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

Pharmacoepidemiological studies

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THE 5 ORIGINAL PAPERS ARE

I. Schmidt M, Maeng M, Pedersen L, Lassen JF, Lash TL, Nielsen TT, Sørensen HT. Nonsteroidal Anti-inflammatory Drug Use and Cardiovascular Risks after Coronary Stent Implantation. Pharmacotherapy. 2011:31(5):458-468
II. Schmidt M, Christiansen CF, Horváth-Puhó E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal Anti-inflammatory Drug Use and Risk of Venous Thromboembolism. J Thromb Haemost. 2011; 9(7):1326-33
III. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: a population-based case-control study. BMJ. 2011;343:d3450
IV. Schmidt M, Horváth-Puhó E, Christiansen CF, Petersen K, Bøtker HE, Sørensen HT. Preadmission Non-steroidal Anti-inflammatory Drug Use and 30-day Stroke Mortality. Neurology. 2014; *83*(22), 2013–22
V. Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other non-steroidal anti-inflammatory drugs in Denmark: Trends in utilization 1999-2012. Clin Epidemiol. 2014;6:155-68

THESIS STRUCTURE

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

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

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

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

INTRODUCTION

NSAID CLASSIFICATION

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

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

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

NSAIDs, some also have a preference for COX-2 (older COX-2 inhibitors), whereas the remaining are classified as nonselective NSAIDs (Figure 1).

NSAID USE IN DENMARK

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

Non-aspirin NSAIDs are designated to treat a range of pain and inflammatory conditions.[16,17] Non-aspirin NSAIDs may be indicated to treat non-inflammatory pain syndromes (*e.g.,* lower back pain, postoperative pain, or cancer-related pain) when the effect of non-pharmacological treatment and other analgesics, such as acetaminophen, is insufficient.[16] It may also be used for pain conditions when concurrent inhibition of prostaglandin synthesis is beneficial, *e.g.*, dysmenorrhea or ureteral stones.[16] The main indication, however, is treatment of inflammatory conditions with painful, stiff and/or swollen joints such as arthritis or ankylosing spondylitis.[16,17] Non-aspirin NSAID use, however, does not improve prognosis of these conditions and should therefore be used in lowest effective dose for the shortest duration possible.[16,17] Still, long-term treatment may become necessary to treat symptoms of chronic inflammatory conditions.[16]

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

NSAIDS' PHARMACODYNAMIC EFFECTS

NSAIDs exhibit their anti-inflammatory effect by inhibiting the COX enzyme, which is the rate-limiting enzyme in prostaglandin synthesis (Figure 3).[10] There are at least two major isoforms of the COX enzyme — COX-1 and COX-2.[10] Both isoforms catalyze the conversion of the unsaturated fatty acid arachidonic acid (C20:4) into prostaglandin H_2 through the intermediate product of prostaglandin G_2.[10] Prostaglandin H_2 is then finally converted by tissue-specific isomerases into bioactive lipids called prostanoids.[10] Acting through multiple G-coupled protein receptors,[21] these prostanoids are mediators of a variety of biological effects, including pain, inflammation, and fever, and are also gastroprotective.

Figure 1. *NSAID classification*

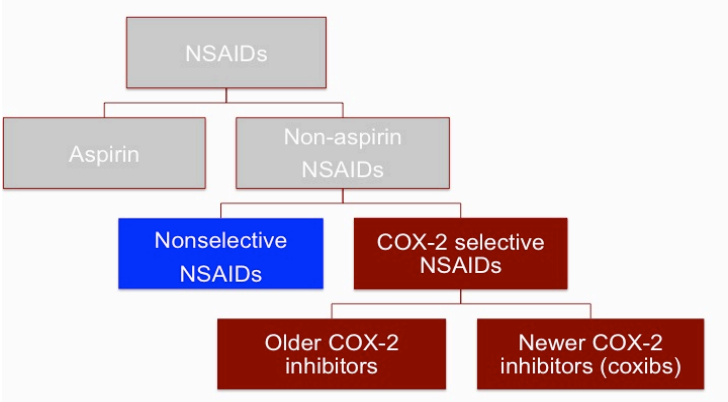


Figure 2. *The one-year prevalence of the Danish population redeeming a prescription for non-aspirin NSAIDs between 1999 and 2013 in gender and age groups. Modified from Schmidt et al., Clin Epidemiol, 2014.*[5]

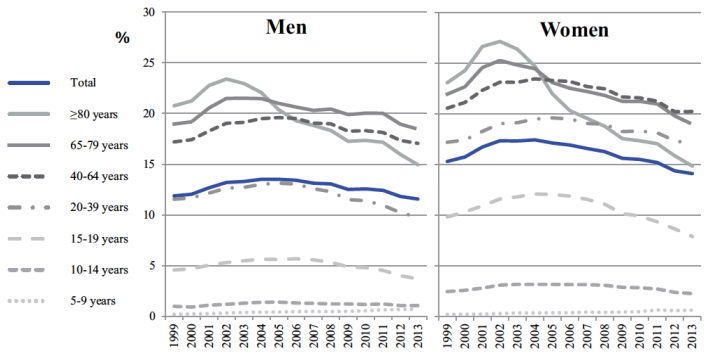
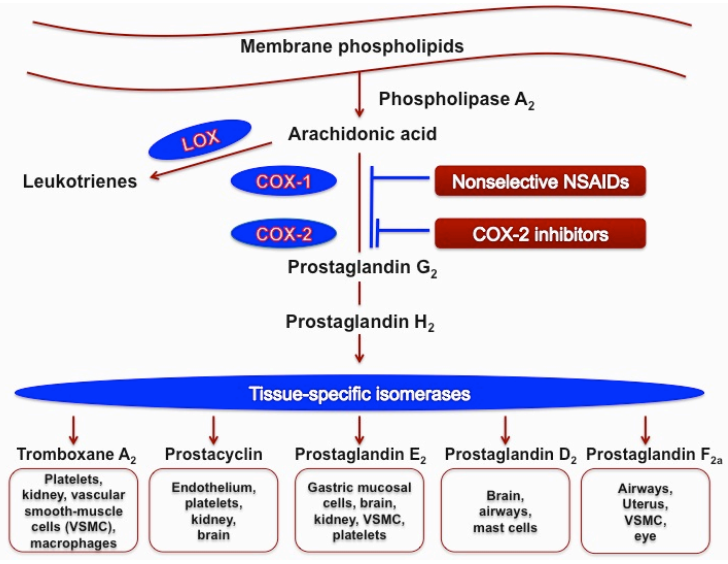


Figure 3. *The effect of NSAIDs on the bio-synthesis of prostanoids from arachidonic acid. Adapted in part from FitzGerald GA et al., New Engl J Med, 2001.*[10]



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

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

COX-2 INHIBITION AND THE CARDIOVASCULAR SYSTEM

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

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

ESTABLISHED CARDIOVASCULAR RISKS ASSOCIATED WITH NON-ASPIRIN NSAID USE

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

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

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

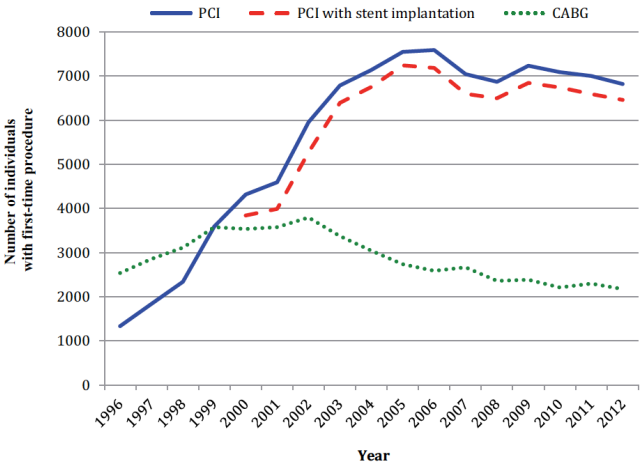
Current evidence, as summarized in meta-analyses, supports that all non-aspirin NSAIDs increase the risk of heart failure and elevated blood pressure, whereas the risk of thrombotic events varies with the type of drug.[28,42] Use of coxibs is associated with the highest vascular risk,[42,43] whereas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

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

According to the American Heart Association, selective COX-2 inhibitors increase the risks of myocardial infarction, stroke, heart failure, and hypertension.[23] However, it is less clear whether use of COX-2 inhibitors or other non-aspirin NSAIDs is also associated with adverse events in the growing proportion of patients with ischemic heart disease who receive percutaneous

coronary intervention (PCI) with stent implantation (Figure 4). Use of non-aspirin NSAIDs may also influence the risk and prognosis of other major cardiovascular diseases. Thus, whether use of non-aspirin NSAIDs increases the risk of venous thromboembolism, atrial fibrillation, or a fatal outcome from stroke remains largely uninvestigated.

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



LITERATURE REVIEW

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

NON-ASPIRIN NSAID USE AND STENT-RELATED OUTCOMES

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

Table 1. *Summary of literature*

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

Study II: Non-aspirin NSAID use and venous thromboembolism risk			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Bergendal A *et al.*[56] - Pharmacoepidemiol Drug Saf - 2013	- Case-control study - Sweden (nationwide) - Thrombo Embolism Hormone Study - 2003–2009	- Females aged 18–64 y - Propionic-, acetic acid derivatives, coxibs - First-time VTE (n=1,433) - Matched population controls (n=1,402)	- aOR: 0.88 (0.72–1.10) for propionic acid derivatives (92% ibuprofen), 1.18 (0.82–1.70) for acetic acid derivatives (97% diclofenac), and 1.76 (0.73–4.27) for coxibs (53% celecoxib, 29% rofecoxib, 15% etoricoxib). aORs increased with cumulative dose for diclofenac/coxibs. - No data on duration of use. Limited precision on coxib estimates.
Biere- Rafi S *et al.*[19] - Pharmacoepidemiol Drug Saf - 2011	- Case-control study - The Netherlands - PHARMO Record Linkage System - 1990–2006	- General population >18 y (source) - NSAIDs, acetaminophen, tramadol - First-time PE (n=4,433) - Matched controls (n=16,802)	- aOR(any NSAIDs): 2.39 (2.06–2.77) for current use, 1.23 (1.14–1.34) for past use, 4.77 (3.92–5.81) for new use, 2.14 (1.48–3.09) for long-term use. aOR highest for tNSAIDs (3.19, 2.73–3.72), diclofenac in any dose (3.85, 3.09–4.81) and >150 mg (6.64, 3.56–12.4). OR=1.74 (1.42–2.14) for acetaminophen, 4.07 (2.86–5.75) for tramadol. - Indications of at least some confounding by underlying pain indication.
Schmidt M *et al.*[2] - J Thromb Haemost - 2011	- Population-based case-control study - Northern Denmark - NPR, PR, CRS - 1999–2006	- General population (source) - nsNSAIDs, older COXIs, coxibs - First-time DVT/PE (n=8,368) - Matched controls (n=82,218)	- aOR(nsNSAIDs)=2.51 (2.29–2.76) overall and 2.06 (1.85–2.29) for long-term users. aOR (COX2Is)=2.19 (1.99–2.41) overall and 1.92 (1.72–2.15) for long-term users. Similarly increased risks were found for unprovoked VTE, DVT, PE, and individual NSAIDs. - Unmeasured confounding cannot be excluded.
Sundström *et al.*[57] - BJOG - 2008	- Nested case-control study - UK - GPRD - 1992–1998	- Women 15–49 y with menorrhagia - Mefenamic acid (prescription≤90 days) - DVT/PE (n=134) - Matched controls (n=552)	- aOR: 5.54 (2.13–14.40). - Small sample size (exposed: 10 cases and 12 controls), only mefenamic acid examined.
Lacut K *et al.*[58] - Haematologica - 2008	- Case-control study - France - The EDITH study - 2000–2004	- General population >18 y (source) - NSAIDs - Unprovoked, first-time VTE (n=402) - Matched controls	- aOR: 0.93 (0.44–1.98) - Small sample size and no data on individual NSAIDs or duration of use.
Nagai N *et al.*[59] - Thromb Res - 2008	- Animal experimental study - Belgium - 2008	- Murine venous thrombosis model - Rofecoxib (4 wk.) - VTE	- Enhanced prothrombotic effect detected in lean mice. - Not population-based clinical setting, only rofecoxib examined.
Huerta C *et al.*[60] - Arch Intern Med - 2007	- Nested case-control study - UK - GPRD - 1994–2000	- General population (source) - tNSAIDs (drugs not specified) - VTE (DVT/PE) (n=6,550) - Matched controls (n=10,000)	- aOR=1.86 (1.65–2.10) for VTE, 2.17 (1.89–2.50) for DVT, 1.60 (1.37–1.87) for PE. OR for VTE=2.82 (2.35–3.39) within 0–30 d, 1.68 (1.39–2.04) within 31–365 d, 1.26 (1.04–1.54) >1 y. No association for long-term users with osteoarthritis (estimates not provided). - No data on individual NSAIDs. No subgroups examined other than osteoarthritis.
Westgate EJ and FitzGerald GA[61] - PLoS Med - 2005	- Case report - US	- 25 y old woman: >3 y oral contraceptive use, nonsmoker, no risk factors, vigorously athletic - Valdecoxib (40 mg/day) due to neck pain - DVT/PE	- DVT and bilateral and multiple PEs 1 month after drug initiation. - Risk of chance or confounding from oral contraceptives (despite 3–y period of apparent tolerance) or prolonged stasis due to a 6–h car trip (despite having taking similar trips on multiple occasions).
Chan AL[62] - Ann Pharmacother - 2005	- Case report - Taiwan - 2003	- 52 y old man with gout, no thrombosis history, previously prescribed indomethacin - Celecoxib 200 mg/day - DVT	- DVT 5 days after drug initiation. Other causes except celecoxib were ruled out. The adverse reaction was determined as probable according to the Naranjo probability scale. - Risk of chance and confounding cannot be ruled out.
Layton D et al.[63] - Rheumatology (Oxford) - 2003	- Cohort study - England - NHS PR, GP-questionnaires - 1996–1997 (meloxicam); 1999 (rofecoxib)	- GP-treated general population cohort - Rofecoxib *vs.* meloxicam (reference) - Thromboembolic (cardiovascular, VTE, or cerebrovascular) events within 9 months	- Number of VTEs=6/15268 (0.05%) for rofecoxib and 20/19 087 (0.10%) for meloxicam users. aRR for VTE=0.29 (0.11–0.78). - COX-2 selective reference group makes comparison to non-users difficult. No data on other NSAIDs. Risk of non-response bias.
Tsai AW *et al.*[64] - Arch Intern Med - 2002	- Cohort study - US (6 communities) - The ARIC and CHS studies - 1987–1998	- General population (n=9,293) - tNSAIDs (drugs not specified) - First-time VTE (n=215)	aHR=1.44 (1.03–2.02) after adjustment for age-, race-, and sex. No association (estimate not provided) after further adjustment for BMI and diabetes. - No data on individual NSAIDs or new-/long-term use. Unclear if the null association relates to an increased, but non-significant HR due to limited sample size.
Bombardier et al.[35] - New Engl J Med - 2000	- RCT (VIGOR) - 301 centers in 22 countries - Randomization - 1999	- RA patients (n=8,076) - Naproxen (500 mg twice/day) *vs.* rofecoxib (50 mg/day) - Peripheral vascular events (VTE)	- aRR for peripheral vascular events=0.17 (0.00–1.37) with rofecoxib as reference.[11,63,65] - Designed to evaluate gastrointestinal toxicity, but not powered to detect differences of individual thromboembolic events. VTE results not part of original paper.
Crofford LJ *et al.*[66] - Arthritis Rheum - 2000	- Case report - US - 1999	- 56 y old woman with systemic sclerosis and lupus anticoagulant - Celecoxib (200 mg/day) for leg pain	- PE two days after drug initiation. - Although temporal relationship, risk of chance and confounding cannot be ruled out. Risk of protopathic bias.

Study III: Non-aspirin NSAID use and atrial fibrillation risk			
Author, journal, year	**Design, setting, registries, period**	**Population, exposure, outcome, controls**	**Results, limitations**
Krijthe BP *et al.*[67] - BMJ Open - 2014	- Cohort study - The Netherlands - Rotterdam Study, PR, NPR, CRS - 1990–2009 (interval follow-up)	- Participants >55 y without AF (n=8,423) - NSAIDs (any type) (time-varying use) - AF (from ECG or MR) (n=857)	- aHR=1.76 (1.07–2.88) for current use and 1.84 (1.34–2.51) for recent past use (within 30 days after discontinuation), but not past use 31–180 days (1.00, 0.77–1.29) or >180 (1.04, 0.88–1.22) after discontinuation. - No data on individual NSAIDs, indications, and limited sample size.
Chao T *et al.*[68] - Int J Cardiol - 2013	- Case-control study - Taiwan (nationwide) - NHIRD - 2000–2009	- General population (source) - tNSAIDs and coxibs - First-time AF ≥18 y (n=7,280) - Matched controls (n=72,800)	- aOR(tNSAIDs or coxibs)=1.14 (1.06–1.23), 1.65 (1.38–1.97) for new use, 1.92 (1.49–2.48) for new use in HF; aOR(coxibs)=1.20 (0.95–1.28), 1.66 (1.14–2.41) in CKD and 1.71 (1.20–2.42) in chronic pulmonary disease; aOR(tNSAIDs *vs.* coxibs)=1.39 (1.18–1.64) - Imprecise coxib estimates potentially leading to type 2 error in interpretation.
Bäck M *et al.*[69] - Eur Heart J - 2012	- Population-based cohort study - Sweden (nationwide) - NPR, PR, CDR, CRS, other - 2005–2008	- General population >18 y (n=6,991,645) - tNSAIDs and coxibs (time-varying use) - First-time AF (n=139,323)	- aHR=1.11 (1.09–1.13) for tNSAIDs, 1.35 (1.19–1.54) for etoricoxib, 0.94 (0.79–1.11) for celecoxib, and 1.16 (1.05–1.29) for coxibs combined. - No data on AF subtypes or individual tNSAIDs.
Schmidt M *et al.*[3] - BMJ - 2011	- Population-based case-control study - Northern Denmark - NPR, PR, CRS - 1999–2008	- General population (source) - nsNSAIDs, older COXIs, coxibs - First-time AF or AFL (n=32,602) - Matched controls (n=325,918)	- aOR(nsNSAIDs)=1.17 (1.10–1.24), 1.46 (1.33–1.62) for new users. OR(COX2Is)=1.27 (1.20–1.34), 1.71 (1.56–1.88) for new users. OR(older COX2Is)=1.31 (1.22–1.40); aOR(coxibs)=1.20 (1.09–1.33). Highest risk for CKD or RA patients initiating COX2Is. - No data on AF subtypes or drug indications.
De Caterina R *et al*.[70] - Arch Intern Med - 2010	- Case-control study - UK - GPRD - 1996	- General population (source) - tNSAIDs - Paroxysmal and chronic AF (n=525/1035) - Matched controls 40–89 y (n=10,000)	- aOR for chronic AF (>1 wk.)=1.44 (1.08–1.91) for current and 1.80 (1.20–2.72) long-term (>1 y) use. aOR for paroxysmal AF(≤1 wk.)=1.18 (0.85–1.66) for current and 1.74 (1.11–2.71) for long-term use. - Imprecise estimates for individual NSAIDs.
Zhang J *et al.*[71] - JAMA - 2006	- Meta-analysis	- 116,094 participants in 114 RCTs - Coxibs - Arrhythmias (any) (n=286)	- aRR=2.90 (1.07–7.88) for rofecoxib, 0.84 (0.45–1.57) for celecoxib, 0.78 (0.62–1.01) for valdecoxib/parecoxib, and 1.16 (0.40–3.38) for etoricoxib. - Imprecise estimates and AF not examined.

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

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

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

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

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

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

NON-ASPIRIN NSAID USE AND VENOUS THROMBOEMBOLISM RISK

Venous thromboembolism is a common disease affecting overall 1–2 per 1,000 individuals in Western populations per year.[81] The annual incidence rate, however, increases exponentially with age for both men and women,[82] from <0.5 per 1,000 persons below 40 years of age to about one per 100 persons aged 80 years or more.[82] The classic risk factors for venous thromboembolism include immobilization, recent surgery, trauma, cancer, pregnancy, and use of oral contraceptives or postmenopausal hormonal replacement therapy.[81] Based on the presence or absence of these classic risk factors, venous thromboembolism can arbitrarily be categorized as provoked (=secondary) or unprovoked (=idiopathic/primary).[81] Venous thromboembolism is associated with increased morbidity and mortality.[81,83] It occurs predominantly in the deep vessels of the lower limbs (*i.e.*, deep vein thrombosis), with subsequent risk of pulmonary embolism and post-thrombotic syndrome.[84] Among patients with pulmonary embolism, 2–4% develop chronic thromboembolic pulmonary hypertension with disabling dyspnea both at rest and with exertion.[85] The recurrence rate after stopping anticoagulant drug therapy is overall 5% per year, and higher after unprovoked (8%) than provoked venous thromboembolism (3%).[86] Recurrent venous thromboembolism is therefore a major clinical problem and recent data show that patients with venous thromboembolism are at considerable increased risk of dying within the first 30 days after diagnosis (3% for deep vein thrombosis and 31% for pulmonary embolism), but also during the remaining 30 years of follow-up with venous thromboembolism as an important cause of death.[83]

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

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

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

NON-ASPIRIN NSAID USE AND ATRIAL FIBRILLATION RISK

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

NSAIDs may reduce any inflammatory-associated risk of atrial inflammation.[102] However, NSAID use may also increase the risk of atrial fibrillation through several cardiovascular- and renal-related effects.[111] First, NSAIDs may elicit direct proarrhythmic effects that render the patient more susceptible to atrial fibrillation.[11] Thus, COX-2-derived prostacyclin acts as an endogenous antiarrhythmic agent through its inhibition of epicardial sympathetic nerve activity.[112-114] This inhibition may be particularly

important during myocardial ischemia where thromboxane and prostacyclin are released from the acutely ischemic myocardium and their balance is related to the risk of arrhythmias.[115] Experimental animal studies have also shown that selective deletion of cardiomyocyte COX-2 expression in mice induces interstitial and perivascular fibrosis associated with an enhanced susceptibility to arrythmias[116] and that coxibs, independent of their COX-2 inhibition, may inhibit delayed rectifier potassium channels and thereby induce arrhythmia.[117]

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

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

NON-ASPIRIN NSAID USE AND STROKE MORTALITY

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

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

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

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

HYPOTHESES AND OBJECTIVES

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

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

METHODS

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

Figure 5. *Record linkage potential of Danish medical registries using the Civil Personal Register (CPR) number. Red circles highlight the data sources used. Figure modified from Schmidt et al., Clin Epidemiol, 2010.*[136]

Table 2. Summary of methods

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

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

SETTING

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

DATA SOURCES

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

Prescription registries (studies I–V)

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

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

The Civil Registration System (studies I–IV)

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

The Western Denmark Heart Registry (study I)

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

The Danish National Patient Registry (studies I–IV)

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

The National Registry of Causes of Death (study I)

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

STUDY DESIGNS

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

STUDY POPULATIONS AND OUTCOMES

Cohort studies (studies I and IV)

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

The outcome measure in the cohort studies was time-to-event.[148] In study I, we defined MACE as the first occurrence of myocardial infarction, stent thrombosis, TLR, or cardiac death. We used the DNPR to identify myocardial infarction admissions.[139] Stent thrombosis and TLR were identified from the

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

Case-control studies (studies II and III)

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

We then used the Civil Registration System to select up to 10 general population controls for each case, matched on age and sex.[134] We selected controls using risk-set sampling, *i.e.*, controls had to be alive and at risk for a first venous thromboembolism/atrial fibrillation on the index date of the case to whom each was matched (Table 2).[150]

NON-ASPIRIN NSAID USE

Prescription and over-the-counter use

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

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

Classification

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

User categories

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

COVARIABLES

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

STATISTICAL ANALYSIS

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

For all studies, we initially created contingency tables for the main study variables.[160] In the time-to-event analyses, we followed all patients until date of a non-fatal outcome, death, emigration, or end of follow-up, whichever came first. We used Cox proportional hazards regression, with time since cohort entry as the underlying time scale, to calculate HRs as a measure of the incidence rate ratio (IRR). We used log-log plots to test the proportional hazards assumption graphically. We used logistic regression for the case-control analyses.[161] Because we used risk-

set sampling of controls, the odds ratio (OR) estimates the IRR.[150] We calculated 95% CIs for all estimates, *i.e.*, upon repeated sampling, 95% of the intervals constructed in the same way would be expected to cover the true parameter assuming no bias and no prior knowledge.[162]

We used different strategies to control for confounding depending on the individual study design (Table 2). In the design phase, we used restriction (I–IV) and propensity score matching (IV).[163,164] Calculating the propensity score, *i.e.*, the conditional probability of non-aspirin NSAID use given all covariables,[165] we included potential confounders and risk factors in a logistic regression, but not factors associated exclusively with NSAID use.[163,166] Using a greedy matching algorithm,[167] we matched each NSAID user with the non-user with the closest propensity score.[167] The propensity score matching was performed without replacement, within a maximum matching range (caliper width) in propensity score of ±0.025, and separately for each class and individual type of NSAID.[167] Of note, we did not propensity score match controls to cases in studies II and III because the control groups in these case–control studies were intended to resemble the population denominator that gives rise to the cases, rather than the cases.[168,169]

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

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

RESULTS

The main findings are summarized in the following sections.

NON-ASPIRIN NSAID USE AND STENT-RELATED OUTCOMES (STUDY I)

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

NON-ASPIRIN NSAID USE AND VENOUS THROMBOEMBOLISM RISK (STUDY II)

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

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

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

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

Abbreviations: MACE=major adverse cardiovascular event (*i.e.*, myocardial infarction, stent thrombosis, TLR, or cardiac death); TLR=target lesion revascularization.
*Rate per 1,000 person years.
†Adjusted for covariables listed in Table 2 using Cox proportional hazards regression.

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

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

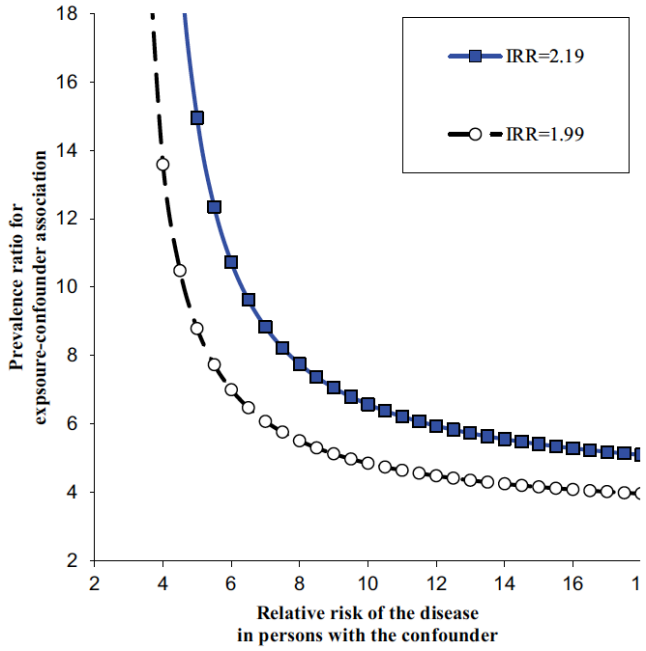
*Adjusted for the matching factors of age and gender.
†Adjusted for covariables listed in Table 2 using unconditional logistic regression.

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

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

*Age- and gender-matched.
†Adjusted for covariables listed in Table 2 using conditional logistic regression.
‡Current use of both nonselective NSAIDs and COX-2 inhibitors.

Figure 6. *Required strength of an unmeasured confounder*



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

NON-ASPIRIN NSAID USE AND ATRIAL FIBRILLATION RISK (STUDY III)

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

Figure 7. *Adjusted incidence rate ratios associating use of non-aspirin NSAIDs and atrial fibrillation risk in patient subgroups*

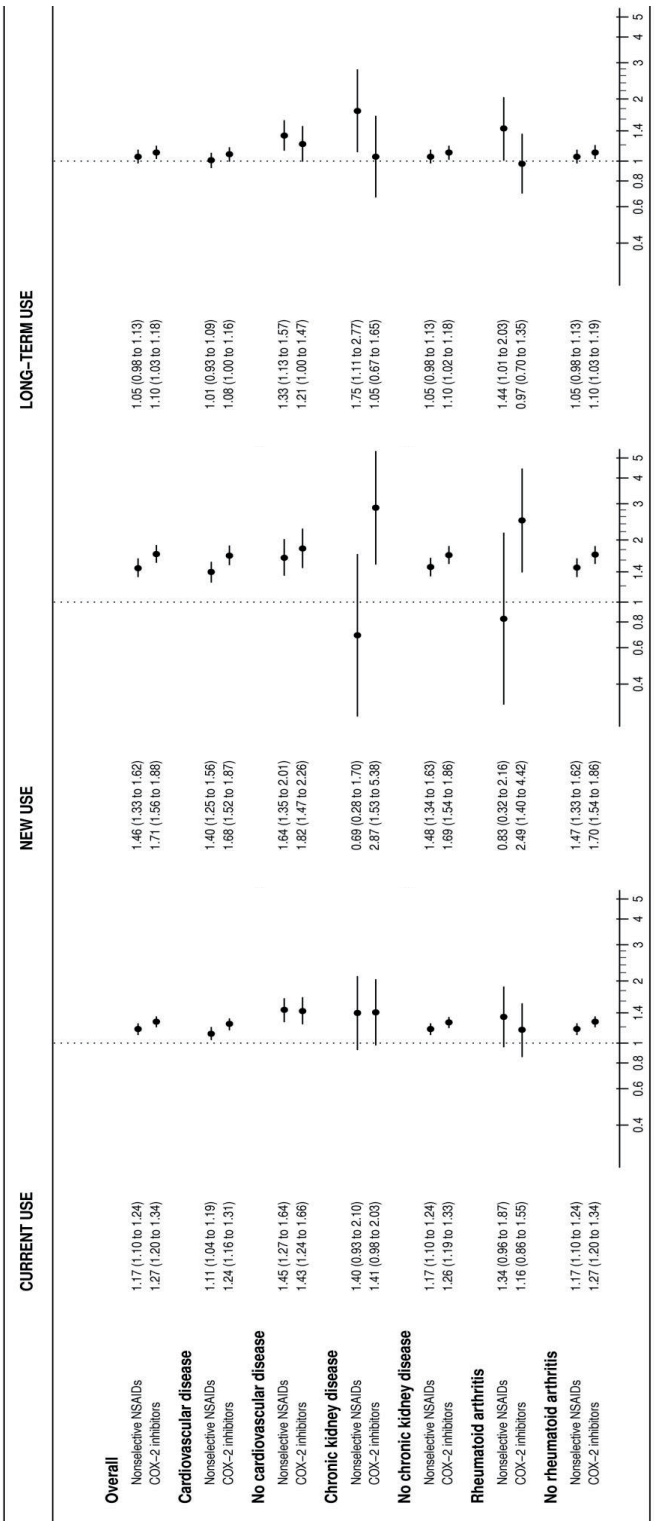


Table 6. *Preadmission use of non-aspirin NSAIDs and 30-day mortality estimates following ischemic stroke.*

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

NON-ASPIRIN NSAID USE AND STROKE MORTALITY (STUDY IV)

We identified 100,043 patients with first-time hospitalization for stroke, among whom 83,736 (84%) had ischemic stroke, 11,779 (12%) had intracerebral hemorrhage, and 4,528 (5%) had subarachnoid hemorrhage. A total of 10.8% were current NSAID users, 8.4% were former users, and 80.8% were non-users. Among the current NSAID users, 51.4% used ibuprofen, 3.2% used naproxen, 27.0% used diclofenac, 10.7% used etodolac, 1.0% used celecoxib, and 0.5% used rofecoxib.

We found that preadmission use of COX-2 inhibitors was associated with increased 30-day mortality following ischemic stroke, but not hemorrhagic stroke. Thus, the 30-day MRR for ischemic stroke was 1.14 (95% CI: 1.03–1.27) for current users of COX-2 inhibitors, driven by the effect among new users (1.31, 95% CI: 1.13–1.52).

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

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

DISCUSSION

MAIN CONCLUSIONS

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

COMPARISON WITH EXISTING LITERATURE

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

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

No previous study has examined the cardiovascular risks, including stent thrombosis and TLR, associated with non-aspirin NSAID use in a large cohort of stent patients. An earlier Danish study of 58,432 patients with first-time myocardial infarction reported an increased risk of re-hospitalization for myocardial infarction and all-cause mortality for any use of ibuprofen, diclofenac, celecoxib, and rofecoxib.[46] The study, however, did not restrict to stent patients or include data on stent-related outcomes.[46] Also, naproxen was not studied separately.[46] A multisite cohort study included 48,566 patients from the US, Canada, and the UK with myocardial infarction, coronary revascularization (PCI or coronary artery bypass grafting), or unstable angina.[54] In this study, naproxen users had a lower rate of adverse cardiovascular events than users of ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib.[54] In the subgroup of patients with coronary revascularization with or without stent implantation, only rofecoxib showed an increased risk of the combined outcome of myocardial infarction and out-of-hospital death from ischemic heart disease, whereas there was no association for naproxen, ibuprofen, diclofenac, and celecoxib.[54] Assessing the efficacy of celecoxib in reducing neointimal hyperplasia after coronary stent implantation,

the randomized COREA-TAXUS trial followed 274 patients after paclitaxel-eluting stent implantation.[53,55] Both the six-month[55] and two-year[53] outcomes from this trial suggested that the adjunctive use of celecoxib for six months after stent implantation in patients with ischemic heart disease was safe (no increased risk of MACE) and actually reduced the risk of TLR.[53,55] Similar results have recently been reported at six months in the Mini-COREA trial, which included 909 patients and a three-month treatment period with celecoxib, but otherwise had similar design and aim as the COREA-TAXUS trial.[51]

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

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

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

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

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

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

Following our study, two other studies have reported data in support of an association.[19] A case-control study from the Netherlands found that long-term NSAID use was associated with more than a two-fold increased risk of pulmonary embolism.[19] The risk was highest for diclofenac with an overall OR of 3.85 (95% CI: 3.09–4.81), increasing to 6.64 (95% CI: 3.56–12.4) for daily doses >150 mg.[19] The study also indicated that the association in part may be explained by confounding from underlying medical conditions for which these drugs were prescribed, because painkillers not related to a prothrombotic state (acetaminophen and tramadol) also were associated with risk of pulmonary embolism.[19] Finally, a Swedish nationwide case-control study found that users of high cumulative doses of acetic acid derivatives and coxibs had the highest risks of venous thromboembolism, which indicates a correlation with COX-2 selectivity and dose.[56]

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

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

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

A UK case-control study of patients diagnosed in 1996 with chronic (n=1,035) or paroxysmal atrial fibrillation (n=525) found that current use of traditional NSAIDs (nonselective NSAIDs or older COX-2 inhibitors) was associated with an increased risk of chronic atrial fibrillation (OR=1.44, 95% CI: 1.08–1.91) and modestly associated with paroxysmal atrial fibrillation (OR=1.18, 95% CI: 0.85–1.66), *i.e.,* with magnitude of the association similar to our results.[70] In contrast to our results, long-term NSAID use (>1 year) was associated with the largest risk increase (OR=1.80, 95% CI: 1.20–2.72).[70] A meta-analysis, involving 116,094 patients using coxibs, identified 6,394 composite renal outcome events, but only 286 composite arrhythmia outcome events, of which ventricular fibrillation, cardiac arrest, and sudden cardiac death accounted for most.[71] Although rofecoxib was associated with an increased relative risk for the composite arrhythmia outcome (2.90, 95% CI:

1.07–7.88), the small number and types of arrhythmias available for analysis did not allow for an examination of atrial fibrillation risk.[71]

Following our study, three other studies have provided data that support our findings. First, a population-based cohort study from Sweden found an increased risk of atrial fibrillation associated with use of both traditional NSAIDs (HR=1.11, 95% CI: 1.09–1.13) and coxibs (HR=1.16, 1.05–1.29).[69] In this study, coxibs included either celecoxib or the more COX-2 selective etoricoxib.[69] Supporting our finding of an effect that is higher the more COX-2 selective, the risk increase was related to etoricoxib (1.35, 95% CI: 1.19–1.54), but not celecoxib (0.94, 0.79–1.11).[69] A nationwide case-control study from Taiwan found that any NSAID use was associated with an increased risk of atrial fibrillation (OR=1.14, 95% CI: 1.06–1.23), especially among new users (OR=1.65, 95% CI: 1.38–1.97) and patients with heart failure (OR=1.92, 95% CI: 1.49–2.48).[68] Use of coxibs was associated with an OR for atrial fibrillation of 1.20 (95% CI: 0.95–1.28), increasing to 1.66 (95% CI: 1.14–2.41) among patients with chronic kidney disease and 1.71 (95% CI: 1.20–2.42) among patients with chronic pulmonary disease.[68] Finally, a cohort study using data from the Rotterdam Study also associated current NSAID use with an increased risk of atrial fibrillation (HR=1.76, 95% CI: 1.07–2.88).[67]

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

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

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

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

METHODOLOGICAL CONSIDERATIONS

Internal validity

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

Precision

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

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

cardiac and cerebral event (MACCE) to acknowledge the importance of stroke as a thromboembolic and hemorrhagic complication to therapy and surgery.[181,182] Still, the choice of MACE was appropriate because study I focused on the stent-related cardiac outcomes

Selection bias

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

Our population-based designs within the setting of a tax-supported universal healthcare system largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups.[133,141] Moreover, the Civil Registration System allowed accurate accounting for censoring due to death or emigration.[134]

Information bias

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

Misclassification of NSAID use

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

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

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

Misclassification of outcomes

The individual components of MACE in study I were adjudicated by a specialist committee in relation to previous studies.[144,149] The positive predictive values of diagnoses in the DNPR have previously been validated using medical record review as standard reference and found to be approximately 92–100% for myocardial infarction,[183-185] 75–90% for venous thromboembolism,[93,186] 93–97% for atrial fibrillation,[187,188] 97% for ischemic stroke,[147] 74% for intracerebral hemorrhage,[147] 67% for subarachnoid hemorrhage,[147] and 98% overall for the comorbidities included in the Charlson Comorbidity Index.[184] Mortality data were virtually complete.[134] While the International Classification of Disease code used to identify atrial fibrillation also includes atrial flutter, our results were driven by atrial fibrillation because more than 90% of patients registered with this code have atrial fibrillation.[188] Study III was limited by its inability to separate paroxysmal, persistent, and permanent atrial fibrillation. However, we were able to restrict to atrial fibrillation cases treated with cardioversion within one year after first diagnosis and thereby relating NSAID use to disease severity. We classified unspecified strokes as ischemic strokes and doing so inevitably misclassified some intracerebral hemorrhages (approximately 6%) as ischemic strokes.[147] Given the lack of association between NSAID use and mortality from intracerebral hemorrhage, such misclassification would bias the results for ischemic stroke towards the null and thus cannot explain our findings. Overall, coding errors of outcomes seem unlikely to have had an important influence on our results, and importantly the accuracy of the hospital diagnoses is unlikely to differ by previous medication exposure, so any misclassification would be non-differential.

Confounding

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

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

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

In study III, we lacked data on lifestyle factors, including smoking and body size, and underlying inflammatory conditions leading to NSAID use. In contrast to study II, former use was not associated with the outcome, indicating an effect of current use. Also, the effect estimates did not change when patients with systemic inflammatory conditions, e.g., rheumatoid arthritis, were excluded. Still, we note that it cannot be ruled out that new users may have more severe underlying inflammation compared with long-term users, which could have increased their risk of atrial fibrillation. In study II and III, we considered the case-control design an efficient alternative to the cohort design for the purpose of estimating relative measures of association, because the OR provides an unbiased estimate of the IRR owing to the risk-set sampling of controls.[150,168,169] Thus, we have no reason to suspect that the results of study II and III would have differed in a cohort setting.[93,169]

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

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

Generalizability

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

CLINICAL IMPLICATIONS

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

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

Physicians should be aware of the potential risk of atrial fibrillation when balancing patient-specific risks and benefits of prescribing treatment with non-aspirin NSAIDs.[196,197] Accordingly, efforts should be made to assess and treat modifiable risk factors for atrial fibrillation before and during treatment with non-aspirin

NSAIDs.[17,48] Non-pharmacological treatment and other analgesics, such as acetaminophen, should be considered as agents to avoid initiation of non-aspirin NSAID therapy.[17,48] Due to the uncertainty of the nature of the association between non-aspirin NSAIDs and venous thromboembolism, it is too early to make recommendations. Regardless of the causality of this association, effective treatment of pain is warranted to reduce pain-related immobilization and the associated risk of venous thromboembolism.

SUMMARY

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

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

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

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

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

In study IV (2004–2012), we included 100,043 patients with first-time hospitalization for stroke in Denmark. After multivariate adjustment, the 30-day mortality rate ratio (MRR) for ischemic stroke was 1.14 (95% CI: 1.03–1.27) for current users of COX-2 inhibitors compared with non-users, driven by the effect among new users (1.31, 95% CI: 1.13–1.52). A propensity score matched analysis yielded similar results, with a 30-day MRR for ischemic stroke of 1.16 (95% CI: 1.01–1.34) among current users and 1.28 (95% CI: 1.07–1.54) among new users. Comparing different types of COX-2 inhibitors, the MRR was driven by new use of older traditional COX-2 inhibitors (1.30, 95% CI: 1.12–1.52), being 1.51 (95% CI: 1.16–1.98) for etodolac and 1.21 (95% CI: 1.01–1.45) for diclofenac. Mortality from hemorrhagic strokes was not associated with preadmission use of non-aspirin NSAIDs.

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

REFERENCES

1. Schmidt M, Pedersen L, Maeng M, et al. Nonsteroidal anti-inflammatory drug use and cardiovascular risks after coronary stent implantation. Pharmacotherapy 2011;31(5):458–68.
2. Schmidt M, Christiansen CF, Horvath-Puho E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. J Thromb Haemost 2011;9(7):1326–33.
3. Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ 2011;343:d3450.
4. Schmidt M, Horváth-Puhó E, Christiansen CF, Petersen K, Bøtker HE, Sørensen HT. Preadmission Non-steroidal Anti-inflammatory Drug Use and 30-day Stroke Mortality. Neurology. 2014; *83*(22), 2013–22
5. Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other non-steroidal anti-inflammatory drugs in Denmark: Trends in utilization 1999-2012. Clin Epidemiol 2014;6:155–68.
6. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ 2013;346:f3195.
7. Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. J Pharm Pharm Sci 2008;11(2):81s–110s.
8. James MW, Hawkey CJ. Assessment of non-steroidal anti-inflammatory drug (NSAID) damage in the human gastrointestinal tract. Br J Clin Pharmacol 2003;56(2):146–55.
9. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Saf 2012;35(12):1127–46.
10. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001;345(6):433–42.
11. Grosser T, Yu Y, FitzGerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. Annu Rev Med 2010;61:17–33.
12. Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase in-

hibitors in humans. Prostaglandins Other Lipid Mediat 2007;82(1-4):85–94.
13. Fuster V, Sweeny JM. Aspirin: A Historical and Contemporary Therapeutic Overview. Circulation 2011;123(7):768–78.
14. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71–86.
15. Chan AT, Arber N, Burn J, et al. Aspirin in the Chemoprevention of Colorectal Neoplasia: An Overview. Cancer Prev Res (Phila) 2012;5(2):164–78.
16. Danish Pharmaceutical Information. NSAIDs. Available at: http://pro.medicin.dk/Laegemiddelgrupper/Grupper/213010 . Accessed on June 20, 2014.
17. American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology white paper. Arthritis Rheum 2008;59(8):1058–73.
18. Fosbøl EL, Gislason GH, Jacobsen S, et al. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. Pharmacoepidem Drug Saf 2008;17(8):822–33.
19. Biere-Rafi S, Di Nisio M, Gerdes V, et al. Non-steroidal anti-inflammatory drugs and risk of pulmonary embolism. Pharmacoepidemiol Drug Saf 2011;20(6):635–42.
20. United Nations. Department of Economic and Social Affairs. Population Division. World Population Ageing 2013. New York, NY: United Nations; 2013.
21. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. J Clin Invest 2006;116(1):4–15.
22. Topper JN, Topper JN, Cai J, et al. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA 1996;93(19):10417–22.
23. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal Antiinflammatory Drugs: An Update for Clinicians: A Scientific Statement From the American Heart Association. Circulation 2007;115(12):1634–42.
24. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA 1999;96(1):272–7.
25. Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther 1999;289(2):735–41.
26. Egan KM, Lawson JA, Fries S, et al. COX-2-derived prostacyclin confers atheroprotection on female mice. Science 2004;306(5703):1954–7.
27. Kobayashi T, Tahara Y, Matsumoto M, et al. Roles of thromboxane A(2) and prostacyclin in the development of atherosclerosis in apoE-deficient mice. J Clin Invest 2004;114(6):784–94.
28. Aw T-J, Haas SJ, Liew D, Krum H. Meta-analysis of Cyclooxygenase-2 Inhibitors and Their Effects on Blood Pressure. Arch Intern Med 2005;165(5):490–6.
29. Solomon SD, Solomon SD, Pfeffer MA, et al. Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas. Circulation 2006;114(10):1028–35.
30. Wang D, Patel VV, Ricciotti E, et al. Cardiomyocyte cyclooxygenase-2 influences cardiac rhythm and function. Proc Natl Acad Sci USA 2009;106(18):7548–52.
31. Huerta C, Huerta C, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. Heart 2006;92(11):1610–5.
32. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 2009;169(2):141–9.
33. Timmers L, Timmers L, Sluijter JPG, et al. Cyclooxygenase-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. Circulation 2007;115(3):326–32.
34. Jugdutt BI. Cyclooxygenase Inhibition and Adverse Remodeling During Healing After Myocardial Infarction. Circulation 2007;115(3):288–91.
35. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343(21):1520–8, 2 p following 1528.
36. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286(8):954–9.
37. Curfman GD, Morrissey S, Drazen JM. Expression of Concern Reaffirmed. N Engl J Med 2006;354(11):1193–3.
38. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284(10):1247–55.
39. Peter Jüni AWRPAD. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? : Adequate analysis of the CLASS trial indicates that this may not be the case. BMJ 2002;324(7349):1287.
40. Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30(6):1196–202.
41. Bresalier RS, sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352(1533-4406):1092–102.
42. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382(9894):769–79.
43. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.
44. Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs

and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation 2011;123(20):2226–35.
45. Olsen AM, Fosbøl EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. Circulation 2012;126(16):1955–63.
46. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation 2006;113(25):2906–13.
47. Danish Health and Medicines Authority. New information about cardiovascular adverse reactions from the use of NSAID. Danish Medicines Agency. 20 November 2008. Available at: http://sundhedsstyrelsen.dk/en/news/2008/new-information-about-cardiovascular-adverse-reactions-from-the-use-of-nsaid. Accessed on 1 December 2013.
48. Gislason GH, Fosbøl EL, Grande P, et al. Danish Society of Cardiology. Recommendations on NSAID use in patients with cardiovascular disease. 2009. Available at: http://www.cardio.dk/rapporter/holdningspapir-menu. Accessed on March 23, 2014.
49. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak 2007;7:16.
50. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club 1995;123(3):A12–3.
51. Kang H-J, Oh I-Y, Chung J-W, et al. Effects of celecoxib on restenosis after coronary intervention and evolution of atherosclerosis (Mini-COREA) trial: celecoxib, a double-edged sword for patients with angina. Eur Heart J 2012;33(21):2653–61.
52. Engoren M, Hadaway J, Schwann TA, Habib RH. Ketorolac improves graft patency after coronary artery bypass grafting: a propensity-matched analysis. Ann Thorac Surg 2011;92(2):603–9.
53. Chung J-W, Yang H-M, Park KW, et al. Long-term outcome of adjunctive celecoxib treatment after paclitaxel-eluting stent implantation for the complex coronary lesions: two-year clinical follow-up of COREA-TAXUS trial. Circ Cardiovasc Interv 2010;3(3):243–8.
54. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes 2009;2(3):155–63.
55. Koo B-K, Kim Y-S, Park KW, et al. Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study. Lancet 2007;370(9587):567–74.
56. Bergendal A, Adami J, Bahmanyar S, et al. Non-steroidal anti-inflammatory drugs and venous thromboembolism in women. Pharmacoepidemiol Drug Saf 2013;22(6):658–66.
57. Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. BJOG 2008;116(1):91–7.
58. Lacut K, van der Maaten J, Le Gal G, Cornily G, Mottier D, Oger E. Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study. Haematologica 2008;93(7):1117–8.
59. Nagai N, Hoylaerts MF, Gallacher DJ, Lu HR, Lijnen HR. Prothrombotic effect of Rofecoxib in a murine venous thrombosis model. Thromb Res 2008;122(5):668–73.
60. Huerta C, Johansson S, Wallander M-A, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 2007;167(9):935–43.
61. Westgate EJ, FitzGerald GA. Pulmonary embolism in a woman taking oral contraceptives and valdecoxib. PLoS Med 2005;2(7):e197.
62. Chan ALF. Celecoxib-induced deep-vein thrombosis. Ann Pharmacother 2005;39(6):1138.
63. Layton D, Heeley E, Hughes K, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. Rheumatology (Oxford) 2003;42(11):1342–53.
64. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med 2002;162(10):1182–9.
65. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. N Engl J Med 2006;354(11):1193.
66. Crofford LJ, Crofford LJ, Oates JC, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors. A report of four cases. Arthritis Rheum 2000;43(8):1891–6.
67. Krijthe BP, Heeringa J, Hofman A, Franco OH, Stricker BH. Non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation: a population-based follow-up study. BMJ Open 2014;4:e004059.
68. Chao T-F, Liu C-J, Chen S-J, et al. The association between the use of non-steroidal anti-inflammatory drugs and atrial fibrillation: A nationwide case-control study. Int J Cardiol 2013;168(1):312–6.
69. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of rofecoxib. Eur Heart J 2012;33(15):1928–33.
70. De Caterina R, Ruigómez A, Rodríguez LAG. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. Arch Intern Med 2010;170(16):1450–5.
71. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006;296(13):1619–32.
72. Rist PM, Glymour MM, Orav EJ, et al. Non-steroidal anti-inflammatory drug use and functional outcome from ischemic cerebral events among women. Eur J Intern Med 2014;25(3):255–8.
73. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370(9591):937–48.
74. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. N Engl J Med 2007;356(10):998–1008.

75. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344–51.
76. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125(23):2873–91.
77. Palmerini T, Biondi-Zoccai G, Riva DD, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379(9824):1393–402.
78. Kushner FG, Hand M, Smith SC, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120(22):2271–306.
79. Fosbøl EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: A nationwide cohort study. Clin Pharmacol Ther 2008;85(2):190–7.
80. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352(11):1081–91.
81. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379(9828):1835–46.
82. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158(6):585–93.
83. Søgaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sørensen HT. 30-Year Mortality following Venous Thromboembolism: a Population-based Cohort Study. Circulation. 2014. [Epub ahead of print].
84. Kahn SR. The Post-Thrombotic Syndrome. Hematology 2011;2010(1):216–20.
85. Piazza G, Goldhaber SZ. Chronic Thromboembolic Pulmonary Hypertension. N Engl J Med 2011;364(4):351–60.
86. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med 2010;170(19):1710–6.
87. Prandoni P. Venous and arterial thrombosis: Two aspects of the same disease? Clin Epidemiol 2009;1:1–6.
88. Prandoni P. Venous and arterial thrombosis: two aspects of the same disease? Eur J Intern Med 2009;20(6):660–1.
89. Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. Lancet 2007;370(9601):1773–9.
90. Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. J Clin Pathol 1974;27(7):517–28.
91. Sevitt S. Pathology and pathogenesis of deep vein thrombi. Proceedings of the Royal Society of Medicine 1975;68(4):261.
92. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366(21):1959–67.
93. Schmidt M, Cannegieter SC, Johannesdottir SA, Dekkers OM, Horvath-Puho E, Sørensen HT. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study. J Thromb Haemost. 2014. [Epub ahead of print].
94. Bishop-Bailey D, Pepper JR, Larkin SW, Mitchell JA. Differential induction of cyclooxygenase-2 in human arterial and venous smooth muscle: role of endogenous prostanoids. Arterioscler Thromb Vasc Biol 1998;18(10):1655–61.
95. Rabausch K, Bretschneider E, Sarbia M, et al. Regulation of thrombomodulin expression in human vascular smooth muscle cells by COX-2-derived prostaglandins. Circ Res 2005;96(1):e1–6.
96. Wilke T, Groth A, Mueller S, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace 2013;15(4):486–93.
97. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271(11):840–4.
98. Chamberlain AM, Agarwal SK, Folsom AR, et al. A Clinical Risk Score for Atrial Fibrillation in a Biracial Prospective Cohort (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 2011;107(1):85–91.
99. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, Mckenna WJ. Atrial fibrillation in hypertrophie cardiomyopathy: A longitudinal study. J Am Coll Cardiol 1990;15(6):1279–85.
100. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001;135(12):1061–73.
101. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108(24):3006–10.
102. Ahlehoff O, Gislason GH, Jørgensen CH, et al. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. Eur Heart J 2012;33(16):2054–64.
103. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or Flutter: a population-based study. Arch Intern Med 2004;164(15):1675–8.
104. Gami AS, Hodge DO, Herges RM, et al. Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation. J Am Coll Cardiol 2007;49(5):565–71.
105. Schmidt M, Bøtker HE, Pedersen L, Sørensen HT. Adult height and risk of ischemic heart disease, atrial fibrillation, stroke, venous thromboembolism, and premature death: a population based 36-year follow-up study. Eur J Epidemiol 2014;29(2):111–8.
106. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36(4):1303–9.
107. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107(23):2920–5.
108. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983–8.

109. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
110. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98(10):946–52.
111. van der Hooft CS, Heeringa J, van Herpen G, Kors JA, Kingma JH, Stricker BHC. Drug-induced atrial fibrillation. J Am Coll Cardiol 2004;44(11):2117–24.
112. Miyazaki T, Pride HP, Zipes DP. Prostaglandins in the pericardial fluid modulate neural regulation of cardiac electrophysiological properties. Circ Res 1990;66(1):163–75.
113. Miyazaki T, Zipes DP. Pericardial prostaglandin biosynthesis prevents the increased incidence of reperfusion-induced ventricular fibrillation produced by efferent sympathetic stimulation in dogs. Circulation 1990;82(3):1008–19.
114. Coker SJ, Parratt JR. The effects of prostaglandins E2, F2 alpha, prostacyclin, flurbiprofen and aspirin on arrhythmias resulting from coronary artery ligation in anaesthetized rats. Br J Pharmacol 1981;74(1):155–9.
115. Coker SJ, Parratt JR, Ledingham IM, Zeitlin IJ. Thromboxane and prostacyclin release from ischaemic myocardium in relation to arrhythmias. Nature 1981;291(5813):323–4.
116. Wang D, Patel VV, Ricciotti E, et al. Cardiomyocyte cyclooxygenase-2 influences cardiac rhythm and function. Proc Natl Acad Sci USA 2009;106(18):7548–52.
117. Frolov RV, Berim IG, Singh S. Inhibition of delayed rectifier potassium channels and induction of arrhythmia: a novel effect of celecoxib and the mechanism underlying it. J Biol Chem 2008;283(3):1518–24.
118. Whelton A. Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2-specific inhibitors. Am J Med 2001;110 Suppl 3A:33S–42S.
119. van den Hondel KE, Eijgelsheim M, Ruiter R, Witteman JCM, Hofman A, Stricker BHC. Effect of short-term NSAID use on echocardiographic parameters in elderly people: a population-based cohort study. Heart 2011;97(7):540–3.
120. Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure-five more years. N Engl J Med 2004;351(23):2437–40.
121. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol 2006;13(6):581–98.
122. Demant MN, Andersson C, Ahlehoff O, et al. Temporal trends in stroke admissions in Denmark 1997--2009. BMC Neurology 2013;13(1):156.
123. Palnum KD, Petersen P, Sørensen HT, et al. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. Age and ageing 2007;37(1):90–5.
124. Schmidt M, Jacobsen JB, Johnsen SP, Bøtker HE, Sørensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. Neurology 2014;82(4):340–50.
125. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf 2011;20(12):1225–36.
126. McCullough L, Wu L, Haughey N, et al. Neuroprotective function of the PGE2 EP2 receptor in cerebral ischemia. J Neurosci 2004;24(1):257–68.
127. Kim EJ, Raval AP, Hirsch N, Perez-Pinzon MA. Ischemic Preconditioning Mediates Cyclooxygenase-2 Expression Via Nuclear Factor-Kappa B Activation in Mixed Cortical Neuronal Cultures. Transl Stroke Res 2010;1(1):40–7.
128. Kim E, Raval AP, Defazio RA, Perez-Pinzon MA. Ischemic preconditioning via epsilon protein kinase C activation requires cyclooxygenase-2 activation in vitro. Neuroscience 2007;145(3):931–41.
129. Horiguchi T, Snipes JA, Kis B, Shimizu K, Busija DW. Cyclooxygenase-2 mediates the development of cortical spreading depression-induced tolerance to transient focal cerebral ischemia in rats. Neuroscience 2006;140(2):723–30.
130. Park H-K, Lee S-H, Chu K, Roh J-K. Effects of celecoxib on volumes of hematoma and edema in patients with primary intracerebral hemorrhage. J Neurol Sci 2009;279(1-2):43–6.
131. Ahmad M, Zhang Y, Liu H, Rose ME, Graham SH. Prolonged opportunity for neuroprotection in experimental stroke with selective blockade of cyclooxygenase-2 activity. Brain Res 2009;1279:168–73.
132. Ayer R, Jadhav V, Sugawara T, Zhang JH. The neuroprotective effects of cyclooxygenase-2 inhibition in a mouse model of aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl 2011;111:145–9.
133. Ministry of Interior and Health. Health Care in Denmark. 2008. Available at: http://www.sum.dk/Aktuelt/Publikationer/~/media/Filer%20-%20Publikationer_i_pdf/2008/UK_Healthcare_in_dk/pdf.ashx. Accessed on 1 December 2013.
134. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29(8):541-9
135. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273–9.
136. Schmidt M, Maeng M, Jakobsen C-J, et al. Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. Clin Epidemiol 2010;2:137–44.
137. Kildemoes HW, Sørensen H, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7 Suppl):38–41.
138. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 2012;4:303–13.
139. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 Suppl):30–3.
140. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39(7 Suppl):26–9.
141. Olsen J, Basso O, Sørensen HT. What is a population-based registry? Scand J Public Health 1999;27(1):78–8.
142. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC Classification Index with DDDs. World Health Organization Collaborating Centre for Drug Statistics Methodology, Oslo, 2013. Available at: http://www.whocc.no/atc_ddd_index/. Accessed on 1 December 2013.
143. Schmidt M, Johansen MB, Lash TL, Christiansen CF, Christensen S, Sørensen HT. Antiplatelet drugs and risk of subarach-

noid hemorrhage: a population-based case-control study. J Thromb Haemost 2010;8(7):1468–74.
144. Maeng M, Jensen L, Rasmussen K, et al. Target lesion revascularisation in patients treated with a sirolimus-eluting or paclitaxel-eluting stent. Heart 2007;93(6):694–7.
145. Rothman KJ, Greenland S, Lash TL. Types of epidemiological studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
146. Thorvaldsen P, Davidsen M, Brønnum-Hansen H, Schroll M. Stable Stroke Occurrence Despite Incidence Reduction in an Aging Population: Stroke Trends in the Danish Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Population. Stroke 1999;30(12):2529–34.
147. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology 2007;28(3):150–4.
148. Greenland S, Rothman KJ, Lash TL. Measures of effect and measures of association. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
149. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50(5):463–70.
150. Rothman KJ, Greenland S, Lash TL. Case–control studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
151. Danish Pharmaceutical Information. Drugs and package sizes on the Danish drug market. Available for search from http://pro.medicin.dk. Accessed December 1, 2013.
152. Danish Health and Medicines Authority. OTC medicines in Denmark. Available at: http://sundhedsstyrelsen.dk/en/medicines/sale/over-the-counter-medicines. Accessed on 1 December 2013.
153. Danish Health and Medicines Authority. Age limit of 18 years introduced for buying painkillers. 7 March 2011. Available at: http://laegemiddelstyrelsen.dk/en/service-menu/news/age-limit-of-18-years-introduced-for-buy--ainkillers. Accessed on 1 December 2013.
154. Danish Health and Medicines Authority. Painkillers to be prescription only in Denmark from 30 September 2013. Available at: http://sundhedsstyrelsen.dk/en/news/2013/painkillers-to-be-prescription-only-in-denmark-from-30-september-2013. Accessed on 1 December 2013.
155. Thomsen RW, Riis A, Christensen S, McLaughlin JK, Sørensen HT. Outcome of peptic ulcer bleeding among users of traditional non-steroidal anti-inflammatory drugs and selective cyclo-oxygenase-2 inhibitors. Aliment Pharmacol Ther 2006;24(10):1431–8.
156. Personal correspondence. Professor Henrik Toft Sørensen, Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark. 2014.
157. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158(9):915–20.
158. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med 1980;68(2):255–8.
159. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
160. Greenland S, Rothman KJ. Fundamentals of epidemiologic data analysis. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
161. Hosmer DW Jr, Lemeshow S, Sturdivant RX. Applied logistic regression. 3rd ed. John Wiley & Sons; 2013.
162. Rothman KJ, Greenland S, Lash TL. Precision and statistics in epidemiologic studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
163. Brookhart MA, Wyss R, Layton JB, Til S. Propensity score methods for confounding control in nonexperimental research. Circ Cardiovasc Qual Outcomes 2013;6(5):604–11.
164. Rothman KJ, Greenland S, Lash TL. Design strategies to improve study accuracy. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
165. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70(1):41–55.
166. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Til S. Variable selection for propensity score models. Am J Epidemiol 2006;163(12):1149–56.
167. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: A systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 2007;134(5):1128–1135.e3.
168. Rothman KJ. Six Persistent Research Misconceptions. J Gen Intern Med 2014;29(7):1060–4.
169. Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. Int J Epidemiol 2012;41(5):1480–9.
170. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10(1):37–48.
171. Greenland S, Rothman KJ. Introduction to stratified analysis. Modern epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
172. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15(5):291–303.
173. Porta MS, Greenland S, Last JM. A dictionary of epidemiology. 5 ed. 2008.
174. Borgdorff P, Tangelder GJ, Paulus WJ. Cyclooxygenase-2 inhibitors enhance shear stress-induced platelet aggregation. J Am Coll Cardiol 2006;48(4):817–23.
175. Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. J Transl Med 2009;7:97.
176. Moons KGM, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009;338:b375.
177. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
178. Tomlinson G, Detsky AS. Composite End Points in Randomized Trials: There Is No Free Lunch. JAMA 2010;303(3):267–8.
179. Detsky AS. Using economic analysis to determine the resource consequences of choices made in planning clinical trials. J Chronic Dis 1985;38(9):753–65.
180. Ferreira-González I, Permanyer-Miralda G, Busse JW, et al. Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. J Clin Epidemiol 2007;60(7):651–7.

181. Sloth AD, Schmidt MR, Munk K, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. Eur Heart J 2014;35(3):168–75.
182. Personal correspondence. Professor Hans Erik Bøtker, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark. 2014.
183. Joensen AM, Jensen MK, Overvad K, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol 2009;62(2):188–94.
184. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.
185. Coloma PM, Valkhoff VE, Mazzaglia G, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open 2013;3(6).
186. Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjønneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. J Clin Epidemiol 2010;63(2):223–8.
187. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. Scand Cardiovasc J 2012;46(3):149–53.
188. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med 2004;164(18):1993–8.
189. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. Int J Epidemiol 1986;15(3):413–9.
190. Friis S, Poulsen AH, Sørensen HT, et al. Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: A Danish cohort study. Cancer Causes Control 2009;20(5):731–40.
191. Jacobs DR, Kroenke C, Crow R, et al. PREDICT: A simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. Circulation 1999;100(6):599–607.
192. Sachdev M, Sun JL, Tsiatis AA, Nelson CL, Mark DB, Jollis JG. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. J Am Coll Cardiol 2004;43(4):576–82.
193. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503–10.
194. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Beh Res 46(3):399–424.
195. European Medicines Agency. Assessment report for non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular risk. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf. Accessed on March 23, 2014.
196. Danish Pharmaceutical Information. NSAIDs: Adverse cardiovascular effects. Thesis study III cited as reference for associated atrial fibrillation risk. Available at: http://pro.medicin.dk/Laegemiddelgrupper/Grupper/213010. Accessed on June 20, 2014.
197. UpToDate. COX-2 selective inhibitors: Adverse cardiovascular effects. Thesis study III cited as reference for associated atrial fibrillation risk. Available at: http://www.uptodate.com/contents/cox-2-selective-inhibitors-adverse-cardiovascular-effects. Accessed on June 20, 2014.