FACULTY OF HEALTH SCIENCES, UNIVERSITY OF AARHUS, DENMARK

Nonselective Nonsteroidal Antiinflammatory Drugs, Selective Cyclooxygenase-2 Inhibitors and 3-Year Cardiovascular Risks after Coronary Stent Implantation

- A Population-based Cohort Study -

Research Year Report

Morten Schmidt

Department of Clinical Epidemiology, Aarhus University Hospital

Department of Cardiology, Aarhus University Hospital, Skejby

2009

Department of Clinical Epidemiology, Aarhus University Hospital

Report no. 46

SUPERVISORS

Henrik Toft Sørensen, Professor
Department of Clinical Epidemiology
Aarhus University Hospital

Torsten Toftegaard Nielsen, Professor
Department of Cardiology
Aarhus University Hospital, Skejby

Michael Mæng, Cardiologist
Department of Cardiology
Aarhus University Hospital, Skejby

Lars Pedersen, Chief Statistician
Department of Clinical Epidemiology
Aarhus University Hospital

PREFACE

In 2005 I was invited by Cardiologist Michael Mæng to join a cardiovascular research group concerning two studies on cardio-protective drugs in an experimental pig model. Michael introduced me to Professor Henrik Toft Sørensen during the planning of my research year, which resulted in a joint focus on cardiology as well as clinical epidemiology.

I would like to express my sincere gratitude to Henrik who was inspiringly engaged in my work throughout the year, and patiently taught me the art of clinical epidemiology, and who also encouraged me to do epidemiological and statistical training in Florence, Italy, as well as Boston, USA.

I would like to thank Michael for guidance through the beginnings of my research career. In spite of being abroad during the year, his help and good advice was always close at hand. I thank Lars Pedersen warmly for his great contributions to the project. Without him, time-varying variables may have defeated me at an early stage in the process. Also, thanks to Torsten Toftegaard Nielsen and Jens Flensted Lassen for their expert cardiological contributions.

I wish to give my thanks to the staff and doctoral students at the Department of Epidemiology at Boston University School of Public Health for their hospitality during my 3-month stay. A special thank you to Timothy L. Lash for his excellent supervision and teaching in "Modern Epidemiology".

Thanks to my colleagues and friends at "DCE" for the warm welcome I got to the department, and for the help I have received during the year.

Finally, my warmest thanks to my girlfriend and my family for their everlasting support.

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Classification
BMS	Bare-metal stent
CABG	Coronary artery bypass grafting
CI	Confidence interval
COX	Cyclooxygenase
Coxibs	Newer selective COX-2 inhibitors
CPR	Central personal registry
DES	Drug-eluting stent
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
MI	Myocardial infarction
NSAID	Nonsteroidal antiinflammatory drug
nsNSAID	Nonselective nonsteroidal antiinflammatory drug
OTC	Over-the-counter
PCI	Percutaneous coronary intervention
sCOX	Selective cyclooxygenase-2
STEMI	ST-segment elevation myocardial infarction
TLR	Target lesion revascularization

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ABSTRACT

Background: Few studies exist on the cardiovascular safety of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with coronary stents. We examined whether use of nonselective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors increased the risk of stent thrombosis, myocardial infarction, target lesion revascularization, and death after coronary stent implantation.

Methods: We conducted a population-based Danish cohort study using medical databases. From 2002 through 2005, we followed all stent patients for three years and computed cumulative 3-year incidence for each outcome. We used regression modeling to compute hazard ratios for each outcome as a measure of relative risk with 95% confidence intervals, controlling for potential confounding factors.

Results: A total of 13,040 stent patients were included. During the 3-year follow-up, 5,520 (42.3%) filled at least one NSAID prescription. There were 144 rehospitalizations for stent thrombosis (1.1%), 685 for myocardial infarction (5.3%), and 1107 for target lesion revascularization (8.5%). A total of 1,286 patients (9.9%) died during follow-up, of which 636 (4.9%) died of cardiac causes. Compared with non users, there was no substantial association between current or former users of nonselective NSAIDs or selective COX-2 inhibitors and stent thrombosis, myocardial infarction, or target lesion revascularization. The adjusted hazard ratio with 95% confidence interval for all-cause mortality was 1.21 (0.96 to 1.54) for current and 1.27 (1.07 to 1.50) for former users of nonselective NSAIDs, and 1.60 (1.28 to 2.00) for current and 1.36 (1.14 to 1.62) for former users of selective COX-2 inhibitors. The adjusted hazard ratio for cardiac death was not substantially increased for current and former users of nonselective NSAIDs or selective COX-2 inhibitors. For celecoxib users the adjusted hazard ratio for cardiac death was 1.80 (95% confidence interval: 0.99 to 3.29).

Conclusions: Overall use of nonselective NSAIDs and selective COX-2 inhibitors was not associated with an increased cardiovascular risk after coronary stent implantation. An exception was use of celecoxib that seemed associated with an increased risk of cardiac death.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide, widely employed for the treatment of inflammatory conditions and a range of pain syndromes. A well-known side effect of nonselective NSAIDs is upper gastrointestinal toxicity, most notably gastrointestinal bleeding and perforation, presumably by inhibiting cyclooxygenase (COX)-1 mediated production of prostaglandins.[1]

Newer selective COX-2 inhibitors (coxibs), introduced into clinical practice in 1998, were specifically developed as NSAIDs with improved gastrointestinal safety and tolerability.[1] However, randomized placebo-controlled trials have demonstrated an increased risk of adverse cardiovascular events associated with several of these drugs.[2-4] The US Food and Drug Administration has indicated that the safety of all marketed coxibs should be carefully reviewed.[5] There is also considerable uncertainty regarding the cardiovascular safety of traditional NSAIDs,[6, 7] since these drugs also display a varying degree of COX-2 selectivity.[8, 9]

Coxibs and traditional NSAIDs increase the risk of reinfarction and death in patients with acute myocardial infarction.[6] However, only one earlier study has investigated whether coronary stented patients, with or without myocardial infarction, have an increased risk of adverse cardiovascular events associated with these drugs.[10] In that study, coronary revascularization was defined as angioplasty, with or without stent implantation, or coronary artery bypass grafting, so even it was not restricted to stent patients. Follow-up did not either include the first 45 days after the qualifying hospitalization, during which period NSAID use may be particular hazardous.[3] Furthermore, the completeness of follow-up was not reported, the patterns of individual NSAID use varied substantially among the study sites, and there was no specific data on stent thrombosis, target lesion revascularization or cardiac death.

Even a modest increased risk of serious adverse events following coronary stent implantation has major public health impact if a drug is not life-saving and is widely used, as is the case with

NSAIDs. Given the limited research on this important topic, we conducted a Danish population-based cohort study within a tax supported free health care system free of referral bias and with a complete follow-up, taking comorbidity and multiple outcomes into consideration. We examined whether use of nonselective NSAIDs and selective COX-2 inhibitors increased the risk of stent thrombosis, myocardial infarction, target lesion revascularization, and death after coronary stent implantation.

METHODS

Setting

We conducted a 3-year follow-up study using medical databases from Western Denmark, which has a population of 3 million (about 55% of the total Danish population). The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals, and partial reimbursement for prescribed medication including NSAIDs. We linked various registries using the unique central personal registry (CPR) number assigned to each Danish citizen at birth and to residents at immigration.[11]

Study Population

We used the Western Denmark Heart Registry to identify all percutaneous coronary interventions (PCIs) performed between January 1, 2002 and June 30, 2005. All patients were followed for 3 years. This registry has since 1999 collected detailed patient and procedure data for all interventions carried out in Western Denmark's 3 coronary intervention centers (Skejby, Aalborg, and Odense).[12, 13] We defined the first PCI with stent implantation during the inclusion period as the index PCI. Those treated by balloon angioplasty without stent implantation were not included in the study.

Procedures and Post-interventional Antiplatelet Therapy

The participating centers were high-volume centers performing >1500 PCI procedures per year. Interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, pre or post dilatation, choice of stent, direct stenting, periprocedural glycoprotein IIb/IIIa inhibitor) left to the operator's discretion. However, the operators were not allowed to implant drug-eluting stents in all patients owing to financial restrictions placed by the health care systems. Thus, drug-eluting stents were in general used in patients with an anticipated higher risk of restenosis.[12]

The recommended post-interventional antiplatelet protocol included lifelong low-dose aspirin (75 to 150 mg once daily) and clopidogrel with a loading dose of 300 mg followed by maintenance with 75 mg daily. The recommended duration of clopidogrel treatment was 3 to 12 months until November 2002 and 12 months thereafter. In patients with stent thrombosis, all medical records from the hospital admission were reviewed to verify the use of antiplatelet therapy.[12]

Nonsteroidal Antiinflammatory Drug Use

We used the Danish Registry of Medical Product Statistics to identify prospectively all prescriptions for NSAIDs filled by the study population 60 days before index PCI discharge date and during follow-up. This registry has since 1995 retained key information on prescriptions dispensed from all pharmacies in Denmark.[14] Pharmacies are equipped with electronic accounting systems, which are primarily used to secure reimbursement from the National Health Service. For each filled prescription the patient's CPR number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date of the drug dispensed, are transferred electronically from the pharmacies to the prescription database.[14]

All types of nonaspirin NSAIDs, except low-dose ibuprofen (200 mg per tablet), were available only by prescription. Pensioners and regular users of ibuprofen are, however, typically all

registered in the databases because the cost is partly refunded when ibuprofen is prescribed by a physician.

Prescriptions were identified (see appendix for ATC codes[15]) for newer COX-2 inhibitors (celecoxib, rofecoxib, and etoricoxib) and for older COX-2 inhibitors (diclofenac, etodolac, nabumeton, and meloxicam).[8, 9] We collapsed the groups of older and newer COX-2 inhibitors into the cluster of selective COX-2 (sCOX-2) inhibitors as described by Capone et al.[8] We identified prescriptions for the following nonselective nonaspirin NSAIDs (nsNSAIDs): ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid. In primary analysis the exposures were the NSAID subclasses of nsNSAIDs and sCOX-2 inhibitors. For comparability with findings from other studies,[6, 10] preplanned analyses were furthermore conducted for the following individual NSAIDs: ibuprofen, naproxen, diclofenac, celecoxib, and rofecoxib.

Cardiovascular Outcomes

We assessed all outcomes within three years of the index PCI. All relevant records were reviewed by a specialist committee, which adjudicated each outcome. We defined and identified the outcomes as described below.

Stent thrombosis: We defined stent thrombosis using the Academic Research Consortium definition.[16] *Definite stent thrombosis*: Angiographic confirmation of stent thrombosis and at least 1 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. *Probable stent thrombosis:* Any unexplained death within the first 30 days after coronary stent implantation. *Possible stent thrombosis:* Any unexplained death occurring from 30 days after coronary stent implantation until the end of the follow-up period. To ensure high positive

predictive value of the stent thrombosis diagnoses, we included only definite stent thrombosis. Stent thrombosis was ascertained by retrieving medical records and reviewing the catheterization films.[12]

Myocardial infarction: We used the Danish National Registry of Patients to identify admissions for acute myocardial infarction (MI). This registry has since 1977 registered all non-psychiatric hospital admissions in Denmark. Each admission is registered by one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases 8th revision (ICD-8) until the end of 1993, and according to the 10th revision (ICD-10) thereafter.[17] We used ICD-10 codes I21-I21.9 to identify MI.

Target lesion revascularization: We defined target lesion revascularization (TLR) as a repeat PCI of the index lesion or coronary artery bypass grafting. TLR was ascertained from the Western Denmark Heart Registry.[12]

Death: We ascertained all-cause mortality from the Danish Civil Registration System. This registry has kept electronic records on all vital statistics — including date of birth, change of address, date of emigration, and exact date of death — for the Danish population since 1 April 1968.[18] We then reviewed original death certificates obtained from the National Registry of Causes of Deaths. This registry has since 1943 collected data on dates and causes of death in Denmark.[19] Deaths were classified according to their underlying causes, as recorded on the death certificate, as either a cardiac or noncardiac death.[12] We defined cardiac death as death due to ischemic heart disease, an arrhythmic event, heart failure, sudden cardiac death, or sudden undefined death.

Covariates

We identified risk factors for cardiovascular events following PCI potentially associated with NSAID use from the National Registry of Patients and the Registry of Medical Product Statistics. Furthermore we retrieved information from the Western Denmark Heart Registry on a wide range of potential predictors of subsequent cardiovascular disease, including PCI indication and stent type. We computed the Charlson comorbidity index score (0=Low, 1-2=medium, and 3+=High) for each study subject based on the complete hospital discharge history before index PCI.[20]

Statistical Analysis

For each outcome follow-up began on the date of index PCI and continued until the date of the outcome, death, emigration, or after 3-years follow-up, whichever came first. A given prescription was assumed to cover a maximum of 60 days (current use), after which the participant was regarded as former user, unless a new prescription was issued. We used non users of any NSAID as the reference category. The exposure window of 60 days was chosen to capture most current NSAID users; NSAID prescriptions are seldom written for more than 60 days in Denmark.[15, 21] In a sensitivity analysis, a given prescription was assumed to cover a maximum of 45 days, after which the participant was regarded as former user, unless a new prescription was issued. The results were consistent with the primary results and are not further reported.

For each outcome we computed rates according to the time-varying NSAID use (current, former, and no use) as well as cumulative 3-year incidence. We used Cox proportional-hazards regression to compute hazard ratios (HRs), as a measure of the relative risk, for each outcome, along with 95% confidence intervals (CIs). In regression analyses, we adjusted for age, gender, PCI indication, stent type, hypertension, diabetes mellitus, cancer, and Charlson comorbidity index score (without scoring for diabetes and cancer). Furthermore, we adjusted for time-varying drug use of statin, clopidogrel, and aspirin. The cohort and methods are well established.[12, 21]

RESULTS

A description of the characteristics of the study population and its distribution according to prescription use and individual NSAID types is shown in tables 1 and 2. The cohort included 13,040 stent patients with a median age of 64 years, of whom 71% were male. During the 3-year follow-up, a total of 5,520 (42.3%) patients claimed at least one NSAID prescription. The indication for PCI was for 29.1% ST-segment elevation MI (STEMI), 30.7% non-STEMI or unstable angina, and 37.5% stable angina. Coxib users were older, more likely to be female, and had a higher prevalence of medium or high comorbidity compared with non users.

During the 3-year follow-up there were 144 rehospitalizations for stent thrombosis (crude risk=1.1%), 685 for MI (crude risk=5.3%), and 1107 for TLR (crude risk=8.5%). A total of 1286 patients (crude risk=9.9%) died during follow-up, of which 636 died of cardiac causes (crude risk=4.9%, 49.5% of deaths). Compared with non users, there was no substantial association between current and former users of nsNSAIDs or sCOX-2 inhibitors and stent thrombosis, MI, or TLR (table 3). The adjusted HR with 95% CI for all-cause mortality was 1.21 (0.96 to 1.54) for current and 1.27 (1.07 to 1.50) for former users of nsNSAIDs, and 1.60 (1.28 to 2.00) for current and 1.36 (1.14 to 1.62) for former users of sCOX-2 inhibitors. The adjusted HR for cardiac death was not substantially increased for current and former users of nsNSAIDs or sCOX-2 inhibitors.

The adjusted HRs for individual NSAIDs are shown in table 4. There was no association between use of ibuprofen, diclofenac, celecoxib, or rofecoxib and stent thrombosis, MI, or TLR. There was a tendency for increased all-cause mortality for all individual NSAIDs. However, the adjusted HR for cardiac death was only found increased among users of naproxen (3.44; 95% CI: 1.28 to 9.21) and celecoxib (1.80; 95% CI: 0.99 to 3.29). Use of naproxen was furthermore associated with an increased HR of TLR (2.56; (95% CI: 1.15 to 5.72)).

DISCUSSION

Our study extends earlier research on the cardiovascular safety of NSAIDs in patients with coronary heart disease. Gislason et al[6] reported an increased risk of reinfarction and all-cause mortality for any use of ibuprofen, diclofenac, celecoxib, and rofecoxib in a cohort of 58,432 Danish patients with first-time AMI. Naproxen was not studied separately in this study. In a cohort of 48,566 patients from United Kingdom, United States, and Canada with AMI, unstable angina or PCI/ coronary artery bypass grafting, Ray et al[10] reported that naproxen had better cardiovascular safety than ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib. In a cohort subgroup of patients with coronary revascularization, only rofecoxib showed an increased risk of the combined outcome of MI and out-of-hospital death from coronary heart disease. The present study included 13,040 patients with stable angina, unstable angina, or MI, all of whom were stented. This study is the first to examine the cardiovascular risks in a complete stent population taking multiple outcomes into consideration.

Our results are consistent with Gislason et al[6] in regard to all-cause mortality, although our relative risks are somewhat nearer the null. While Gislason et al's[6] results suggest that the excess mortality may derive from cardiac deaths, our results suggest it derives more from non-cardiac deaths. This difference may be due to differences in the study populations. In contrast to Gislason et al's[6] population of MI patients, more than one third of our stent patients had stable angina rather than MI, and this fraction may make our study cohort on average less susceptible to the cardiovascular risks of NSAIDs.

Metaanalysis of both clinical trials[7] and observational studies[22, 23] in low risk populations suggest that naproxen does not increase the risk of adverse cardiovascular events. Moreover, Ray et al[10] concluded that naproxen is safer than ibuprofen, diclofenac, and higher doses of celecoxib and rofecoxib to use in patients with serious coronary heart disease. Our results suggest, however, that naproxen increases the cardiovascular risks in stent patients. In presumed aspirin-covered stent

patients, an increased cardiovascular risk of naproxen could be due to pharmacodynamic interactions. Both naproxen and ibuprofen interfere with the irreversible inhibitory effect of aspirin.[24] Thus, naproxen in combination with aspirin may undermine the sustained inhibition of platelet COX-1 necessary for cardio protection from aspirin.[24] The precision of our risk estimates for naproxen was low, however, because we observed only 199 current users of naproxen. Caution should therefore be taken before drawing conclusions that differ from those summarized above.

The low incidence of stent thrombosis made interpretation of the risk estimates difficult, but apparently use of nsNSAIDs and sCOX-2 inhibitors did not increase the risk of stent thrombosis.

The mechanisms underlying our overall near-null findings are not clear considering the previously reported cardiovascular risks of particularly sCOX-2 inhibitors.[2-4, 6] It may be that the irreversible COX-1 inhibition of aspirin was likely to have a protective role on the associated excess cardiovascular risk of sCOX-2 inhibitors when balancing the COX inhibition. However, the theory of balanced versus unbalanced COX inhibition is debatable because nsNSAIDs also have been associated with an increased cardiovascular risk.[6, 7] The relative COX-2 selectivity in vitro for celecoxib (30) (measured as the COX-1/COX-2 IC_{50} ratio, where IC_{50} is the concentration of the drug required to inhibit COX activity by 50%), equals that of diclofenac (29), but is only one tenth of that of rofecoxib (272).[8] Thus, COX-2 selectivity does not explain why celecoxib, more than other sCOX-2 inhibitors, seemed to be associated with an increased cardiovascular risk.

The main strengths of this study are its large size and the tax supported uniformly organized healthcare system allowing a population-based design with complete follow-up. This design considerably reduced the likelihood that our findings were due to selection bias.

A number of issues should be considered when interpreting our results. We had to rely on redeemed prescriptions as a proxy for actual drug use, which may not always be entirely correct. However, the fact that the drug exposure information was based on actual dispensing at pharmacies and the co-payment requirements suggests high adherence with the prescription for the dispensed

medications. Nonetheless, some misclassification because of nonadherence was possible, which would attenuate the estimates of association.

We lacked information on over-the-counter use of low-dose ibuprofen, which accounts for only 13% of total NSAID sales in Denmark.[21] Over-the-counter use was, however, likely to be less common among subjects with prescription use, so any bias would lead to underestimation of the risk estimates.

Using the registries to ascertain the study outcomes has previously been validated,[12] and the National Registry of Patients as well as the Registry of Medical Product Statistics has shown to be accurate.[14, 25, 26] Information on drug use, hospitalizations, and confounding factors were collected independently from medical databases thus avoiding reliance upon self-reporting and thereby reducing information bias.

Although we controlled for important predictors of cardiovascular events, it is possible that uncontrolled confounding influenced our results. We lacked information on tobacco and alcohol use, which increase the risk of the outcomes and are likely to be more prevalent among NSAID users than non users. This pattern of unadjusted associations would bias our results away from the null.[27] Although we controlled for comorbidity using Charlson comorbidity index, residual confounding by comorbidity increased the noncardiac mortality, as reflected in the increased all-cause mortality. The increased HRs for former users of nsNSAIDs and sCOX-2 inhibitors also suggested that it was not the current use of the drugs that increased the all-cause mortality, but rather the high degree of comorbidity among NSAID users.

CONCLUSIONS

Overall use of nonselective NSAIDs and selective COX-2 inhibitors was not associated with an increased cardiovascular risk in patients receiving coronary stent implantation. An exception was use of celecoxib that seemed associated with an increased risk of cardiac death. The data were inconclusive for naproxen.

FUNDING

My work was made possible through financial support from:

- Danish Medical Research Council, Danish Agency of Science, Technology and Innovation (Forskningsrådet for Sundhed og Sygdom, Forskningsstyrelsen)
- Helga and Peter Korning Fund (Helga og Peter Kornings Fond)
- Mrs Gudrun Elboth born Døbelinds Memorial (Fru Gudrun Elboth født Døbelinds mindelegat),
- Family Hede Nielsens Fund (Familien Hede Nielsens fond)
- Institute of Experimental Clinical Research (Klinisk Institut), Aarhus University Hospital, Skejby.

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TABLE 1

Characteristics of the study population and distribution according to prescription use of nonselective NSAIDs and selective COX-2 inhibitors

	Non Users*	Total Users	Nonselective NSAIDs			Selective COX-2 inhibitors		
			Number of prescriptions			Number of prescriptions		
			<5	5-9	>10	<5	5-9	>10
No. of patients	7520	5520	2929	602	414	2078	350	285
Male, %	73.3	71.1	72.6	69.6	63.8	69.5	68.9	62.8
Age < 65, %	50.2	54.0	56.7	49.3	51.9	52.6	48.6	53.7
PCI indication, %								
STEMI	32.0	25.2	25.6	20.3	18.8	25.6	28.3	23.9
Stable angina	34.6	41.5	41.4	47.2	44.0	41.9	38.3	42.8
Non-STEMI or unstable angina	30.3	31.2	30.8	30.7	35.0	30.6	32.9	31.9
Other	3.1	2.1	2.2	1.8	2.2	2.0	0.6	1.4
Year of entry, %								
2002	23.1	25.4	25.6	22.3	19.8	25.9	30.6	34.7
2003	28.3	29.1	28.2	31.4	29.2	30.4	28.3	29.1
2004	30.7	30.4	30.5	32.4	31.9	29.5	29.1	27.4
2005	17.9	15.1	15.6	14.0	19.1	14.2	12.0	8.8
Stent type, %								
BMS	67.3	68.6	67.1	68.1	66.9	69.8	73.4	76.8
DES	27.9	26.3	28.0	26.4	27.8	25.6	20.6	17.5
DES+BMS	4.6	4.8	4.6	5.1	4.8	4.1	5.7	4.9
Diabetes, %	9.7	10.4	9.7	10.1	11.4	10.0	13.7	17.5
Hypertension, %	2.8	3.3	3.0	3.5	3.6	3.8	2.9	4.6
Cancer, %	7.0	6.6	6.6	6.6	5.8	7.3	7.4	6.7
Comorbidity†, %								
Low (0)	67.5	65.1	67.2	67.1	61.1	62.8	60.0	57.9
Medium (1-2)	27.3	30.8	28.9	29.9	35.0	32.6	34.3	36.5
High (3+)	5.2	4.1	3.9	3.0	3.9	4.5	5.7	5.6
Drug use, %								
Statin	89.1	95.1	95.8	96.0	95.2	94.5	91.4	94.7
Aspirin	93.1	97.8	98.0	97.7	98.3	97.4	97.1	98.9
Plavix	93.1	98.7	98.7	98.7	99.0	98.8	99.1	98.6

* Non users of both nonselective NSAIDs and selective COX-2 inhibitors
† Categories of Charlson comorbidity index score

TABLE 2

Characteristics of the study population and distribution according to individual NSAID use

	Non Users*	Total Users	Nonselective NSAIDs			Selective COX-2 inhibitors			
			Ibuprofen	Naproxen	Other†	Diclofenac	Celecoxib	Rofecoxib	Other‡
No. of patients	7520	5520	3014	199	1491	1861	476	298	815
Male, %	73.3	71.1	73.7	71.9	64.9	73.2	57.6	56.4	61.7
Age < 65, %	50.2	54.0	59.6	52.8	44.4	55.5	42.9	43.0	48.6
PCI indication, %									
STEMI	32.0	25.2	25.5	23.6	22.3	26.9	24.6	24.2	28.5
Stable angina	34.6	41.5	31.3	34.2	44.9	30.5	33.6	38.6	39.8
Non-STEMI or Unstable angina	30.3	31.2	40.8	41.7	30.7	40.9	39.9	35.9	30.1
Other	3.1	2.1	2.3	0.5	2.1	1.7	1.9	1.3	1.7
Year of entry, %									
2002	23.1	25.4	24.2	27.1	22.7	21.0	47.1	53.7	27.5
2003	28.3	29.1	28.6	25.1	28.6	28.7	33.6	32.6	28.1
2004	30.7	30.4	31.0	32.2	31.9	33.7	18.1	13.8	30.3
2005	17.9	15.1	16.3	15.6	16.8	16.6	1.3	0	14.1
Stent type, %									
BMS	67.3	68.6	66.8	67.3	67.7	67.2	83.8	89.3	72.0
DES	27.9	26.3	28.3	27.1	27.2	27.9	13.4	8.4	23.1
DES+BMS	4.6	4.8	4.6	5.0	4.8	4.7	2.3	2.0	4.4
Diabetes, %	9.7	10.4	9.9	8.0	9.5	10.8	14.3	11.7	10.8
Hypertension, %	2.8	3.3	3.0	4.5	3.0	3.7	4.6	4.0	2.9
Cancer, %	7.0	6.6	5.8	5.0	7.7	6.6	7.4	6.4	8.0
Comorbidity§, %									
Low (0)	67.5	65.1	67.2	69.3	64.1	63.7	52.7	53.4	62.2
Medium (1-2)	27.3	30.8	28.8	27.6	32.4	32.2	38.9	39.6	32.3
High (3+)	5.2	4.1	4.0	3.0	3.5	4.1	8.4	7.0	5.5
Drug use, %									
Statins	89.1	95.1	95.6	93.5	95.7	94.9	89.5	81.5	93.1
Aspirin	93.1	97.8	97.6	97.0	97.7	97.9	96.4	95.3	96.9
Plavix	93.1	98.7	98.4	97.5	98.7	98.1	97.3	96.3	98.0

*Non users of both nonselective NSAIDs and selective COX-2 inhibitors
†Ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid.
‡Etoricoxib, etodolac, nabumeton, and meloxicam.
§Categories of Charlson comorbidity index score

TABLE 3

Hazard ratios for adverse outcomes associated with use of nonselective NSAIDs and selective COX-2 inhibitors estimated by Cox proportional hazards regression

	Nonselective NSAIDs				Selective COX-2 inhibitors			
	No. of events	**Rate per 1000 PY**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***	**No. of events**	**Rate per 1000 PY**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***
Stent thrombosis								
Non users	128	4.53	1	1	126	4.17	1	1
Former users	7	1.28	0.66 (0.30-1.48)	0.67 (0.30-1.49)	12	2.84	1.74 (0.91-3.30)	1.82 (0.96-3.46)
Current users	9	4.23	1.06 (0.52-2.17)	1.10 (0.54-2.25)	6	4.34	0.87 (0.35-2.12)	0.91 (0.37-2.23)
Myocardial infarction								
Non users	553	19.96	1	1	582	19.64	1	1
Former users	91	17.08	1.05 (0.84-1.32)	1.08 (0.86-1.36)	81	19.69	1.20 (0.95-1.53)	1.16 (0.92-1.48)
Current users	41	19.68	1.11 (0.81-1.52)	1.17 (0.85-1.61)	22	16.16	0.89 (0.59-1.35)	0.85 (0.56-1.29)
Target lesion revascularization								
Non users	956	35.84	1	1	985	34.45	1	1
Former users	98	19.19	1.06 (0.86-1.31)	1.08 (0.87-1.34)	79	20.35	1.11 (0.88-1.40)	1.09 (0.86-1.38)
Current users	53	26.58	0.93 (0.70-1.23)	0.96 (0.73-1.27)	43	32.90	0.96 (0.71-1.31)	0.93 (0.68-1.27)
Cardiac death								
Non users	549	19.29	1	1	547	17.94	1	1
Former users	51	9.21	1.00 (0.74-1.35)	1.14 (0.84-1.54)	51	11.96	1.39 (1.03-1.88)	1.27 (0.94-1.72)
Current users	36	16.79	0.97 (0.68-1.40)	1.07 (0.74-1.54)	38	27.35	1.52 (1.09-2.14)	1.33 (0.94-1.86)
All-cause death								
Non users	1038	36.47	1	1	1043	34.20	1	1
Former users	169	30.51	1.14 (0.96-1.35)	1.27 (1.07-1.50)	159	37.30	1.49 (1.25-1.77)	1.36 (1.14-1.62)
Current users	79	36.85	1.09 (0.86-1.38)	1.21 (0.96-1.54)	84	60.46	1.79 (1.43-2.24)	1.60 (1.28-2.00)

*****Adjusted for age, gender, PCI indication, stent type, hypertension, diabetes mellitus, cancer, Charlson comorbidity index score, time-varying use of statins, clopidogrel, and aspirin.

TABLE 4

Adjusted hazard ratios for adverse outcomes associated with use of individual NSAIDs estimated by Cox proportional hazards regression

	No. of users	Adjusted* hazard ratio (95% confidence interval)				
		Stent thrombosis	Myocardial infarction	Target lesion revascularization	Cardiac death	All-cause death
Nonselective NSAIDs						
Ibuprofen	3014	0.81 (0.30-2.18)	1.21 (0.81-1.80)	0.94 (0.66-1.34)	1.04 (0.65-1.66)	1.45 (1.10-1.92)
Naproxen	199	-	1.43 (0.36-5.72)	2.56 (1.15-5.72)	3.44 (1.28-9.21)	2.03 (0.84-4.88)
Other†	1491	2.32 (0.94-5.71)	1.12 (0.68-1.85)	0.85 (0.52-1.39)	0.85 (0.45-1.59)	0.75 (0.49-1.16)
Selective COX-2 inhibitors						
Diclofenac	1861	0.91 (0.29-2.88)	0.89 (0.50-1.58)	0.92 (0.59-1.44)	1.35 (0.82-2.22)	1.80 (1.32-2.45)
Celecoxib	476	-	0.91 (0.34-2.43)	0.81 (0.39-1.72)	1.80 (0.99-3.29)	2.14 (1.40-3.28)
Rofecoxib	298	1.57 (0.22-11.34)	0.67 (0.17-2.68)	1.61 (0.83-3.11)	1.15 (0.51-2.59)	1.62 (0.95-2.76)
Other‡	815	0.85 (0.12-6.08)	0.85 (0.38-1.90)	0.69 (0.33-1.45)	0.83 (0.35-2.01)	0.58 (0.29-1.17)

*Adjusted for age, gender, PCI indication, stent type, hypertension, diabetes mellitus, cancer, Charlson comorbidity index score, time-varying use of statins, clopidogrel, and aspirin.
†Ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid.
‡Etoricoxib, etodolac, nabumeton, and meloxicam.

APPENDIX: ICD and ATC Codes

NSAIDs

Selective COX-2 inhibitors (sCOX-2 inhibitors)

Newer COX-2 inhibitors (coxibs):

- Celecoxib (ATC code): M01AH01
- Rofecoxib (ATC code): M01AH02
- Etoricoxib (ATC code): M01AH05

Older COX-2 inhibitors:

- Diclofenac (ATC codes): M01AB05, M01AB55
- Etodolac (ATC code): M01AB08
- Nabumeton (ATC code): M01AX01
- Meloxicam (ATC code): M01AC06

Nonselective nonaspirin NSAIDs (nsNSAIDs)

- Ibuprofen (ATC codes): M01AE01, M01AE51
- Naproxen (ATC code): M01AE02
- Ketoprofen (ATC codes): M01AE03, M01AE53
- Dexibuprofen (ATC code): M01AE14
- Piroxicam (ATC code): M01AC01
- Tolfenamic acid (ATC code): M01AG02
- Other nsNSAIDs : all other M01AA-G codes

Covariates

- Low-dose aspirin (ATC code): B01AC06
- Clopidogrel (ATC code): B01AC04
- Statins (ATC codes): C10AA, B04AB0
- PCI indication: From Western Denmark Heart Registry
- Stent types: From Western Denmark Heart Registry
- Hypertension: ICD8: 40199, ICD10: DI10-DI15
- Diabetes: ICD8: 249-250, ICD10 E10-E14, O24, H36.0, ATC: A10B, A10A
- Cancer (see codes in Charlson comorbidity index)
- Charlson Comorbidity Index:

Charlson comorbidity category		ICD-8	ICD-10	Charlson Score
1	Myocardial infarction	410	I21;I22;I23	1
2	Congestive heart failure	427.09;427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430-438	I60-I69; G45; G46	1
5	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
10	Diabetes type1 Diabetes type2	249.00;249.06; 249.07; 249.09 250.00;250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9	1
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580-583;584;590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes with end organ damage	249.01-249.05; 249.08 250.01-250.05; 250.08	E10.2-E10.8 E11.2-E11.8	2
14	Any tumor	140-194	C00-C75	2
15	Leukemia	204-207	C91-C95	2
16	Lymphoma	200-203;275.59	C81-C85; C88; C90; C96	2
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumor	195-198; 199	C76-C80	6
19	AIDS	079.83	B21-B24	6

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