Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction

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IMPORTANCE Antithrombotic treatment is indicated for use in patients after myocardial infarction (MI); however, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) could pose safety concerns.

OBJECTIVE To examine the risk of bleeding and cardiovascular events among patients with prior MI taking antithrombotic drugs and for whom NSAID therapy was then prescribed.

DESIGN, SETTING, AND PARTICIPANTS Using nationwide administrative registries in Denmark (2002-2011), we studied patients 30 years or older admitted with first-time MI and alive 30 days after discharge. Subsequent treatment with aspirin, clopidogrel, or oral anticoagulants and their combinations, as well as ongoing concomitant NSAID use, was determined.

EXPOSURES Use of NSAIDs with ongoing antithrombotic treatment after first-time MI.

MAIN OUTCOMES AND MEASURES Risk of bleeding (requiring hospitalization) or a composite cardiovascular outcome (cardiovascular death, nonfatal recurrent MI, and stroke) according to ongoing NSAID and antithrombotic therapy, calculated using adjusted time-dependent Cox regression models.

RESULTS We included 61,971 patients (mean age, 67.7 [SD, 13.6] years; 63% men); of these, 34% filled at least 1 NSAID prescription. The number of deaths during a median follow-up of 3.5 years was 18,105 (29.2%). A total of 5,288 bleeding events (8.5%) and 18,568 cardiovascular events (30.0%) occurred. The crude incidence rates of bleeding (events per 100 person-years) were 4.2 (95% CI, 3.8-4.6) with concomitant NSAID treatment and 2.2 (95% CI, 2.1-2.3) without NSAID treatment, whereas the rates of cardiovascular events were 11.2 (95% CI, 10.5-11.9) and 8.3 (95% CI, 8.2-8.4). The multivariate-adjusted Cox regression analysis found increased risk of bleeding with NSAID treatment compared with no NSAID treatment (hazard ratio, 2.02 [95% CI, 1.81-2.26]), and the cardiovascular risk was also increased (hazard ratio, 1.40 [95% CI, 1.30-1.49]). An increased risk of bleeding and cardiovascular events was evident with concomitant use of NSAIDs, regardless of antithrombotic treatment, types of NSAIDs, or duration of use.

CONCLUSIONS AND RELEVANCE Among patients receiving antithrombotic therapy after MI, the use of NSAIDs was associated with increased risk of bleeding and excess thrombotic events, even after short-term treatment. More research is needed to confirm these findings; however, physicians should exercise appropriate caution when prescribing NSAIDs for patients who have recently experienced MI.
through the past decade, much attention has been given to the cardiovascular safety of the commonly used nonsteroidal anti-inflammatory drugs (NSAIDs). Studies have shown increased risk of thrombotic cardiovascular events associated with the use of a number of individual agents. Current guidelines discourage the use of NSAIDs in patients with cardiovascular disease, yet during a period of 13 years, up to 44% of patients with a history of myocardial infarction (MI) were exposed to these agents in Denmark. Aspirin, clopidogrel, and oral anticoagulants are widely used by patients after MI to lower the risk of thromboembolic complications and mortality. Management guidelines advise that all patients with MI should be prescribed dual antithrombotic therapy (aspirin and clopidogrel) for up to 12 months and 1 agent thereafter, and a substantial proportion of patients has additional indication for antithrombotic agents. Although bleeding risks associated with antithrombotic agents are increased by NSAIDs, certain agents (eg, ibuprofen) may impede the antithrombotic effects of aspirin. NSAIDs may not only increase bleeding risks but also may increase risk of cardiovascular events. These risks are of considerable public health concern, given the widespread use of NSAIDs. Aside from the use of NSAID aspirin, the safety of antithrombotic-NSAID combinations in patients after MI has not been examined. We therefore conducted this study to investigate the association of the concomitant use of NSAIDs with risk of bleeding and cardiovascular events in patients receiving antithrombotic treatment after MI.

Methods

Ethics

The Danish Data Protection Agency approved this study (No 2007-58-0015, internal reference: GEH-2014-014, J-Suite 02732) and made all data available in anonymous form so patients could not be identified. In Denmark by law, retrospective registry studies do not require ethics committee approval.

Registries

In Denmark, each resident has a unique and permanent identification number that enables individual-level linkage between several Danish nationwide administrative registries. Four nationwide registers were linked at the individual level in this study. The Danish National Patient Registry records admission by the International Classification of Diseases (ICD-8 until 1994 and ICD-10 from 1994). Each hospital admission is registered with one main discharge diagnosis and, if appropriate, 1 or more supplementary diagnoses. The civil registration registry contains vital status data for all citizens in Denmark. The National Causes of Death Registry contains primary, secondary, and contributing causes of death recorded by a physician. The National Prescription Registry holds information on the date of dispensing, quantity dispensed, strength, and formulation of all prescriptions dispensed from Danish pharmacies and is based on the Anatomical Therapeutic Chemical system. Because of partial reimbursement of drug expenses by the Danish health care system, all pharmacies are required to register each drug dispensing in the national prescription registry, ensuring complete registration.

During the study period, the only NSAID available in Denmark over the counter without a prescription was ibuprofen (since November 1, 2001) and only in low (200-mg) doses and in limited quantity (100 tablets) at each purchase. This sale constituted approximately 15% to 20% of all NSAIDs after 2001. All other NSAIDs analyzed were available by prescription only. Anatomical Therapeutic Chemical and ICD codes used are reported in eTable IA-B in the Supplement.

Study Population and Follow-up

We identified a cohort including all patients aged 30 years or older admitted with a first-time MI from 2002 to 2011. The diagnosis of MI has been validated, with specificity exceeding 90%. We used the period from the day of discharge to 30 days after discharge to allow claiming of prescriptions to characterize the population and to minimize potential complications related to the hospitalization (ie, bleeding and thromboembolism). The cohort was restricted to individuals alive 30 days after discharge, which was the date of study inclusion, and thereby minimized the risk of immortal-time bias. Patients were followed up until one of the following events (whichever came first): event of interest, emigration, death, or end of study period through December 31, 2011.

Antithrombotic and NSAID Treatment

Claimed prescriptions for aspirin, clopidogrel, or vitamin K antagonists were used to classify patients to 1 or more of the following drug regimen groups: monotherapy with aspirin, clopidogrel, or a vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus a vitamin K antagonist, or clopidogrel plus a vitamin K antagonist; or triple therapy including all 3 drugs. In a similar manner we identified all claims for NSAIDs (Anatomical Therapeutic Chemical M01A, excluding glucosamine [M01AX05]). Rofecoxib and celecoxib were categorized as selective cyclooxygenase 2 (COX-2) inhibitors, and ibuprofen, diclofenac, and naproxen as nonselective NSAIDs; all other NSAIDs were grouped into “other NSAIDs.”

Exposure for each individual was calculated by estimating a daily dose after comparing the accumulated dose and the elapsed time from consecutive prescriptions for the drug under investigation. Ongoing exposure was then calculated by dividing the number of tablets dispensed by the estimated average dosage. If only 1 prescription was registered for an individual, a standard dosage defined as the minimal recommended dosage was used to estimate the daily dose. We defined exposure as the point at which patients had medication available and defined discontinuation as the point at which patients had no more medication available. The method used to determine the dose and treatment duration has been described.

For most patients, treatment regimens changed during the study period. The drug exposure groups were therefore created as time-varying covariates. Patients were allowed in only 1 drug exposure group at a time but could change groups during the study period according to claimed prescriptions. Each

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patient's exposure group at time of discharge from hospitalization for first-time MI to study inclusion at 30 days after discharge defined baseline treatment. In our method, exposures to NSAIDs and antithrombotic treatment were included as time-dependent covariates, ensuring that patients were only considered at risk when exposed to the respective drug.

Comorbidity and Medication
The Ontario acute myocardial infarction mortality prediction rule, modified for the ICD-10, was used to define comorbidity. To further enhance the comorbidity score, we identified discharge diagnoses up to 1 year before the index hospitalization. Glucose-lowering drugs were used as a proxy for prevalent diabetes, as done previously. Defined concomitant medications were β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers, statins, loop diuretics, spironolactone, and proton pump inhibitors.

Outcome
The primary outcome of bleeding was defined as admission or death from diagnoses of intracranial bleeding, gastrointestinal bleeding (bleeding ulcer, haematemia, melena, and unspecified gastrointestinal bleeding), bleeding from the respiratory or urinary tract, and anemia caused by bleeding. These methods have been used previously, and diagnoses of bleeding in hospital databases have a positive predictive value of 89% to 99%. Gastrointestinal bleeding was also defined as a separate outcome because this is a known adverse effect of both aspirin and NSAID use.

The secondary cardiovascular outcome was a combined outcome of cardiovascular death, nonfatal recurrent MI, and ischemic stroke, transient ischemic attack, or systemic arterial emboli. The diagnoses have been validated and found reliable, with a sensitivity of 91% and a positive predictive value of 93% for the MI diagnosis and 74% to 97% for stroke.

Statistical Methods
Crude incidence rates were calculated as number of events per 100 person-years. We analyzed adjusted hazard ratios (HRs) for bleeding and the risk of the combined cardiovascular endpoint by use of Cox proportional hazards models with the drug exposure groups as time-varying covariates. This model implies that patients were only deemed at risk for each exposure group while taking the corresponding antithrombotic drugs and NSAIDs. In assessment of the relation of both antithrombotic and NSAID use in the entire population, we used dual therapy with aspirin and clopidogrel as the reference, since this is the recommended treatment for patients after an MI (Figure 1). In all other analyses, the reference was the analyzed antithrombotic treatment regimen without concomitant NSAID treatment.

To assess the initial bleeding risk related to NSAID therapy, we defined 5 exposure periods from the start of uninterrupted NSAID use: 0 to 3, 4 to 7, 8 to 30, 31 to 90, and more than 90 days. In any given exposure period, NSAID users were compared with the reference population (at similar point in time). Because rheumatic diseases are common reasons for NSAID use, and previous studies have reported an increased risk of coronary artery disease among patients with rheumatoid arthritis, we performed a sensitivity analysis excluding patients with rheumatic diseases. All models were adjusted for all the covariates reported in Table 1. The proportional hazard assumption, linearity of continuous variables, and lack of interaction were found to be valid unless otherwise indicated. For all analyses, statistical significance was defined as a 2-sided probability value below 0.05.

All statistical calculations were performed using SAS version 9.2 (SAS Institute Inc) and Stata 11.0 (StataCorp).

Results
A total of 88 662 patients were admitted with first-time MI in the period 2002 to 2011; of these, 61 971 (69.8%) were included in the study. The mean age was 67.7 (SD, 13.6) years; 63.2% were men (Table 1 and eFigure 1 in the Supplement). The distribution of antithrombotic treatment at study inception among NSAID users and non-NSAID users were equal (eTable 3 in the Supplement). At least 1 prescription claim for NSAID treatment after discharge was identified for 20 931 patients (23.8%). The number of deaths during a median duration follow-up of 3.5 years (1 day-9.9 years) was 18 105 (29.2%). We counted 5288 bleeding events (8.5%), of which fatal bleeds comprised 799 (15.0%) events. Distribution of type of bleeding with and without NSAIDs is reported in eTable 4 in the Supplement. Gastrointestinal bleeding comprised 2157 events (40.8%). A total of 18 568 patients (30.0%) experienced the combined cardiovascular end point.

Bleeding Complications
The crude incidence rates of bleeding (events per 100 person-years) were 4.2 events (95% CI, 3.8-4.6) with concomitant NSAID treatment and 2.2 events (95% CI, 2.1-2.3) without NSAID treatment. In the adjusted analysis, the risk of bleeding associated with concomitant NSAIDs was increased (HR, 2.02 [95% CI, 1.81-2.26]) compared with no use of NSAIDs. Figure 1A shows bleeding risk for each antithrombotic and concomitant NSAID group with standard therapy as reference (ie, dual antiplatelet treatment). Table 2 and Table 3 report bleeding risk (crude and adjusted, respectively) with concomitant NSAID use according to the most prevalent antithrombotic regimens. The combinations of aspirin plus clopidogrel with NSAIDs (HR, 2.41 [95% CI, 1.93-3.01]) and oral anticoagulants plus single antiplatelet drug with NSAIDs (HR, 2.66 [95% CI, 1.79-3.95]) was associated with a marked increase in bleeding risk compared with either treatment without a concomitant NSAID. In evaluation of different groups of NSAIDs, COX-2 inhibitors, nonselective NSAIDs, and other NSAIDs, all were associated with both increased crude and adjusted risks compared with no NSAID use (Figure 2). The combination of no antithrombotic treatment with NSAIDs was associated with an increased risk of bleeding (crude incidence rate, 3.3 [95% CI, 2.9-3.7]) compared with no NSAID use (crude incidence rate, 2.0 [95% CI, 1.8-2.2]). In evaluation of individual NSAIDs, all types of NSAIDs were associated with increased risk. Use of any NSAID was associated with a marked risk of bleeding from the beginning of
treatment (day 0-3 crude incidence rate, 7.3 [95% CI, 5.6-9.9]; adjusted HR, 3.37 [95% CI, 2.57-4.41]), and the risk persisted (days 31-90 crude incidence rate, 3.3 [95% CI, 2.6-4.2]; HR, 1.67 [95% CI, 1.32-2.11]). The same pattern of an association of increased early (0-3 days) bleeding risk was present for the individual antithrombotic groups (Figure 3). The associated risks of bleeding in different periods of NSAID treatment according to antithrombotic treatment are reported in Table 2 in the Supplement.

Considering gastrointestinal bleeding specifically, increased risk was associated with NSAIDs; crude incidence rates were 2.1 events (95% CI, 1.8-2.4) with NSAID treatment and 0.8 events (95% CI, 0.8-0.9) without NSAID treatment (HR, 2.65 [95% CI, 2.28-3.09]).

Cardiovascular Complications

The crude incidence rates for the combined cardiovascular end point were 11.2 (95% CI, 10.5-11.9) with ongoing NSAID treatment and 8.3 (95% CI, 8.2-8.4) without NSAID treatment. In the adjusted analysis, an increased risk for the combined cardiovascular end point was associated with NSAIDs (HR, 1.40 [95% CI, 1.30-1.49]) compared with no NSAID treatment. Figure 1B shows cardiovascular risk for each antithrombotic and concomitant NSAID group with standard therapy (ie, dual antiplatelet treatment) as reference. Table 2 and Table 3 show the cardiovascular risk (crude and adjusted, respectively) with concomitant NSAID treatment according to the most prevalent antithrombotic treatment regimens. The combination of aspirin plus clopidogrel with concomitant NSAIDs (HR, 2.59 [95% CI, 1.16-5.80]) and aspirin with NSAIDs (HR, 1.58 [95% CI, 1.33-1.88]) was associated with increased cardiovascular risk. The same pattern of associations with cardiovascular risk was present for the other individual antithrombotic groups.

Sensitivity Analyses

When excluding patients who received NSAIDs before inclusion (n = 4632), our estimates of bleeding risk remain the same (eFigure 2 in the Supplement). The risk of subsequent mortality after a hospitalization for bleeding was HR, 1.51 (95% CI, 1.28-1.83).

Table 2 in the Supplement shows the cardiovascular risk (crude and adjusted, respectively) with concomitant NSAID treatment according to the most prevalent antithrombotic treatment regimens. The combination of aspirin plus clopidogrel with concomitant NSAIDs (HR, 2.59 [95% CI, 1.16-5.80]) and aspirin with NSAIDs (HR, 1.58 [95% CI, 1.33-1.88]) was associated with increased cardiovascular risk. The same pattern of associations with cardiovascular risk was present for the other individual antithrombotic groups.
Proton pump inhibitors have been found to reduce the risk of gastrointestinal bleeding. Using the Wald test, we did not find any significant interactions between each of the regimens (NSAID + antithrombotic) with proton pump inhibitors. Dabigatran came on the market in Denmark in August 2011; we therefore undertook a sensitivity analysis with the follow-up period ending in December 2010. The results were similar to those from the main analysis. We performed an analysis excluding patients with rheumatoid arthritis, which did not change the results (HR for NSAID treatment vs no NSAID treatment, 2.02 [95% CI, 1.81-2.26]). There was an imbalance of key bleeding risks among the no NSAID vs NSAID groups, including a higher incidence of malignancy, acute or chronic renal failure, and previous bleeding; we therefore performed a sensitivity analysis excluding these subgroup of patients. Results were unchanged.

**Discussion**

In this Danish nationwide study, concomitant use of NSAIDs was associated with increased risk of bleeding in patients who

### Table 1. Baseline Characteristics of the Total Study Population and Individual Antithrombotic Treatment Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population</th>
<th>No Treatment</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Aspirin + Clopidogrel</th>
<th>Oral Anticoagulant</th>
<th>Oral Anticoagulant + Single Antiplatelet</th>
<th>Triple Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>61,971 (100.0)</td>
<td>2561 (2.0)</td>
<td>13,365 (18.0)</td>
<td>1145 (1.7)</td>
<td>37,407 (64.9)</td>
<td>551 (0.5)</td>
<td>2895 (4.4)</td>
<td>4047 (8.5)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.7 (13.6)</td>
<td>66.0 (17.0)</td>
<td>72.8 (13.7)</td>
<td>71.0 (12.4)</td>
<td>65.3 (13.2)</td>
<td>71.6 (13.0)</td>
<td>72.8 (10.6)</td>
<td>69.3 (10.9)</td>
</tr>
<tr>
<td>Women</td>
<td>22,809 (36.8)</td>
<td>1153 (45.0)</td>
<td>6144 (46.0)</td>
<td>529 (46.0)</td>
<td>12,321 (32.9)</td>
<td>245 (44.5)</td>
<td>1195 (41.3)</td>
<td>1222 (30.2)</td>
</tr>
<tr>
<td>Men</td>
<td>39,162 (63.2)</td>
<td>1408 (56.0)</td>
<td>7221 (54.0)</td>
<td>616 (54.0)</td>
<td>25,086 (64.9)</td>
<td>306 (56.5)</td>
<td>1700 (59.7)</td>
<td>2825 (69.8)</td>
</tr>
</tbody>
</table>

**NSAID Use**

- **None**: 41,040 (66.2)
- **Any**: 20,931 (33.8)
- **Rofecoxib**: 501 (0.8)
- **Celecoxib**: 753 (1.2)
- **Diclofenac**: 6157 (9.9)
- **Ibuprofen**: 14,326 (23.1)
- **Naproxen**: 1055 (1.7)
- **Other**: 4099 (6.6)

**Comorbidity**

- **Cardiac arrhythmias**: 6544 (10.6)
- **Peripheral vascular disease**: 2461 (4.0)
- **Cerebral vascular disease**: 3045 (4.9)
- **Diabetes with complications**: 2745 (4.4)
- **Acute renal failure**: 644 (1.0)
- **Chronic renal failure**: 1013 (1.6)
- **Malignancy**: 1593 (2.6)
- **Shock**: 202 (0.3)
- **COPD**: 552 (0.9)
- **Previous bleeding**: 5032 (8.1)
- **PCI**: 29,288 (47.3)

**Concomitant Medical Treatment**

- **β-Blockers**: 48,387 (78.1)
- **ACE inhibitors and ARBs**: 30,847 (49.8)
- **Statins**: 46,556 (75.1)
- **Spirinolactone**: 5089 (8.2)
- **Loop diuretics**: 19,412 (31.3)
- **Glucose-lowering drugs**: 7108 (11.5)
- **PPIs**: 15,056 (24.3)

**Abbreviations**: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.
found that all types of NSAIDs were associated with increased bleeding risk. We most commonly used medications worldwide and any anti-thrombotic treatment regimen, we found that addition of NSAIDs was associated with increased bleeding when used concomitantly with antithrombotics. Regardless of the antithrombotic treatment regimen, we found that addition of NSAIDs was associated with increased risks of bleeding. This is of considerable public health relevance because NSAIDs are among the most commonly used medications worldwide and any antithrombotic treatment invariably increases bleeding risk. We found that all types of NSAIDs were associated with increased risk, especially celecoxib and diclofenac. Meta-analyses of randomized and observational data have shown that naproxen, celecoxib, ibuprofen, and diclofenac are associated with increased risk of upper gastrointestinal tract bleeding compared with nonuse of these agents.4,24,25

Several studies have reported on the risks of bleeding in patients with acute coronary syndromes treated with antithrombotic drugs22-23; however, to our knowledge, the present study is the first to investigate the bleeding risk associated with NSAIDs prescribed concomitantly with antithrombotic treatment in patients who have recently experienced an MI. Sørensen et al22 reported in 2009 that among Danish patients with prior MI the risk of hospital admission for bleeding increased with the number of antithrombotic drugs. From a functional perspective, the antiplatelet properties of NSAIDs would be expected to increase bleeding risk when used concomitantly with antithrombotics. However, our results correspond with previous findings of an increased risk associated with short-term NSAID treatment,6,26 and our results challenge the implied safety of the duration restriction by demonstrating that even short-term treatment is associated with increased bleeding risk in patients with prior MI who are already taking antithrombotic drugs.

Through the past decade, much attention has been given to the cardiovascular safety of NSAIDs. It is now widely accepted that any NSAID with antiplatelet plus oral anticoagulant combination.

Table 2. Bleeding and Cardiovascular Crude Risk According to Antithrombotic Treatment and Concomitant Use of Specific NSAIDs

<table>
<thead>
<tr>
<th>Serious Bleeding</th>
<th>Overall*</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Aspirin + Clopidogrel</th>
<th>Oral Anticoagulant + Single Antiplatelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NSAID</td>
<td>4949</td>
<td>2.2 (2.1-2.3)</td>
<td>2109</td>
<td>1.5 (1.5-1.6)</td>
<td>258</td>
</tr>
<tr>
<td>Any NSAID</td>
<td>339</td>
<td>4.2 (3.8-4.6)</td>
<td>176</td>
<td>3.2 (2.8-3.8)</td>
<td>11</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>5</td>
<td>4.6 (1.9-11.0)</td>
<td>1</td>
<td>1.7 (0.2-11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>21</td>
<td>9.1 (5.9-14.0)</td>
<td>15</td>
<td>12.1 (7.3-20.1)</td>
<td>1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>105</td>
<td>6.1 (5.0-7.4)</td>
<td>54</td>
<td>4.8 (3.7-6.2)</td>
<td>5</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>132</td>
<td>3.1 (2.7-3.7)</td>
<td>70</td>
<td>2.4 (1.9-3.1)</td>
<td>4</td>
</tr>
<tr>
<td>Naproxen</td>
<td>10</td>
<td>3.3 (1.8-6.1)</td>
<td>5</td>
<td>2.7 (1.1-6.4)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>66</td>
<td>4.2 (3.3-5.3)</td>
<td>31</td>
<td>3.0 (2.1-4.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Cardiovascular Risk

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Events, No.</th>
<th>Crude Rate (95% CI)b</th>
<th>Crude Rate (95% CI)b</th>
<th>Crude Rate (95% CI)b</th>
<th>Crude Rate (95% CI)b</th>
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</thead>
<tbody>
<tr>
<td>No NSAID</td>
<td>17708</td>
<td>8.3 (8.2-8.4)</td>
<td>9194</td>
<td>7.1 (6.9-7.2)</td>
<td>822</td>
</tr>
<tr>
<td>Any NSAID</td>
<td>860</td>
<td>11.2 (10.5-11.9)</td>
<td>529</td>
<td>10.3 (9.4-11.2)</td>
<td>37</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>25</td>
<td>19.9 (13.0-30.5)</td>
<td>11</td>
<td>18.8 (10.4-33.9)</td>
<td>1</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>59</td>
<td>25.9 (20.0-33.4)</td>
<td>39</td>
<td>32.1 (23.4-43.9)</td>
<td>1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>200</td>
<td>12.0 (10.5-13.8)</td>
<td>117</td>
<td>10.7 (8.9-12.8)</td>
<td>5</td>
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<tr>
<td>Ibuprofen</td>
<td>395</td>
<td>10.0 (9.1-11.0)</td>
<td>253</td>
<td>9.3 (8.2-10.5)</td>
<td>21</td>
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<tr>
<td>Naproxen</td>
<td>21</td>
<td>7.4 (4.8-11.3)</td>
<td>11</td>
<td>6.1 (3.4-11.1)</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>164</td>
<td>11.1 (9.6-13.0)</td>
<td>98</td>
<td>10.0 (8.2-12.2)</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug.

*All NSAIDs with any antiplatelet plus oral anticoagulant combination.

bAll crude rates are events per 100 person-years.
cepted that commonly used agents, including diclofenac and higher doses of celecoxib and ibuprofen, increase risks of thrombotic events, although naproxen has not been associated with increased risk. The biological explanation of the cardiovascular risk with NSAIDs is still unresolved but is likely to involve inhibition of COX-2–mediated prostacyclin va-

Table 3. Bleeding and Cardiovascular Adjusted Risk According to Antithrombotic Treatment and Concomitant Use of Specific NSAIDs

| Table 3. Bleeding and Cardiovascular Adjusted Risk According to Antithrombotic Treatment and Concomitant Use of Specific NSAIDs |
|---|---|---|---|---|---|
| | Overalla | Aspirin | Clopidogrel | Aspirin + Clopidogrel | Oral Anticoagulants + Single Antiplatelet |
| | Events, No. | Adjusted HR (95% CI)a | Events, No. | Adjusted HR (95% CI)a | Events, No. | Adjusted HR (95% CI)a | Events, No. | Adjusted HR (95% CI)a |
| Serious Bleeding | | | | | | | | |
| Any NSAID | 339 | 2.02 (1.81-2.26) | 176 | 2.16 (1.84-2.51) | 11 | 1.86 (1.03-3.38) | 83 | 2.41 (1.93-3.01) |
| Rofecoxib | 5 | 1.30 (0.53-3.12) | 1 | 0.62 (0.09-4.46) | 0 | NA | | |
| Celecoxib | 25 | 2.59 (1.68-3.98) | 15 | 4.24 (2.55-7.07) | 1 | 2.06 (0.29-14.03) | 4 | 2.55 (1.00-6.80) |
|Diclofenac | 105 | 3.09 (2.55-3.75) | 54 | 3.32 (2.53-4.35) | 5 | 3.09 (1.28-7.50) | 24 | 3.30 (2.21-4.95) |
| Ibuprofen | 132 | 1.56 (0.84-2.90) | 5 | 1.84 (0.76-4.42) | 1 | 2.27 (0.32-16.18) | 2 | 2.57 (1.16-5.80) |
| Naproxen | 1 | 1.56 (0.84-2.90) | 0 | NA | 1 | 2.27 (0.32-16.18) | 2 | 2.57 (1.16-5.80) |
| Other | 66 | 1.87 (1.46-2.38) | 31 | 1.80 (1.26-2.56) | 0 | NA | 20 | 2.80 (1.80-4.36) |

Cardiovascular Risk

<table>
<thead>
<tr>
<th>NSAID</th>
<th>17708</th>
<th>1 [Reference]</th>
<th>9194</th>
<th>1 [Reference]</th>
<th>822</th>
<th>1 [Reference]</th>
<th>3229</th>
<th>1 [Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any NSAID</td>
<td>860</td>
<td>1.40 (1.30-1.49)</td>
<td>529</td>
<td>1.58 (1.33-1.88)</td>
<td>37</td>
<td>1.34 (1.12-1.62)</td>
<td>123</td>
<td>2.59 (1.92-3.50)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>21</td>
<td>1.06 (0.69-1.63)</td>
<td>11</td>
<td>1.10 (0.61-1.98)</td>
<td>1</td>
<td>0.50 (0.07-3.56)</td>
<td>2</td>
<td>2.02 (0.22-3.68)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>59</td>
<td>1.46 (1.13-1.89)</td>
<td>39</td>
<td>1.78 (1.30-2.44)</td>
<td>1</td>
<td>0.50 (0.07-3.58)</td>
<td>5</td>
<td>0.87 (0.36-2.09)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>200</td>
<td>1.65 (1.44-1.90)</td>
<td>117</td>
<td>1.74 (1.44-2.08)</td>
<td>5</td>
<td>1.01 (0.42-2.43)</td>
<td>34</td>
<td>1.74 (1.24-2.45)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>31</td>
<td>1.42 (1.28-1.57)</td>
<td>23</td>
<td>1.50 (1.33-1.70)</td>
<td>21</td>
<td>2.38 (1.54-3.67)</td>
<td>52</td>
<td>1.20 (1.00-1.57)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1</td>
<td>0.86 (0.52-1.36)</td>
<td>1</td>
<td>0.94 (0.52-1.70)</td>
<td>2</td>
<td>1.41 (0.35-5.67)</td>
<td>4</td>
<td>0.93 (0.35-2.47)</td>
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<tr>
<td>Other</td>
<td>164</td>
<td>1.24 (1.07-1.45)</td>
<td>98</td>
<td>1.26 (1.04-1.54)</td>
<td>7</td>
<td>1.30 (0.62-2.75)</td>
<td>26</td>
<td>1.32 (0.90-1.94)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug. a All NSAIDs with any antiplatelet plus oral anticoagulant combination. b Adjusted for age, sex, year, cardiac arrhythmias, peripheral vascular disease, cerebral vascular disease, diabetes with complications, acute renal failure, chronic renal failure, malignancy, shock, chronic obstructive pulmonary disease, previous bleeding, percutaneous coronary intervention, and use of β-blockers, angiotensin-converting enzyme inhibitors, statins, spironolactone, loop diuretics, and glucose-lowering drugs.

![Figure 2. Cox Proportional Hazard Analysis Risk of Bleeding With and Without Use of Individual NSAIDs in Patients With Prior Myocardial Infarction](image-url)

NSAID indicates nonsteroidal anti-inflammatory drug. Sample size indicates the sample size receiving treatment. One patient could have multiple treatment courses with 1 drug or with different drugs. Reference is antiplatelet or anti-thrombotic treatment without NSAIDs (vertical line indicates reference level).
sodilatation as well as pharmacodynamic interactions associated with individual drugs, including ibuprofen. Recent studies have shown that NSAIDs, including ibuprofen and naproxen, may interact with aspirin at the level of platelet COX-1 to increase atherothrombotic risk. We found an increased cardiovascular risk for NSAID use with ongoing aspirin monotherapy, which may be attributable to reduction of the antithrombotic protection afforded by antiplatelet drugs and oral anticoagulants. Novel oral anticoagulants have shown similar or even safer overall bleeding risk profiles compared with warfarin, but high-dose dabigatran (150 mg twice daily) has been associated with significantly more gastrointestinal bleeding than both warfarin and dabigatran (110 mg twice daily). Similarly, rivaroxiban has also been shown to be significantly associated with increased gastrointestinal bleeding risk compared with warfarin. Investigation is needed to determine if concomitant use of NSAIDs with new oral anticoagulants is likely to augment gastrointestinal risks. Although it seems unlikely that physicians can completely avoid prescription of NSAIDs, even among high-risk patients, these results highlight the importance of considering the balance of benefits and risks before initiating any NSAID treatment.

**Limitations**

The main limitation of our study is its observational design. There is a lack of information about important clinical parameters including blood pressure, body mass index, smoking habits, lipid levels, and coagulation profile; hence, the effect of unmeasured confounders cannot be excluded. Information about the precise indication for initiation of NSAID treatment or changing therapy was not available—but NSAIDs are not recommended in the treatment of ischemic heart disease, and it is not likely that angina pectoris would be treated with NSAIDs. Analyzing data from users treated with the drugs under investigation prior to study inclusion can possibly result in confounding (healthy-user effect), eg, patients not experiencing any bleeding while taking NSAIDs still receive treatment, whereas patients experiencing bleeding events while taking NSAIDs discontinue treatment. Our estimates when ex-
Including prevalent NSAID users remained the same (eFigure 2 in the Supplement). Furthermore, sensitivity analyses excluding subgroups of patients with malignancy, acute or chronic renal failure, and previous bleeding did not change our results. Therefore, it is unlikely that confounding by indication alone would drive the observed results.

Another possible bias when using prescription data is the uncertainty about adherence to treatment. Indeed, in observational studies there is always a possibility that the patients do not take their prescribed medications. Our definition of NSAID therapy was based on prescriptions, with the dates of NSAID prescription claims, in our view, reflecting actual consumption most precisely. The increased bleeding risk after only 3 days is concerning. On the other hand, nonadherence would dilute the association between the exposure and outcome. Rheumatic diseases are common reasons for NSAID use, and previous studies have reported an increased risk of coronary artery disease among patients with rheumatoid arthritis.33,34 We therefore performed the analysis excluding patients with rheumatoid arthritis, which did not change the results. Our definition of bleeding ensures that only bleeding severe enough to warrant hospitalization is included. In Denmark the only NSAID available over the counter without a prescription is ibuprofen (since November 1, 2001) and only in a low (200-mg) dose and in limited quantity (maximum, 100 tablets per package) at each purchase. All other NSAIDs analyzed in this study are only available by prescription. Aspirin is also available over the counter, but because of partial reimbursement of drug expenses chronic users are most likely to be prescribed aspirin as thromboprophylaxis.33,35 For these reasons we believe unrecorded use of over-the-counter drugs is unlikely to have had a major effect on the study results, and a potential bias would only dilute our findings toward the null (nondifferential misclassification).

Conclusions

Among patients receiving antithrombotic therapy after MI, the use of NSAIDs was associated with increased risk of bleeding and excess thrombotic events, even after short-term treatment. More research is needed to confirm these findings; however, physicians should exercise appropriate caution when prescribing NSAIDs for patients who have recently experienced MI.

REFERENCES


