6)	1,010,819 (28.5)
25-50th percentile	2,709,096 (24.0)	3,184,335 (28.2)	1,009,129 (28.4)
50-75th percentile	2,923,665 (25.9)	2,550,629 (22.6)	796,914 (22.4)
75-100th percentile	2,983,468 (26.4)	2,320,993 (20.6)	735,150 (20.7)
Concomitant medication			
Tricyclic antidepressants	62,527 (0.6)	139,309 (1.2)	40,118 (1.1)
Serotonin and norepinephrine reuptake inhibitors	67,634 (0.6)	109,288 (1.0)	32,697 (0.9)
Selective serotonin reuptake Inhibitors	304,361 (2.7)	594,155 (5.3)	177,315 (5.0)
Benzodiazepine derivates	298,120 (2.6)	663,969 (5.9)	194,956 (5.5)

Antiepileptics	133,341 (1.2)	300,669 (2.7)	86,306 (2.4)
Oral corticosteroids	177,394 (1.6)	196,796 (1.7)	61,021 (1.7)
Anxiotytics,	303,233 (2.7)	675,649 (6.0)	198,390 (5.6)
Anti-arrythmics	11,028 (0.1)	41,080 (0.4)	10,692 (0.3)
Beta blockers	381,308 (3.4)	820,890 (7.3)	240,414 (6.8)
Calcium channel blockers	351,318 (3.1)	681,187 (6.0)	203,906 (5.7)
Digitalis	52,765 (0.5)	233,656 (2.1)	61,582 (1.7)
Insulin	96,863 (0.9)	236,052 (2.1)	64,067 (1.8)
Lipotronics	424,585 (3.8)	837,640 (7.4)	244,661 (6.9)
Loop diuretics	168,853 (1.5)	646,882 (5.7)	174,492 (4.9)
Potassium replacements	146,465 (1.3)	523,041 (4.6)	143,740 (4.0)
Thiazide	300,043 (2.7)	487,620 (4.3)	151,764 (4.3)
Vasodilators	67,198 (0.6)	247,076 (2.2)	66,505 (1.9)
Comorbidity			
History of pneumonia	236,222 (2.1)	729,920 (6.5)	199,511 (5.6)
Opioid abuse	4,363 (0.0)	11,823 (0.1)	2,991 (0.1)
Alcohol abuse	76,674 (0.7)	149,322 (1.3)	42,081 (1.2)

Schizophrenia-spectrum disorders	71,902 (0.6)	96,380 (0.9)	29,277 (0.8)
Depression	166,526 (1.5)	270,912 (2.4)	80,042 (2.3)
Mania and/or bipolar disorders	27,286 (0.2)	49,082 (0.4)	14,325 (0.4)
Anxiety disorders	258,390 (2.3)	353,431 (3.1)	105,940 (3.0)
Personality disorder	96,185 (0.9)	130,532 (1.2)	39,091 (1.1)
Myocardial infarction	145,963 (1.3)	411,691 (3.6)	110,265 (3.1)
Congestive heart failure	97,996 (0.9)	458,492 (4.1)	115,999 (3.3)
Peripheral vascular disease	143,782 (1.3)	485,585 (4.3)	132,246 (3.7)
Cerebrovascular disease	259,979 (2.3)	783,114 (6.9)	219,435 (6.2)
Dementia	31,085 (0.3)	195,806 (1.7)	50,771 (1.4)
Chronic pulmonary disease	402,417 (3.6)	860,347 (7.6)	244,793 (6.9)
Connective tissue disease	224,545 (2.0)	365,817 (3.2)	111,870 (3.1)
Ulcer disease	133,222 (1.2)	482,246 (4.3)	128,128 (3.6)
Mild liver disease	53,956 (0.5)	148,814 (1.3)	39,106 (1.1)

Diabetes without end-organ failure	255,272 (2.3)	627,508 (5.6)	173,845 (4.9)
Renal disease	55,091 (0.5)	249,697 (2.2)	60,080 (1.7)
Diabetes with end-organ failure	109,215 (1.0)	351,814 (3.1)	92,158 (2.6)
Any tumor	378,680 (3.4)	940,566 (8.3)	277,199 (7.8)
Leukemia	9,979 (0.1)	362,87 (0.3)	9,601 (0.3)
Lymphoma	20,504 (0.2)	71,373 (0.6)	18,452 (0.5)
Moderate to severe liver disease	53,956 (0.5)	148,814 (1.3)	39,106 (1.1)
Metastatic solid tumor	30,032 (0.3)	151,926 (1.3)	42,317 (1.2)
AIDS	6,680 (0.1)	15,722 (0.1)	3,750 (0.1)

SMRW= Standardized Mortality Ratio Weighted

[a]Translated to U.S. dollars, the income groups were Cutoff between percentiles $21,426 or less, $21,426-$32,939, $32,939-$47,459, $47,459 or more (as of August 1, 2018)

Table 2. Risk of pneumonia requiring hospitalization within 7 days after drug initiation, by type of drug.

Drug type	Deaths without hospitalization n (%)	Hospital admissions, n (%)	Crude, OR (95% CI)	Absolute SMRW, n (%)	SMR weighted, OR (95% CI)
NSAID, n=11,285,112	1,729 (0.02)	4,275 (0.04)	ref	11,131 (0.10)	Ref
Opioid, n=3,552,012	27,448 (0.77)	8,331 (0.23)	6.20 (5.98-6.44)	8,331 (0.23)	2.38 (2.19-2.58)
Strong, n=1,564,586	12,896 (0.83)	3,660 (0.23)	6.19 (5.92-6.47)	3,660 (0.23)	2.37 (2.18-2.59)
Weak, n=1,627,931	7,347 (0.45)	4,079 (0.25)	6.63 (6.35-6.92)	4,079 (0.25)	2.54 (2.34-2.77)
Other, n=359,495	7,205 (2.01)	592 (0.16)	4.35 (3.99-4.74)	592 (0.16)	1.67 (1.49-1.87)

SMRW= Standardized Mortality Ratio Weighted

Table 3. Risk of ICU admission within 30 days of a hospitalization for pneumonia occurring within 7 days after drug initiation, accounting for death as a competing risk.

Drug type	Absolute, n (%)	Crude, SHR (95% CI)	Absolute SMRW, n (%)	SMR-weighted, SHR (95% CI)
NSAID, n=2,809	142 (5.1)	ref	147 (5.2)	Ref
Opioid, n=6,375	214 (3.4)	0.66 (0.54-0.82)	214 (3.4)	0.64 (0.50-0.83)
Strong, n=2,556	79 (3.1)	0.61 (0.47-0.80)	79 (3.1)	0.59 (0.43-0.81)
Weak, n=3,467	128 (3.7)	0.73 (0.58-0.92)	128 (3.7)	0.71 (0.53-0.93)
Other, n=352	7 (2.0)	0.39 (0.19-0.83)	7 (2.0)	0.38 (0.18-0.82)

Supplemental Material

Supplemental Table 1. Codes used to identify outcomes, exposures, and covariates.

	ICD-8	ICD-10	ATC codes
Outcome codes			
Pneumonia		J12−J18, A48.1, A70.9	
Intensive care		NABB/NABE	
Exposure codes			
Opioids			MN02A
Opioid, cough-suppressant			MR05DA
Morphine			MN02AA01, MN02AA51
Hydromorphone			MN02AA03
Nicomorphine			MN02AA04
Oxycodone			MN02AA05, MN02AA55
Ketobemidone			MN02AB01, MN02AG02
Pethidine			MN02AB02, MN02AB72
Fentanyl			MN02AB03
Dextroproproxyphen			MN02AC04
Pentazocin			MN02AD01
Buprenorphine			MN02AE01

Tramadol	MN02AX02
Tapentadol	MN02AX06
Codeine	MN02AA59
nsNSAIDs	MM01A excluding MM01AX05 (Glucosamine)
Codes for concomitant drugs	
Acetylsalicylic acid, high-dose	MN02BA01
Acetylsalicylic acid, low-dose	MB01AC06
Oral corticosteroids	MR01AD
Benzodiazepine-derivates	MN05BA
Tricyclic antidepressants	MN06AA
Selective serotonin reuptake inhibitors	MN06AB
Serotonin and norepinephrine	MN06AX16, MN06AX21, MN06AX23

reuptake inhibitors			
Antiepileptics			MN03A
Lipotronics			C10
Beta-blockers			C07
Calcium channel blockers			C08
ACE-inhibitors			C09A
Peripheral vasodilators			C04
Thiazides			C03A
Insulin			A10A
Digitalis			C01AA
Anti-arrythmics			C01B
Loop diuretics			C03CA
Potassium			A12B
Warfarin			B01AA03
Comorbidity codes			
Myocardial infarction	410	I21, I22, I23	

Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430-438	I60-I69, G45, G46
Dementia	290.09-290.19, 293.09	F00-F03, F05.1, G30
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31,M32, M33, M34, M35, M36, D86
Ulcer disease	530.91, 530.98, 531-534	K22.1, K25-K28
Mild liver disease		B18, K70.0-K70.3, K70.9, K71, K73
Diabetes without end-organ damage	249.00, 249.06, 249.07, 249.09,	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9

	250.00, 250.06, 50.07, 250.09	
Diabetes with end-organ damage	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8, E11.2-E11.8
Hemiplegia	344	G81, G82
Moderate to severe renal disease	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Non-metastatic solid tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
HIV/AIDS		
Metastatic cancer	195-198, 199	C76-C80
Opioid abuse	30409	DF11

Alcohol abuse	303	DF10
Schizophrenia	295	DF20
Depression	29609, 29629, 29809, 30049	DF32, DF33
Mania	29619, 29639, 29819	DF30, DF31
Anxiety	300, excluding 30049	DF40-DF49
Personality disorders	301	DF6-DF69

Supplemental Table 2. Frequency and proportion of NSAID and opioid initiators across covariates among patients hospitalized for pneumonia within 7 days of drug initiation.

	NSAIDs, n=2,809 (30.6%)		Opioids, n= 6,375 (69.4%)
	Original cohort	SMRW-weighted	
	n (%)	n (%)	n (%)
Age [median (IQR)]	62.8 (43.8-77.1)	74.6 (62.2-83.5)	74.7 (61.4-83.9)
Male	1246 (44.3)	1334 (47.5)	2937 (46.1)
Marital status			
Never married	604 (21.5)	341 (12.2)	815 (12.8)
Married/Registered partnership	1351 (48.1)	1321 (47.1)	2954 (46.3)
Divorced/widowed	841 (29.9)	1137 (40.5)	2589 (40.6)
Educational level			
Low	1026 (36.5)	1164 (41.5)	2648 (41.5)
Medium	956 (34.0)	868 (30.9)	1914 (30.0)
High	443 (15.8)	338 (12.1)	835 (13.1)
Missing	384 (13.7)	436 (15.5)	978 (15.3)
Employment status			

Employed	929 (33.1)	433 (15.4)	965 (15.1)
Unemployed/student	214 (7.6)	109 (3.9)	288 (4.5)
Retired	1550 (55.2)	2198 (78.3)	4995 (78.4)
Other	116 (4.1)	68 (2.4)	127 (2.0)
Income level, DKK[a]			
0-25%	778 (27.7)	1022 (36.4)	2470 (38.8)
25%-50%	791 (28.2)	929 (33.1)	1947 (30.5)
50%-75%	565 (20.1)	474 (16.9)	1064 (16.7)
75%-100%	675 (24.0)	382 (13.6)	894 (14.0)
Concomitant medication			
Tricyclic antidepressants	38 (1.4)	58 (2.1)	114 (1.8)
Serotonin and norepinephrine reuptake inhibitors	41 (1.5)	42 (1.5)	80 (1.3)
Selective serotonin reuptake inhibitors	190 (6.8)	273 (9.7)	654 (10.3)
Benzodiazepine derivates	170 (6.1)	256 (9.1)	501 (7.9)
Antiepileptics	115 (4.1)	140 (5.0)	345 (5.4)

Oral corticosteroids	61 (2.2)	40 (1.4)	91 (1.4)
Anxiolytics	177 (6.4)	260 (9.3)	511 (8.0)
Anti-arrythmics	16 (0.6)	29 (1.0)	67 (1.1)
Beta blockers	265 (9.4)	392 (14.0)	860 (13.5)
Calcium channel blockers	233 (8.3)	374 (13.3)	743 (11.7)
Digitalis	82 (2.9)	197 (7.0)	412 (6.5)
Insulin	80 (2.9)	124 (4.4)	253 (4.0)
Lipotronics	249 (8.9)	420 (15.0)	869 (13.6)
Loop diuretics	260 (9.3)	570 (20.3)	1209 (19.0)
Potassium replacements	184 (6.6)	432 (15.4)	943 (14.8)
Thiazide	145 (5.2)	170 (6.1)	432 (6.8)
Vasodilators	75 (2.7)	148 (5.3)	279 (4.4)
Comorbidity			
History of pneumonia	683 (24.3)	1023 (36.4)	2376 (37.3)
Alcohol abuse	57 (2.0)	42 (1.5)	86 (1.4)
Schizophrenia-spectrum disorder	38 (1.4)	24 (0.8)	71 (1.1)
Depression	92 (3.3)	63 (2.2)	187 (2.9)

Mania and/or bipolar disorder	13 (0.5)	10 (0.4)	35 (0.6)
Anxiety disorders	90 (3.2)	63 (2.3)	150 (2.4)
Personality disorder	30 (1.1)	13 (0.5)	38 (0.6)
Myocardial infarction	133 (4.7)	242 (8.6)	492 (7.7)
Congestive heart failure	171 (6.1)	395 (14.1)	850 (13.3)
Peripheral vascular disease	168 (6.0)	301 (10.7)	640 (10.0)
Cerebrovascular disease	255 (9.1)	493 (17.6)	1141 (17.9)
Dementia	69 (2.5)	220 (7.9)	477 (7.5)
Chronic pulmonary disease	549 (19.5)	765 (27.2)	1637 (25.7)
Connective tissue disease	90 (3.2)	162 (5.8)	332 (5.2)
Ulcer disease	94 (3.4)	223 (7.9)	447 (7.0)
Mild liver disease	52 (1.9)	52 (1.9)	130 (2.0)
Diabetes without end-organ failure	202 (7.2)	360 (12.8)	743 (11.7)
Renal disease	68 (2.4)	188 (6.7)	434 (6.8)
Diabetes with end-organ failure	105 (3.7)	255 (9.1)	471 (7.4)
Any tumor	311 (11.1)	635 (22.6)	1411 (22.1)
Leukemia	19 (0.7)	46 (1.6)	105 (1.7)

Lymphoma	37 (1.3)	85 (3.0)	168 (2.6)
Moderate to severe liver disease	16 (0.6)	29 (1.1)	57 (0.9)
Metastatic solid tumor	41 (1.5)	122 (4.3)	281 (4.4)

SMRW= Standardized Mortality Ratio Weighted

[a]Translated to U.S. dollars, the income groups were Cutoff between percentiles $21,426 or less, $21,426-$32,939, $32,939-$47,459, $47,459 or more (as of August 1, 2018)

Supplemental Table 3. Sensitivity analyses of risk of pneumonia requiring hospitalization after drug initiation, by different follow-up periods, trimming of patients treated contrary to prediction and restriction to cases with primary diagnosis of pneumonia and to incident cases.

	Group	Absolute, n (%)	Crude, OR (95% CI)	Absolute SMRW, n (%)	SMRW-adjusted, OR (95% CI)
14-day window	NSAID, n=11,285,112	6,722 (0.06)	ref	18,644 (0.17)	ref
	Opioid, n=3,552,012	12,227 (0.34)	5.80 (5.62-5.97)	12,227 (0.34)	2.09 (1.96-2.22)
30-day window	NSAID, n=11,285,112	11,034 (0.10)	ref	33,453 (0.3)	ref
	Opioid, n=3,552,012	18,037 (0.51)	5.24 (5.12-5.37)	18,037 (0.51)	1.71 (1.61-1.81)
1%-99% trim	NSAID, n=10,958,486	3,693 (0.03)	ref	5,413 (0.05)	ref
	Opioid, n=3,270,839	5,629 (0.17)	5.11 (4.91-5.33)	5,629 (0.17)	3.5 (3.3-3.7)
5%-95% trim	NSAID, n=9,704,580	2,773 (0.03)	ref	3,249 (0.03)	ref
	Opioid, n=2,705,417	3,473 (0.13)	4.50 (4.28-4.73)	3,473 (0.13)	3.84 (3.65-4.04)
Primary diagnosis only	NSAID, n=11,285,112	3,190 (0.03)	ref	7,156 (0.06)	ref
	Opioid, n=3,552,012	6,053 (0.17)	6.04 (5.78-6.30)	6,053 (0.17)	2.69 (2.44-2.96)
Incident diagnosis only	NSAID, n=3,152,877	1,158 (0.04)	ref	2,494 (0.08)	ref
	Opioid, n=845,061	1,747 (0.21)	5.64 (5.23-6.07)	1,747 (0.21)	2,62 (1.93-3.56)

SMRW=Standardized Mortality Ratio Weighted

Supplemental Table 4. Risk of pneumonia requiring hospitalization within 7 days after drug initiation within strata of deciles of propensity scores.

Decile	Group	Absolute, n (%)	Crude, OR (95% CI)	Absolute, n (%) SMRW	SMRW-adjusted, OR (95% CI)
0-10	NSAID	291 (0.02)	4.66 (3.93-5.53)	289 (0.02)	4.68 (3.95-5.56)
	Opioid	240 (0.11)		240 (0.11)	
10-20	NSAID	238 (0.02)	4.52 (3.75-5.45)	238 (0.02)	4.52 (3.75-5.44)
	Opioid	209 (0.09)		209 (0.09)	
20-30	NSAID	258 (0.02)	4.20 (3.51-5.04)	258 (0.02)	4.21 (3.51-5.04)
	Opioid	217 (0.09)		217 (0.09)	
30-40	NSAID	245 (0.02)	4.65 (3.90-5.55)	245 (0.02)	4.65 (3.89-5.55)
	Opioid	246 (0.09)		246 (0.09)	
40-50	NSAID	255 (0.02)	3.98 (3.33-4.75)	255 (0.02)	3.97 (3.32-4.74)
	Opioid	231 (0.08)		231 (0.08)	
50-60	NSAID	272 (0.02)	3.62 (3.06-4.29)	273 (0.02)	3.61 (3.05-4.27)
	Opioid	268 (0.08)		268 (0.08)	
60-70	NSAID	318 (0.03)	3.97 (3.43-4.60)	320 (0.03)	3.95 (3.41-4.57)
	Opioid	401 (0.11)		401 (0.11)	
70-80	NSAID	446 (0.04)	3.72 (3.29-4.22)	448 (0.04)	3.71 (3.28-4.20)
	Opioid	568 (0.15)		568 (0.15)	
80-90	NSAID	538 (0.05)	3.92 (3.53-4.36)	551 (0.05)	3.83 (3.45-4.25)
	Opioid	1,006 (0.21)		1,006 (0.21)	
90-100	NSAID	1,414 (0.20)	3.27 (3.09-3.47)	2,426 (0.34)	1.90 (1.71-2.12)
	Opioid	4,945 (0.64)		4,945 (0.64)	

SMRW=Standardized Mortality Ratio Weighted

Supplemental Table 5. Sensitivity analysis of risk of ICU admission during hospitalization for pneumonia by different follow-up time to hospitalization and trimming of those treated contrary to prediction.

	Group	Absolute, n (%)	Crude, SHR (95% CI)	Absolute SMRW, n (%)	SMRW-adjusted, SHR (95% CI)
14-day window	NSAID, n=4,472	219 (4.9)	Ref	227 (5.1)	Ref
	Opioid, n=9,503	315 (3.3)	0.68 (0.57-0.80)	366 (3.9)	0.65 (0.53-0.80)
30-day window	NSAID, n=7,550	390 (5.2)	Ref	391 (5.2)	Ref
	Opioid, n=14,308	528 (3.7)	0.71 (0.63-0.81)	528 (3.7)	0.72 (0.61-0.83)
1-99% trim	NSAID, n=2,657	136 (5.1)	Ref	137 (5.2)	Ref
	Opioid, n=5,840	200 (3.4)	0.67 (0.54-0.82)	200 (3.4)	0.66 (0.52-0.84)
5-95% trim	NSAID, n=6,056	124 (5.6)	Ref	127 (5.8)	Ref
	Opioid, n=10,897	165 (3.5)	0.62 (0.50-0.78)	165 (3.5)	0.61 (0.48-0.78)

SMRW=Standardized Mortality Ratio Weighted

Supplemental Table 6. Risk of ICU admission following hospitalization for pneumonia within strata of deciles of propensity scores.

Decile	Group	Absolute, n (%)	ICU crude, SHR (95% CI)	Absolute SMRW, n (%)	ICU SMRW-adjusted, SHR (95% CI)
0-10	NSAID	15 (2.8)	0.55 (0.22-1.41)	15 (2.9)	0.54 (0.21-1.40)
	Opioid	6 (1.6)		6 (1.6)	
10-20	NSAID	19 (4.1)	0.54 (0.25-1.14)	19 (4.1)	0.54 (0.26-1.16)
	Opioid	10 (2.2)		10 (2.2)	
20-30	NSAID	27 (6.4)	0.66 (0.38-1.15)	27 (6.5)	0.65 (0.37-1.13)
	Opioid	21 (4.2)		21 (4.2)	
30-40	NSAID	18 (5.0)	0.80 (0.44-1.48)	18 (5.0)	0.80 (0.43-1.47)
	Opioid	22 (4.0)		22 (4.0)	
40-50	NSAID	22 (7.9)	0.41 (0.23-0.74)	22 (7.9)	0.42 (0.23-0.74)
	Opioid	21 (3.3)		21 (3.3)	
50-60	NSAID	13 (5.9)	0.56 (0.29-1.10)	13 (5.8)	0.57 (0.29-1.11)
	Opioid	23 (3.3)		23 (3.3)	
60-70	NSAID	11 (5.6)	0.67 (0.34-1.33)	11 (5.8)	0.65 (0.33-1.29)
	Opioid	27 (3.8)		27 (3.8)	
70-80	NSAID	19 (7.1)	0.56 (0.28-1.13)	10 (7.1)	0.57 (0.28-1.13)
	Opioid	31 (4.0)		31 (4.0)	
80-90	NSAID	5 (3.9)	0.88 (0.34-2.24)	5 (4.0)	0.86 (0.34-2.21)
	Opioid	27 (3.4)		27 (3.4)	
90-100	NSAID	≤3 (≤3.0)	1.01 (0.25-4.18)	≤3 (≤3.0)	0.87 (0.21-3.58)
	Opioid	26 (3.0)		26 (3.0)	

SMRW=Standardized Mortality Ratio Weighted

Supplemental Table 7. Risk of hospitalization within 7 days of drug initiation stratified by age.

Age	Crude, OR (95% CI)	SMRW-adjusted, OR (95% CI)
Overall		
<50 n=7,748,373	4.30 (4.01-4.60)	3.15 (2.89-3.42)
50-65 n=3,961,216	5.11 (4.72-5.54)	2.71 (2.34-3.13)
65-75 n=1,771,398	5.71 (5.22-6.26)	2.51 (2.07-3.03)
75+ n=1,355,299	4.52 (4.22-4.84)	1.95 (1.70-2.23)
Strong		
<50 n=6,961,336	5.19 (4.79-5.62)	3.80 (3.46-4.18)
50-65 n=3,443,047	5.90 (5.36-6.49)	3.12 (2.68-3.64)
65-75 n=1,457,579	5.69 (5.11-6.34)	2.50 (2.04-3.05)
75+ n=987,232	4.39 (4.05-4.77)	1.89 (1.64-2.18)
Weak		
<50 n=6,848,578	3.21 (2.91-3.55)	2.35 (2.11-2.63)
50-65 n=3,466,375	4.63 (4.18-5.11)	2.45 (2.09-2.86)
65-75 n=1,505,345	6.03 (5.45-6.68)	2.65 (2.18-3.22)
75+ n=1,092,432	4.85 (4.50-5.23)	2.09 (1.82-2.40)
Other		
<50 n=6,406,013	4.38 (3.77-5.09)	3.21 (2.74-3.75)
50-65 n=3,129,684	3.91 (3.22-4.76)	2.07 (1.65-2.61)
65-75 n=1,290,990	4.11 (3.36-5.03)	1.80 (1.39-2.35)
75+ n=817,611	2.91 (2.39-3.29)	1.21 (0.99-1.47)

SMRW=Standardized Mortality Ratio Weighted

Supplemental Table 8. Sensitivity analysis treating patients who died without hospitalization within 7 days of drug initiation as having been hospitalized.

Scenario	Crude, OR (95% CI)	SMRW-adjusted, OR (95% CI)
All NSAID[a]	4.42 (4.27-4.57)	1.15 (1.07-1.24)
All opioid[b]	26.86 (26.02-27.72)	10.31 (9.52-11.16)
Equal proportion[c]	13.72 (13.3-14.14)	4.07 (3.75-4.42)

SMRW=Standardized Mortality Ratio Weighted

[a] Scenario in which all NSAID initiators who died within 7 days of drug initiation without being hospitalized would have been admitted with pneumonia and no opioid initiators who died would have been admitted.

[b] Scenario in which all opioid initiators who died within 7 days of drug initiation without being hospitalized would have been admitted with pneumonia and no the NSAID initiators who died would have been admitted.

[c] Scenario in which an equal proportion (50%) of NSAID and opioid initiators who died within 7 days of drug initiation without being hospitalized were admitted with pneumonia.

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. PhD thesis. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. PhD thesis. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. PhD thesis. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. PhD thesis. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. PhD thesis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. PhD thesis. *2002*.

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11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. PhD thesis. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. PhD thesis. *2004*.

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15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

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20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. PhD thesis. *2006*.

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22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

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24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. PhD thesis. *2006*.

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27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. Research year report. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

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32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. PhD thesis. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. PhD thesis. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. PhD thesis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. PhD thesis. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

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44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. PhD thesis. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. PhD thesis. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. Research year report. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. PhD thesis. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. PhD thesis. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. PhD thesis. *2009*.

51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. PhD thesis. *2010*.

52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. PhD thesis. *2010*.

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54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. PhD thesis. *2010*.

56. Thomas Patrick Ahern: Estimating the impact of molecular profiles and prescription drugs on breast cancer outcomes. PhD thesis. *2010*.

57. Annette Ingeman: Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome. PhD thesis. *2010*.

58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. PhD thesis. *2010*.

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63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. Research year report. *2011*.

64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. PhD thesis. *2011*.

65. Gitte Vrelits Sørensen: Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. Research year report. *2011*.

66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. PhD thesis. *2012*.

67. Marie Louise Overgaard Svendsen: Early stroke care: studies on structure, process, and outcome. PhD thesis. *2012*.

68. Christian Fynbo Christiansen: Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis. PhD thesis. *2012*.

69. Jennie Maria Christin Strid: Hospitalization rate and 30-day mortality of patients with status asthmaticus in Denmark – A 16-year nationwide population-based cohort study. Research year report. *2012*.

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71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. PhD thesis. *2012*.

72. Anna Maria Platon: The impact of chronic obstructive pulmonary disease on intensive care unit admission and 30-day mortality in patients undergoing colorectal cancer surgery: a Danish population-based cohort study. Research year report. *2012*.

73. Rune Erichsen: Prognosis after Colorectal Cancer - A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment. PhD thesis. *2013*.

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75. Kristina Laugesen: In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder (ADHD). Research year report. *2013*.

76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. Research year report. *2013*.

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81. Dennis Fristrup Simonsen: Patient-Related Risk Factors for Postoperative Pneumonia following Lung Cancer Surgery and Impact of Pneumonia on Survival. Research year report. *2014*.

82. Anne Ording: Breast cancer and comorbidity: Risk and prognosis. PhD thesis. *2014*.

83. Kristoffer Koch: Socioeconomic Status and Bacteremia: Risk, Prognosis, and Treatment. PhD thesis. *2014*.

84. Anne Fia Grann: Melanoma: the impact of comorbidities and postdiagnostic treatments on prognosis. PhD thesis. *2014*.

85. Michael Dalager-Pedersen: Prognosis of adults admitted to medical departments with community-acquired bacteremia. PhD thesis. *2014*.

86. Henrik Solli: Venous thromboembolism: risk factors and risk of subsequent arterial thromboembolic events. Research year report. *2014*.

87. Eva Bjerre Ostenfeld: Glucocorticoid use and colorectal cancer: risk and postoperative outcomes. PhD thesis. *2014*.

88. Tobias Pilgaard Ottosen: Trends in intracerebral haemorrhage epidemiology in Denmark between 2004 and 2012: Incidence, risk-profile and case-fatality. Research year report. *2014*.

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92. Jonathan Montomoli: Short-term prognosis after colorectal surgery: The impact of liver disease and serum albumin. PhD thesis. *2014*.

93. Morten Schmidt: Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use: Pharmacoepidemiological studies. PhD thesis. *2014*.

94. Betina Vest Hansen: Acute admission to internal medicine departments in Denmark - studies on admission rate, diagnosis, and prognosis. PhD thesis. *2015*.

95. Jacob Gamst: Atrial Fibrillation: Risk and Prognosis in Critical Illness. PhD thesis. *2015*.

96. Søren Viborg: Lower gastrointestinal bleeding and risk of gastrointestinal cancer. Research year report. *2015*.

97. Heidi Theresa Ørum Cueto: Folic acid supplement use in Danish pregnancy planners: The impact on the menstrual cycle and fecundability. PhD thesis. *2015*.

98. Niwar Faisal Mohamad: Improving logistics for acute ischaemic stroke treatment: Reducing system delay before revascularisation therapy by reorganisation of the prehospital visitation and centralization of stroke care. Research year report. *2015*.

99. Malene Schou Nielsson: Elderly patients, bacteremia, and intensive care: Risk and prognosis. PhD thesis. *2015*.

100. Jens Tilma: Treatment Injuries in Danish Public Hospitals 2006-2012. Research year report. *2015*.

101. Thomas Lyngaa: Intensive care at the end-of-life in patients dying of cancer and non-cancer chronic diseases: A nationwide study. Research year report. *2015*.

102. Lone Winther Lietzen: Markers of immune competence and the clinical course of breast cancer. PhD thesis. *2015*.

103. Anne Høy Seemann Vestergaard: Geographical Variation in Use of Intensive Care in Denmark: A Nationwide Study. Research year report. *2015*.

104. Cathrine Wildenschild Nielsen: Fecundability among Danish pregnancy planners. Studies on birth weight, gestational age and history of miscarriage. PhD thesis. *2015*.

105. Kathrine Dyhr Lycke: Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study. Research year report. *2015*.

106. Louise Bill: Hyponatremia in acute internal medicine patients: prevalence and prognosis. PhD thesis. *2015*.

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108. Rikke Nørgaard Pedersen: Reoperation due to surgical bleeding in breast cancer patients and breast cancer recurrence: A Danish population-based cohort study. Research year report. *2015*.

109. Thomas Deleuran: Cirrhosis of the liver and diseases of the large joints. PhD Thesis. *2016*.

110. Anne Mette Falstie-Jensen: Hospital accreditation – what's in it for the patients? PhD thesis. *2016*.

111. Sandra Kruchov Thygesen: Respiratory distress syndrome in moderately late and late preterm infants and selected long-term neurodevelopmental outcomes. PhD thesis. *2016*.

112. Alma Bečić Pedersen: Total hip replacement surgery - occurrence and prognosis. Doctoral dissertation. *2016*.

113. Anil Mor: Type 2 Diabetes and Risk of Infections. PhD thesis. *2016*.

114. Aske Hess Rosenquist: Behavioral Development Following Early Life Organochlorine Exposure. Research year report. *2016*.

115. Simon Ramsdal Sørensen: Anti-platelet and Anti-coagulant Prescriptions and Breast Cancer Recurrence: a Danish Nationwide Prospective Cohort Study. Research year report. *2016*.

116. Regional Differences in Treatment of Patients with Inflammatory Bowel Disease in Denmark

117. Clara Reece Medici: Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation. Research year report. *2016*.

118. Johan Frederik Håkonsen Arendt. Clinical implications and biochemical understanding of high plasma vitamin B12 levels. PhD thesis. *2016*.
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120. Søren Christiansen: Timing of renal replacement therapy and long-term risk of chronic kidney disease and death in intensive care patients with acute kidney injury. Research year report. *2017*.

121. Ellen Hollands Steffensen: Preadmission antidepressant use and bladder cancer: a population-based cohort study of stage at diagnosis, time to surgery, and surgical outcomes. Research year report. *2017*.

122. Sara Søndergaard Schwartz: Incidence and mortality of pulmonary hypertension in adults with congenital heart disease. Research year report. *2017*.

123. Jesper Smit: Community-acquired Staphylococcus aureus bacteremia: Studies of risk and prognosis with special attention to diabetes mellitus and chronic heart failure. PhD thesis. *2017*.

124. Carina Nørskov Bagge: Risk of Dementia in Adults with Congenital Heart Disease: A Nationwide Population-Based Cohort Study. Research year report. *2017*.

125. Pia Kjær Kristensen: Hip fracture in Denmark: Quality of in-hospital care and clinical outcomes. PhD thesis. *2017*.

126. Anne Nakano Jensen: Incident heart failure in Denmark: Studies on a nationwide quality improvement initiative. PhD thesis. *2017*.

127. Kasper Adelborg: Neurological and psychiatric comorbidity in patients with heart failure − Risk and prognosis. PhD thesis. *2017*.

128. Jens Sundbøll: Depression, stroke, and dementia in patients with myocardial infarction — Studies of risk and prognosis. PhD thesis. *2017*.

129. Sigrún Alba Jóhannesdóttir Schmidt: Herpes zoster: Occurrence and risk factors. PhD thesis. *2017*.

130. Mette Glavind Bülow Pedersen: Ischemic Stroke in Adults with Congenital Heart Disease: a population-based cohort study. Research year report. *2017*.

131. Sidse Høyer: Male alcohol intake and couples' time to pregnancy - A prospective cohort study. Research year report. *2017*.

132. Cecilie Daugaard: Socioeconomic inequality in drug reimbursement during end-of-life care: A nationwide study. Research year report. *2018*.

133. Stine Bakkensen Bruun: Selective Serotonin Reuptake Inhibitor Use and Mortality, Postoperative Complications, and Quality of Care in Hip Fracture Patients - A population-based cohort study. Research year report. *2018*.

134. Maria Møller Pedersen: Prognostic role of neutrophil-lymphocyte ratio in localized and metastatic renal cell carcinoma: A population-based cohort study. Research year report. *2018*.

135. Hanne Vangsgaard Nielsen: Proton pump inhibitor prescriptions and breast cancer recurrence: A Danish nationwide prospective cohort study. Research year report. *2018*.

136. Jaimie Gradus: The Long-Term Consequences of Trauma and Stress Disorders: Evidence from the Danish Registries. Doctoral dissertation. *2018*.

137. Mette Holland-Fischer: Rheumatoid arthritis, ankylosing spondylitis and hospitalization with pneumonia. PhD thesis. *2018*.

138. Kaja Kristiane Eriksrud Kjørholt: Increasing risk of postoperative infections among hip fracture patients: A nationwide study 2005-2016. Research year report. *2018*.