ORIGINAL RESEARCH | Annals of Internal Medicine

Relation of Nonsteroidal Anti-inflammatory Drugs to Serious Bleeding and Thromboembolism Risk in Patients With Atrial Fibrillation Receiving Antithrombotic Therapy

A Nationwide Cohort Study

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are assumed to increase bleeding risk, but their actual relation to serious bleeding in patients with atrial fibrillation (AF) who are receiving antithrombotic medication is unknown.

Objective: To investigate the risk for serious bleeding and thromboembolism associated with ongoing NSAID and antithrombotic therapy.

Design: Observational cohort study.

Setting: Nationwide registries.

Patients: Danish patients with AF hospitalized between 1997 and 2011.

Measurements: Absolute risk for serious bleeding and thromboembolism with ongoing NSAID and antithrombotic therapy, assessed by using Cox models.

Results: Of 150 900 patients with AF (median age, 75 years [interquartile range, 65 to 83 years]; 47% female), 53 732 (35.6%) were prescribed an NSAID during a median follow-up of 6.2 years (interquartile range, 2.1 to 14.0 years). There were 17 187 (11.4%) and 19 561 (13.0%) occurrences of serious bleeding and thromboembolism, respectively. At 3 months, the absolute risk for serious bleeding within 14 days of NSAID exposure was 3.5 events per 1000 patients compared with 1.5 events per 1000 patients without NSAID exposure. The risk difference was 1.9 events per 1000 patients. In patients selected for oral anticoagulant therapy, the absolute risk difference was 2.5 events per 1000 patients. Use of NSAIDs was associated with increased absolute risks for serious bleeding and thromboembolism across all antithrombotic regimens and NSAID types. An NSAID dosage above the recommended minimum was associated with a substantially increased hazard ratio for bleeding.

Limitation: Observational design and unmeasured confounders.

Conclusion: Use of NSAIDs was associated with an independent risk for serious bleeding and thromboembolism in patients with AF. Short-term NSAID exposure was associated with increased bleeding risk. Physicians should exercise caution with NSAIDs in patients with AF.

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Antithrombotic therapy is a cornerstone of the treatment of patients with atrial fibrillation (AF). It decreases the risk for thromboembolic complications and death (1) and should be prescribed after in-depth assessment of thromboembolic risk factors; however, it has also been found to increase the risk for bleeding (2, 3). European and Canadian guidelines (4, 5) suggest using the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INRs, Elderly, Drug Therapy/Alcohol intake) score, which includes use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a bleeding risk factor (6), for assessment of bleeding risk in patients with AF. Studies have firmly linked NSAIDs to increased risk for coronary thrombosis and death in patients with ischemic heart disease (7–9). This is especially a concern with cyclooxygenase (COX)-2–selective inhibitors, which were developed to diminish the common gastrointestinal adverse effects of NSAID treatment. Although NSAIDs are known to interact with aspirin and vitamin K antagonists (10–12), the assumed effect of NSAID use on bleeding risk in patients receiving antithrombotic treatment has never been investigated and the magnitude of risk has never been defined in a contemporary cohort of patients with AF. This is a major public health concern given the extent of NSAID use among these patients.

We investigated the risk for serious bleeding with ongoing antithrombotic and NSAID therapy in patients with AF. In a secondary analysis, we investigated the effect on hospitalization or death from thromboembolism. We tested the hypothesis that an increased risk for serious bleeding was present regardless of antithrombotic treatment type and that all types of NSAIDs were hazardous, with no beneficial effect on thromboembolism.

See also:

Summary for Patients I-38

METHODS

Registries

Information from any hospitalization and any claimed prescription in Denmark can be linked to residents by using a unique personal identifier (13). We used records

coded as either primary or secondary diagnosis in the National Patient Registry, which records hospitalizations by using codes from the International Classification of Diseases (ICD) (eighth revision until 1994 and 10th revision thereafter). The National Prescription Registry contains information on dosage, strength, and date of dispensation for each prescription filled and uses codes from the Anatomical Therapeutic Chemical (ATC) Classification System. The primary, secondary, and contributing causes of death recorded by a physician were obtained from the National Causes of Death Registry, and vital status was obtained from the Civil Registration System. The ATC and ICD codes that were used are shown in **Appendix Tables 1** and **2** (available at www.annals.org).

Population

All patients aged 30 years or older who were hospitalized with a first-time diagnosis of AF between 1997 and 2011 were eligible for inclusion. Exclusion criteria were presence of valvular disease and death or rehospitalization for stroke or bleeding within 7 days from discharge (15). The diagnosis of AF in the National Patient Registry has been validated, with a positive predictive value of 97% (16). We used a new-user design as suggested by Ray (17) and excluded NSAID users who filled a prescription 30 days before inclusion ($n = 7815$). We also excluded patients selected for an infrequently used antithrombotic treatment strategy for AF (oral anticoagulant [OAC] plus aspirin plus clopidogrel [$n = 1294$] or aspirin plus clopidogrel [$n = 3141$]).

Antithrombotic and NSAID Treatment

All filled prescriptions for aspirin, clopidogrel, and OACs (warfarin and phenprocoumon) were recorded to define the following antithrombotic treatment regimens: single-antiplatelet therapy with either aspirin or clopidogrel, monotherapy with OACs, or dual therapy with an OAC and a single antiplatelet. Treatment with NSAIDs was identified in a similar manner (8, 18). Although glucosamine is classified as an NSAID (ATC code M01AX05), we did not consider it as such for our analyses. We categorized rofecoxib and celecoxib as selective COX-2 inhibitors; ibuprofen, diclofenac, and naproxen as nonselective NSAIDs; and all other NSAIDs as "other" NSAIDs. Assessment of ongoing exposure for each patient with AF was done by estimating a daily dose after comparing the cumulative dose and the elapsed time from consecutive prescriptions for the drug under investigation. If only 1 prescription was registered for a patient, the daily dosage was estimated as the minimum recommended dosage. This approach also allowed the dose to increase if subsequent prescriptions were filled before tablets were consumed. The approximation of drug exposure was based on continuous assessment of new prescriptions during exposure and not on future prescriptions; hence, no condition on future use was assumed and exposure to specific NSAIDs and antithrombotic therapy was determined continuously. This method has been described in detail elsewhere (7, 19). To analyze whether there was a dose-related response in risk for bleeding, we divided the COX-2 inhibitors and the nonselective NSAIDs into low and high dosages, with the latter defined as a dosage above the upper limit of the recommended minimum for each drug (1200 mg for ibuprofen, 100 mg for diclofenac, 500 mg for naproxen, 25 mg for rofecoxib, and 200 mg for celecoxib). Baseline antithrombotic and NSAID treatment were defined as availability of tablets up to 30 days after discharge, which allowed time for patients to fill prescriptions after hospitalization (2, 20, 21). Ibuprofen has been the only NSAID available in Denmark without a prescription since 2001, but only in low doses (200 mg) and limited quantities. It has accounted for approximately 15% to 20% of all NSAID sales since 2001.

Context

Little is known about what happens when patients with atrial fibrillation (AF) who are receiving anticoagulants also receive nonsteroidal anti-inflammatory drugs (NSAIDs).

Contribution

The researchers studied all citizens of Denmark who had a first-time diagnosis of AF during a hospitalization between 1997 and 2011. They found that NSAIDs increased the risk for bleeding and thromboembolism, even when they were used for short periods.

Caution

Observational studies like this one can identify associations but cannot establish a cause-and-effect relationship.

Implication

Persons with AF who are using anticoagulants should use NSAIDs with caution.

—The Editors

Outcomes

The primary outcome was serious bleeding, defined as hospitalization or death from intracranial bleeding, gastrointestinal bleeding (such as bleeding ulcer, hematemesis, or melena), or bleeding from the respiratory or urinary tract or anemia caused by bleeding. These outcome parameters have been used previously (2, 21, 22). Bleeding diagnoses in hospital databases have a positive predictive value of 89% to 99% (23). Intracranial and gastrointestinal bleeding were also defined as separate outcomes; this included major and clinically nonmajor bleeding according to criteria from the International Society on Thrombosis and Haemostasis, but only if the patient was hospitalized (24). The secondary outcome was hospitalization or death from thromboembolism, defined as ischemic stroke (predictive value, 97% to 100%); unspecified stroke (approximately 60% predicted as ischemic stroke); or systemic arterial embolism, which has been used previously (14, 25, 26). For additional insight, we also defined all-cause mortality as an outcome.

Comorbidity and Medication

The HAS-BLED and CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, Stroke, Vascular disease, Sex female) scores were calculated from recorded comorbid conditions as previously described (14, 22, 27). We did not include use of NSAIDs or aspirin in the HAS-BLED score because both were explanatory variables and data on international normalized ratios (INRs) were unavailable in the registries. Prescriptions for renin–angiotensin system inhibitors, antiarrhythmic drugs (β-blockers, digoxin, class 1C antiarrhythmic drugs, calcium-channel blockers, and amiodarone), or proton-pump inhibitors dispensed 180 days before inclusion were defined as concomitant medication.

Statistical Analysis

We estimated hazard ratios (HRs) with 95% CIs for the bleeding and thromboembolism outcomes by using Cox regression models. We also estimated the cumulative baseline hazards for both outcomes. In our primary model, we assessed NSAID use (as a time-varying explanatory variable) in the overall population. The model was adjusted for age, sex, and year of inclusion. It was also adjusted for factors in the modified HAS-BLED score (excluding NSAID or aspirin use because these were explanatory variables) for the serious bleeding outcome and for factors incorporated in the CHA_2DS_2-VASc score for the thromboembolism outcome. The estimates of covariate effects are provided in **Appendix Table 3** (available at www.annals.org). In a subsequent model, we fitted all combinations of antithrombotic therapy and concomitant NSAID use, which allowed patients to switch between exposure groups according to claimed prescriptions with adjustments similar to those reported earlier.

We estimated the absolute risk for the outcome with and without NSAID exposure during 14-day periods starting at 3 months and 2 years from inclusion by combining the estimated HRs with the estimated cumulative baseline hazards in the Cox regression models. Because absolute risk predictions were done for a short period, the competing risk for death without the outcome was neglected. The individual-patient risk predictions were averaged over the patients still at risk at each time point, as explained by Austin (28), and 95% CIs were obtained for the absolute risk in each treatment scenario and for the risk differences by using a nonparametric bootstrap with 200 replications. For the subsequent model, estimation of the absolute risk with or without NSAID use was done in subgroups of patients receiving concomitant antithrombotic therapy and for specific NSAIDs. We defined a sequence of use (rofecoxib, celecoxib, diclofenac, ibuprofen, naproxen, other) to allow all explanatory variables in 1 model if patients were exposed to more than 1 NSAID. The short-term (14-day) absolute risk differences with and without NSAID exposure were also obtained from additional Cox regression analyses for bleeding (HAS-BLED score) and thromboembolism (CHA_2DS_2-VASc score), both adjusted for age, sex, and year of inclusion. To assess the potential effect of an unmeasured confounder on the rate of bleeding with concomitant NSAID use, we used a sensitivity analysis as suggested by Schneeweiss (29). We report results for a hypothetical confounder with 20% prevalence in the population (more prevalent than obesity [body mass index >30 kg/m^2]), where we also set the prevalence of NSAID use to 30%. All models were tested for assumptions and were found to be valid unless otherwise indicated. We followed all patients until the end of the study or death. All statistical analyses were performed using SAS, version 9.2 (SAS Institute); Stata, version 11.0 (StataCorp); or R, version 3.1 (R Foundation for Statistical Computing).

Ethics

All patient data were deidentified. Retrospective, register-based studies do not require ethical approval in Denmark, and the Danish Data Protection Agency approved this study (reference no. 2007-58-0015; internal reference no. GEH-2010-001).

Role of the Funding Source

This study received no direct funding.

RESULTS

We included 150 900 patients with AF. The median age was 75 years (interquartile range, 65 to 83 years), and 47% were female (**Table 1**). Mean HAS-BLED and CHA_2DS_2-VASc scores were 1.5 (SD, 0.9) and 2.8 (SD, 1.7), respectively. A total of 105 279 patients (69.8%) were treated with an antiplatelet or OAC at baseline, whereas 7507 (5.0%) were treated with a concomitant NSAID. During follow-up, 53 732 (35.6%) claimed at least 1 NSAID prescription. In these patients, a total of 254 124 periods of uninterrupted NSAID exposure was defined, and after 3 and 8 weeks of exposure, fewer than 50% and 10%, respectively, were still defined as exposed (**Appendix Table 4**, available at www.annals.org). There were 73 701 deaths (48.8%) during a median follow-up of 6.2 years (interquartile range, 2.1 to 14.0 years).

Bleeding and Thromboembolic Complications

We identified 17 187 (11.4%) serious bleeding events and 19 561 (13.0%) thromboembolic events. A total of 2133 bleeding events (12.4%) was fatal. **Figure 1** shows the absolute risks for serious bleeding and thromboembolism within 14 days of NSAID exposure starting at 3 months and 2 years from inclusion. At 3 months, the absolute risk for serious bleeding with 14 days of continuous NSAID exposure was 3.5 events per 1000 patients versus 1.5 events per 1000 patients without NSAID exposure. The absolute risk difference was 1.9 events per 1000 patients. In patients selected for OAC therapy, the absolute risk difference was 2.5 events per 1000 patients. Use of NSAIDs was associated with increased absolute risks for serious bleeding and thromboembolism across all anti-

Table 1. **Characteristics of the Study Population***

Characteristic	Overall (*n* = 150 900)		No Treatment (*n* = 45 191)		Single Antiplatelet† (*n* = 44 136)		Oral Anticoagulant (*n* = 39 556)		Oral Anticoagulant + Single Antiplatelet (*n* = 21 587)	
	No NSAID	NSAID	No NSAID	NSAID	No NSAID	NSAID	No NSAID	NSAID	No NSAID	NSAID
Total, *n*	143 393	7507	43 191	2430	37 942	1614	41 660	2476	20 600	987
Female	46.4	51.2	49.0	55.4	53.6	55.3	38.9	44.2	40.0	42.1
Median age (IQR), *y*	75 (65–83)	76 (66–83)	73 (61–83)	75 (64–83)	80 (71–86)	80 (71–86)	71 (63–79)	72 (64–78)	74 (67–80)	74 (66–80)
CHA_2DS_2-VASc score										
Low (0)	9.9	7.0	15.6	10.6	4.1	3.6	12.7	9.1	4.3	3.3
Moderate (1)	14.0	12.7	17.5	15.8	8.6	7.5	17.9	17.9	10.1	9.3
High (≥2)	76.2	80.3	66.9	73.6	87.3	88.9	69.5	73.0	85.7	87.3
HAS-BLED score										
Low (0–1)	53.5	51.8	63.7	61.2	44.9	44.0	69.3	57.6	38.7	38.5
Moderate (2)	33.7	35.7	26.3	30.3	38.1	40.4	32.0	32.6	43.5	42.5
High (≥3)	12.8	12.5	9.9	8.6	17.1	15.6	8.7	9.8	17.7	19.1
Medical history										
Peptic disease	5.6	5.9	7.0	7.2	7.0	7.1	3.2	3.6	4.3	3.3
Ischemic stroke	15.4	14.1	10.1	7.5	20.1	19.5	12.5	11.5	22.5	21.3
Bleeding	9.1	9.3	10.9	9.9	11.4	11.2	5.6	7.0	7.2	7.0
Vascular disease	13.5	13.1	8.4	7.6	21.0	19.1	6.5	6.4	22.4	22.2
Hypertension	37.2	39.0	24.2	28.3	40.3	40.6	38.7	40.6	56.2	58.8
Heart failure	12.3	13.6	8.9	10.0	15.6	15.2	10.4	13.9	16.2	17.5
Diabetes mellitus	8.0	9.6	5.8	7.5	9.2	9.1	6.9	10.1	12.0	15.0
Osteoarthritis	7.3	14.2	6.4	13.6	8.1	13.7	7.1	16.1	8.3	13.8
Chronic kidney disease	4.2	4.1	4.8	4.3	5.2	4.3	2.6	3.4	4.0	4.3
Other pharmacotherapy										
Renin–angiotensin system inhibitor	26.0	26.5	15.8	18.6	27.5	25.9	27.5	28.9	41.6	43.4
Antiarrhythmic drug‡	57.0	55.4	42.8	42.6	60.5	59.9	62.7	59.1	71.6	69.8
Proton-pump inhibitor	12.1	15.7	12.7	15.7	15.4	17.6	8.0	13.7	12.0	14.5
Previous oral anticoagulant	25.1	18.7	2.3	1.2	1.3	0.9	61.4	52.9	54.3	50.2
Previous antiplatelet	17.5	16.2	0.1	0.1	38.9	33.0	0.1	0.1	42.8	39.8

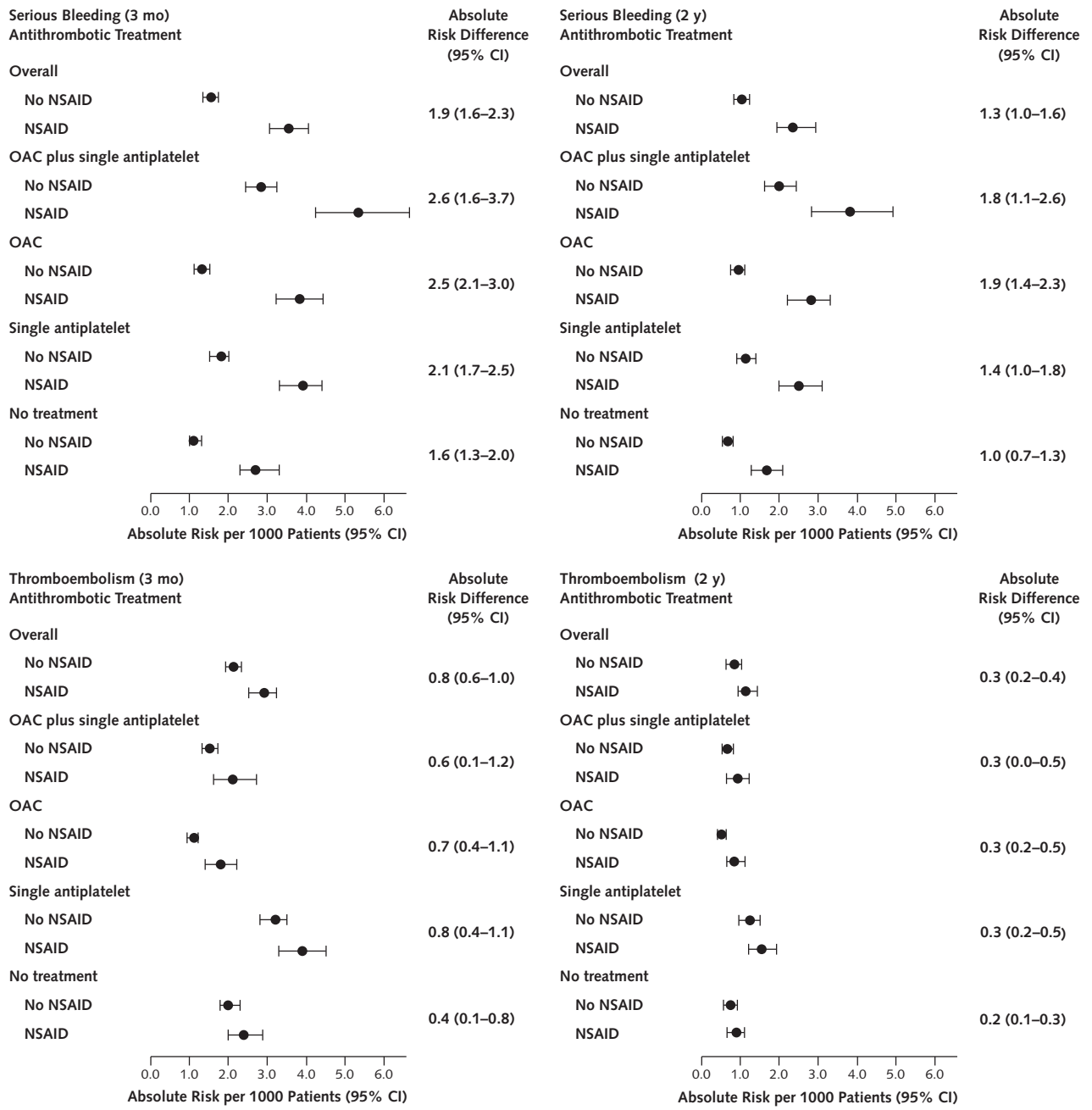
CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, Stroke, Vascular disease, Sex female; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INRs, Elderly, Drug Therapy/Alcohol intake; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.
* Data are percentages unless otherwise indicated.
† Aspirin or clopidogrel.
‡ β-Blocker, digoxin, class 1C antiarrhythmic drug, calcium-channel blocker, or amiodarone.

thrombotic regimens. **Tables 2** and **3** show HRs for serious bleeding with NSAID exposure according to antithrombotic treatment regimen and specific NSAID. The HR for serious bleeding with NSAID treatment was doubled (2.27 [95% CI, 2.15 to 2.40]) compared with no NSAID treatment, and the HR for thromboembolism was also increased (1.36 [CI, 1.27 to 1.45]). The risks for serious bleeding and thromboembolism were increased with NSAID use regardless of HAS-BLED and CHA_2DS_2-VASc score, respectively (**Figure 2**). A total of 6647 serious bleeding events (38.7%) was gastrointestinal, and 3251 (18.9%) were intracranial. The HRs with ongoing NSAID use were 3.54 (CI, 3.29 to 3.82) for gastrointestinal bleeding and 1.22 (CI, 1.03 to 1.44) for intracranial bleeding. Details are provided in **Appendix Table 5** (available at www.annals.org). The HR for all-cause mortality was increased with concomitant NSAID use (**Appendix Table 6**, available at www.annals.org). Of patients hospitalized with nonfatal bleeding, 10 375 were not exposed to an NSAID and 547 were. A poorer prognosis was found in patients exposed to an NSAID at the time of nonfatal bleeding (HR, 1.22 [CI, 1.12 to 1.33]). A dosage above the recommended minimum was associated with a further increase in HRs for bleeding (**Appendix Table 7**, available at www.annals.org).

Sensitivity Analysis

When we restricted the study to years without over-the-counter NSAID availability (1997 to 2001), our results for bleeding risk did not change (data not shown). No important interactions were noted among patients with antithrombotic exposure and concomitant NSAID exposure or different patient subgroups. We found no evidence to suggest that unmeasured confounders had any substan-

Figure 1. **Risks for serious bleeding and thromboembolism at 3 mo and 2 y, with and without 14 d of NSAID exposure.**



Absolute risk differences were reported as NSAID exposure minus no NSAID exposure for each antithrombotic treatment group. The absolute risks were derived from Cox regression analysis, and 95% CIs were determined as quantiles of results in 200 bootstrap samples. "Single antiplatelet" denotes aspirin or clopidogrel. NSAID = nonsteroidal anti-inflammatory drug; OAC = oral anticoagulant.

tial effect on our findings (**Appendix Figure**, available at www.annals.org).

DISCUSSION

This nationwide study is the first, to our knowledge, to suggest an independently increased absolute risk for bleeding associated with 14 days of concomitant NSAID treatment in patients with AF receiving OAC therapy and/or antiplatelet therapy and an elevated absolute risk regardless of NSAID type (such as selective COX-2 inhibitors or nonselective NSAIDs). Thromboembolic risk and the risk for death after a nonfatal episode of serious bleed-

ing during NSAID treatment were also increased. In addition, a high NSAID dosage was associated with incremental risk for bleeding, which suggests a dose–response relationship.

Although concomitant NSAID use with antithrombotic treatment is presumed to increase bleeding risk, this has never been shown for patients with AF and the magnitude of the hazard has never been defined. During a 14-day period of NSAID use compared with no NSAID use, we found absolute risk differences for serious bleeding of 1.9 events per 1000 patients in the overall population and 2.5 events per 1000 patients in those selected for OAC therapy. This suggests a serious bleeding event in 1 of 400 to 500 patients exposed to an NSAID for 14 days. Diclofenac and naproxen were especially associated with substantial bleeding risk. Of note, these data suggest that even short-term (14 days) NSAID treatment was associated with increased risk. Use of an OAC with aspirin or clopidogrel clearly increases bleeding risk in patients receiving warfarin; for example, risk for intracranial bleeding is increased by 2.4-fold (30). We now show that adding an NSAID to OAC therapy is also associated with significant complications in terms of serious bleeding, including intracranial and gastrointestinal bleeding. This absolute risk is even greater if an NSAID is added to an OAC plus aspirin. The HAS-BLED score is clearly increased with NSAID use, which supports the applicability of using these scoring schemes for estimation of bleeding risk profile. A further increase in bleeding was present when a dosage above the recommended minimum was used, suggesting a dose–response relationship. Also, increased mortality is associated with NSAID use at the time of a nonfatal serious bleeding event, which suggests not only that the risk for bleeding is increased with concomitant NSAID use but that NSAIDs are associated with poorer prognosis.

Use of NSAIDs not only was hazardous from a safety perspective but also seems to be related to thromboembolism, as shown in studies of patients with myocardial infarction and congestive heart failure (7, 31, 32). An asso-

Table 2. **Risks for Serious Bleeding and Thromboembolism***

NSAID	Absolute Risk per 1000 Patients (95% CI)	Absolute Risk Difference (95% CI)
Rofecoxib		
3 mo	5.4 (4.4–6.5)	3.8 (2.9–4.9)
2 y	3.6 (2.8–4.7)	2.6 (1.9–3.5)
Celecoxib		
3 mo	2.8 (2.2–3.5)	1.3 (0.8–1.8)
2 y	1.9 (1.4–2.5)	0.9 (0.5–1.3)
Diclofenac		
3 mo	4.7 (4.0–5.5)	3.1 (2.6–3.8)
2 y	3.1 (2.4–4.0)	2.1 (1.6–2.8)
Ibuprofen		
3 mo	3.0 (2.5–3.5)	1.5 (1.1–1.8)
2 y	2.0 (1.6–2.5)	1.0 (0.7–1.3)
Naproxen		
3 mo	4.1 (3.1–5.3)	2.6 (1.7–3.6)
2 y	2.7 (2.0–3.7)	1.7 (1.1–2.6)
Other		
3 mo	2.9 (2.4–3.4)	1.4 (1.0–1.8)
2 y	1.9 (1.5–2.4)	0.9 (0.7–1.2)

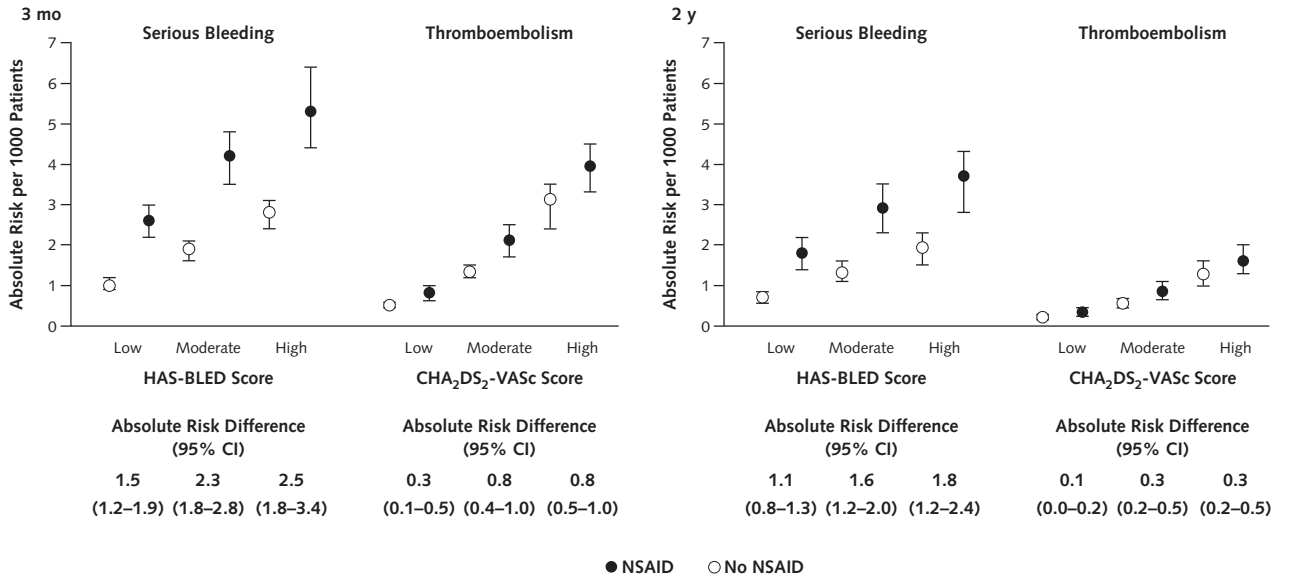
NSAID = nonsteroidal anti-inflammatory drug.
* Within 14 d of NSAID exposure starting at 3 mo and 2 y after inclusion, reported as NSAID exposure minus no exposure. Results were derived from Cox regression analysis, and CIs were based on 200 bootstrap samples.

Table 3. **Hazard Ratios for Serious Bleeding and Thromboembolism, by Antithrombotic Therapy and NSAID***

Variable	Overall	No Treatment	Single Antiplatelet†	Oral Anticoagulant	Oral Anticoagulant + Single Antiplatelet
Serious bleeding					
No NSAID	Reference	Reference	Reference	Reference	Reference
Any NSAID	2.27 (2.15–2.40)	2.39 (2.14–2.67)	2.20 (2.01–2.40)	2.96 (2.64–3.31)	1.92 (1.64–2.26)
Rofecoxib	3.53 (3.00–4.21)	3.10 (2.15–4.46)	4.19 (3.28–5.36)	3.61 (2.44–5.36)	2.06 (0.98–4.32)
Celecoxib	1.85 (1.52–2.26)	1.66 (1.10–2.51)	2.16 (1.63–2.86)	1.38 (0.81–2.33)	1.99 (1.15–3.44)
Diclofenac	3.08 (2.77–3.43)	2.81 (2.24–3.52)	3.53 (2.98–4.19)	3.03 (2.41–3.81)	3.30 (2.51–4.33)
Ibuprofen	1.98 (1.81–2.16)	2.30 (1.94–2.72)	1.58 (1.35–1.85)	3.37 (2.85–3.99)	1.52 (1.15–2.00)
Naproxen	2.69 (2.08–3.48)	3.48 (2.16–5.60)	2.19 (1.39–3.43)	4.38 (2.72–7.05)	1.41 (0.59–3.40)
Other	1.91 (1.69–2.16)	2.15 (1.69–2.73)	1.85 (1.52–2.26)	2.40 (1.84–3.14)	1.52 (1.05–2.21)
Thromboembolism					
No NSAID	Reference	Reference	Reference	Reference	Reference
Any NSAID	1.36 (1.27–1.45)	1.22 (1.08–1.37)	1.25 (1.13–1.37)	1.67 (1.41–1.98)	1.41 (1.07–1.85)
Risk-time, *person-years*‡					
Total	620 125	195 697	188 599	172 070	59 451
NSAID	23 920	8151	8990	4897	1747

NSAID = nonsteroidal anti-inflammatory drug.
* Data are adjusted hazard ratios (95% CIs) unless otherwise indicated.
† Aspirin or clopidogrel.
‡ Total accumulated until death.

Figure 2. **Risks for serious bleeding and thromboembolism at 3 mo and 2 y, by predicted risk and concomitant NSAID use.**



Vertical bars indicate 95% CIs, determined as quantiles of results in 200 bootstrap samples. CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, Stroke, Vascular disease, Sex female; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INRs, Elderly, Drug therapy/alcohol intake; NSAID = nonsteroidal anti-inflammatory drug.

ciation of increased ischemic stroke risk with NSAID use in both low- and high-risk non-AF populations has previously been found (33, 34), but the effect of NSAIDs in patients with AF receiving antithrombotic therapies has never been investigated. Our findings are important because one of the primary goals in AF treatment strategies is to prevent thromboembolic episodes. A recent nonrandomized substudy of patients with deep venous thrombosis and pulmonary embolism that compared a novel OAC (rivaroxaban) with enoxaparin–vitamin K antagonist treatment showed significant increases in clinically relevant bleeding (1.8-fold) and major bleeding (2.4-fold) in patients coadministered NSAIDs and anticoagulation (35).

Our data support previous recommendations that NSAIDs should be discouraged unless other possibilities (such as physical therapy, acetaminophen, or alternative analgesics) have been exhausted. This highlights the double-edged nature of NSAIDs in patients with AF: They not only increase the risk for bleeding but also predispose patients to thromboembolism and seem to cancel the protective effect of OACs on thromboembolism.

Use of NSAIDs is widespread in the general population, and most patients in our study were treated intermittently, with more than 50% being treated for less than 3 weeks (19). Concomitant NSAID use should be a concern for all physicians and other health care providers treating patients with AF, and because of the lack of randomized clinical trials in this field, our data should be taken into account by providers issuing recommendations for management of AF.

Non–vitamin K antagonist OACs (NOACs) have shown a similar or better overall bleeding risk profile compared with warfarin, and physicians might consider a change in thromboprophylaxis from vitamin K antagonists to NOACs in patients needing NSAIDs (36, 37). However, a high dose of dabigatran (150 mg twice daily) resulted in significantly more gastrointestinal bleeding than either warfarin or a 110-mg twice-daily dose, and rivaroxiban was also associated with significantly increased gastrointestinal bleeding risk compared with warfarin (38, 39). Therefore, adding NSAIDs to some new NOACs might pose an even greater risk for gastrointestinal bleeding than adding them to vitamin K antagonists.

Our study has limitations. Although our data set included patients with AF in a nationwide setting (which minimized selection bias) with ongoing use of antithrombotic therapy and NSAIDs, limitations are inherent in the observational design of such studies. Our study population comprised a cohort of unselected patients with nonvalvular AF, and coexisting conditions, such as vascular disease and heart and renal failure, might have influenced the choice of antithrombotic and NSAID treatment. We included only patients with AF discharged from the hospital, and the potential for greater susceptibility to bleeding is present compared with patients with AF seen only in the primary care sector. Although diagnoses of AF, stroke, and many other comorbid conditions have been validated in the National Patient Registry and bleeding diagnoses have shown high accuracy in hospital registries, our outcome defini-

tions were based on discharge coding rather than review of medical charts or diagnostic investigations.

Our definition of serious bleeding ensured that only events severe enough to warrant hospitalization were included. Thus, the estimates of bleeding risk could be considered conservative and do not include minor bleeding events not requiring hospitalization. Because information on bleeding not requiring hospitalization was unavailable, we had no knowledge of episodes resulting in withdrawal of prophylactic life-saving antithrombotic therapy. We did not have any information on the type of AF (paroxysmal, persistent, or permanent), but given that our objective was to investigate bleeding (and thromboembolic) rates associated with use of NSAIDs in addition to antithrombotic medication, this probably did not affect our results. Also, if the AF episode was triggered by an acute illness, this might have resulted in reluctance to initiate antithrombotic treatment. The indication for NSAID use was not available, but because NSAIDs are not indicated for treatment of AF and bleeding hazard is assumed, NSAIDs are most likely to be prescribed to patients less likely to bleed. This would affect our estimates conservatively (that is, minimize confounding by indication). Having users treated with the drugs under investigation before their inclusion may have resulted in confounding by the healthy user effect (when patients without bleeding events during NSAID therapy continue receiving treatment), whereas bleeding events in others result in discontinuation of treatment. Hence, we excluded patients with prior NSAID use. Finally, some potential unmeasured confounders were not accounted for, such as smoking, body mass index, and left ventricular ejection fraction. We also lacked information on INRs, and the possibility of serious bleeding with out-of-range INRs or a further influence on INR control during exposure to an NSAID should be acknowledged when the results are being interpreted. Since 2001, ibuprofen has been the only NSAID available without a prescription in Denmark, and the results for bleeding rates from our primary analysis did not change when we restricted the analyses to before 2001. Aspirin and ibuprofen are available over the counter in limited dosages or quantities, and persistent NSAID and aspirin users would probably claim drugs by physician prescription to receive reimbursement of drug expenses. The calculation of exposure was an approximation. Because an NSAID prescription usually follows an episode of pain, actual consumption would probably be better reflected at the beginning of a treatment course (initial exposure) than at the end of the course when the pain has diminished (prolonged exposure). Over-the-counter drug use probably did not have a major effect on the study results, and a potential bias would only dilute our estimates toward the null. A sensitivity analysis measuring the potential effect of an unmeasured confounder (such as over-the-counter drug use) showed that a confounder would have to be unevenly distributed among the groups and have a strong association with the outcome to affect our results, which probably was not the case in our study (**Appendix Figure**).

In conclusion, our study showed that concomitant use of any NSAIDs carries a substantial independent absolute risk for bleeding and thromboembolism in patients with AF, especially when these drugs are prescribed in addition to antithrombotic therapies. Of note, even short-term NSAID exposure was associated with increased bleeding complications. These results suggest that physicians should exercise caution when prescribing any NSAIDs in patients with AF receiving antithrombotic therapy and should choose safer alternative analgesic agents when possible.

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Appendix Table 1. **ICD Codes**

Variable	Definition	Diagnostic Code or Treatment
Atrial fibrillation	Diagnosis	ICD-10: I48 ICD-8: 42793, 42794
Comorbid conditions		
Thromboembolism	Diagnosis, including ischemic stroke, transient ischemic attack, and arterial systemic thromboembolism	ICD-10: I63, I64, I26, I74, G458, G459 ICD-8: 433–438, 444, 450
Vascular disease	Diagnosis, including myocardial infarction, aortic plaque, and peripheral arterial disease	ICD-10: I21, I22, I700, I702–I709 ICD-8: 410, 440
Alcohol abuse	Diagnosis and adverse alcohol consumption reported during hospitalization	ICD-10: E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721
Liver disease	Diagnosis of liver cancer, chronic liver disease, liver surgery, cirrhosis, or hepatitis	ICD-10: B15–B19, C22, D684C, I982B, K70–K77, DQ618A, Z944
Osteoarthritis	Diagnosis	ICD: M19
Peptic ulcer	Diagnosis	ICD: K25–K27, K29
Diabetes mellitus	Treatment	Glucose-lowering medication
Hypertension	Combination treatment with ≥2 classes of antihypertensive drugs*	Adrenergic α-antagonist, nonloop diuretic, vasodilator, β-blocker, calcium-channel blocker, or renin–angiotensin system inhibitor
Heart failure	Diagnosis plus treatment	ICD-10: I110, I42, I50, J819 ICD-8: 425, 4270, 4271 Treatment with loop diuretic
Chronic renal failure	Diagnosis of chronic glomerulonephritis, chronic tubulointestinal nephropathy, non–end-stage chronic kidney disease, or diabetic and hypertensive nephropathy	ICD-10: E102, E112, E132, E142, I120, M200, M313, M319, M321B, N02–N08, N11, N12, N14, N18, N19, N26, N158–N160, N162–N164, N168, Q612, Q613, Q615, Q619 ICD-8: 403, 404, 580–584, 590, 223, 25002, 40039, 59009, 59320, 75310, 75311, 75319
Bleeding	Diagnosis of gastrointestinal, intracranial, respiratory, or urinary tract bleeding; anemia caused by bleeding	ICD-10: I60–I62, I690–I692, J942, K250, K254, K260, K264, K270, K280, K920–K922, N02, R04, R31, S064–S066 ICD-8: 430–432
Outcomes		
Bleeding	Death from or diagnosis of gastrointestinal, intracranial, respiratory, or urinary tract bleeding; anemia caused by bleeding	ICD-10: I60–I62, I690–I692, J942, K250, K254, K260, K264, K270, K280, K920–K922, N02, R04, R31, S064–S066
Thromboembolism	Death from or diagnosis of thromboembolism, including ischemic stroke and systemic arterial embolism	ICD-10: I63, I64, I74

ICD-8 = International Classification of Diseases, Eighth Revision; ICD-10 = International Classification of Diseases, 10th Revision.
* Positive predictive value of 80.0% and specificity of 94.7% (14).

Appendix Table 2. ATC Codes

Treatment	Code	Comment
Oral anticoagulant	BO11AA03–4	Vitamin K antagonists, including warfarin and phenprocoumon
Aspirin	BO1AC06, NO2BA01	Acetylsalicylic acid
Clopidogrel	BO1AC04	–
NSAID	M01A	Includes rofecoxib (M01AH02), celecoxib (M01AH01), naproxen (M01AE02), diclofenac (M01AB05), and ibuprofen (M01AE01); excludes glucosamine (M01AX05)
Statin	C10A	–
β-Blocker	C07	–
Renin–angiotensin system inhibitor	C09	Includes angiotensin-converting enzyme inhibitors and angiotensin II–receptor blockers
Loop diuretic	C03C	–
Thiazide	C03A	–
Antiarrhythmic drug	C07, C08, C01AA05, C01BD01, C07AA07, C01BC	Includes β-blockers, calcium-channel blockers, digoxin, amiodarone, sotalol, and class 1C drugs
Proton-pump inhibitor	A02BC	–
Oral glucose-lowering drug	A10	–
Glucocorticoid	H02AB	Includes prednisolone

ATC = Anatomical Therapeutic Chemical Classification System; NSAID = nonsteroidal anti-inflammatory drug.

Appendix Table 3. Results From the Multivariable Analysis of Bleeding and Thromboembolic Risk*

Covariate	HR (95% CI)	
	Bleeding	Thromboembolism
Age (per 1-y increase)	1.05 (1.05–1.05)	1.05 (1.05–1.05)
Male sex	1.41 (1.37–1.46)	0.93 (0.91–0.96)
Hypertension	1.06 (1.03–1.10)	1.08 (1.05–1.11)
Chronic renal failure	1.68 (1.57–1.80)	–
Liver failure	1.52 (1.36–1.69)	–
Previous stroke	1.11 (1.07–1.16)	–
History of alcohol misuse	1.76 (1.63–1.90)	–
Previous bleeding event	2.12 (2.03–2.22)	–
Heart failure	–	1.07 (0.99–1.08)
Diabetes	–	1.31 (1.25–1.38)
Previous embolism	–	3.14 (3.05–3.24)
Vascular disease	–	1.11 (1.07–1.15)

HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.
* Estimated covariates from the primary Cox regression models are shown. The estimates for antithrombotic therapy and concomitant NSAID use are reported in **Figure 1**. Year of inclusion (1997–2011) was used as a categorical covariate in the model and is not shown in the table. Definitions of comorbidity are provided in **Appendix Tables 1** and **2**.

Appendix Table 4. Adherence to NSAID Therapy*

Period Receiving NSAID, *d*	Prescription Periods†, *n*	Patients Still Receiving NSAID, %
0–6	254 124	100
7–13	218 162	86
14–20	162 829	64
21–27	113 576	47
28–34	94 870	37
35–41	65 967	26
42–48	57 879	23
49–55	51 324	20
56–62	30 070	12
63–69	24 986	10
70–76	21 660	9
77–83	19 357	8
84–90	16 668	7
>90	15 146	6

NSAID = nonsteroidal anti-inflammatory drug.
* Includes 53 732 patients (35.6%) who filled ≥1 NSAID prescription and were followed in 7-d intervals.
† Uninterrupted NSAID exposure (based on prescription claims).

Appendix Table 5. HRs for Gastrointestinal and Intracranial Bleeding, by Antithrombotic Therapy and Concomitant NSAID Use*

Variable	Adjusted HR (95% CI)			
	No Treatment	Single Antiplatelet†	Oral Anticoagulant	Oral Anticoagulant + Single Antiplatelet
Intracranial bleeding				
No NSAID	Reference	Reference	Reference	Reference
Any NSAID	1.36 (0.99–1.87)	0.96 (0.69–1.33)	1.80 (1.35–2.35)	1.04 (0.62–1.78)
Gastrointestinal bleeding				
No NSAID	Reference	Reference	Reference	Reference
Selective COX-2 inhibitor	2.87 (1.97–4.18)	4.33 (3.42–5.47)	3.79 (2.41–5.97)	2.87 (1.54–5.35)
Nonselective NSAID	3.75 (3.14–4.48)	3.20 (2.76–3.70)	6.26 (5.20–7.54)	3.48 (2.70–4.47)
Other NSAID	2.73 (1.95–3.82)	2.63 (2.05–3.39)	4.53 (3.15–6.51)	2.45 (1.50–4.02)

COX-2 = cyclooxygenase-2; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.
* Among 150 900 patients with atrial fibrillation.
† Aspirin or clopidogrel.

Appendix Table 6. HRs for All-Cause Mortality, by Antithrombotic Therapy and Concomitant NSAID Use

Variable	Adjusted HR (95% CI)*			
	No Treatment	Single Antiplatelet†	Oral Anticoagulant	Oral Anticoagulant + Single Antiplatelet
No NSAID	Reference	Reference	Reference	Reference
Any NSAID	1.40 (1.32–1.47)	1.48 (1.42–1.55)	1.70 (1.54–1.88)	1.41 (1.21–1.64)

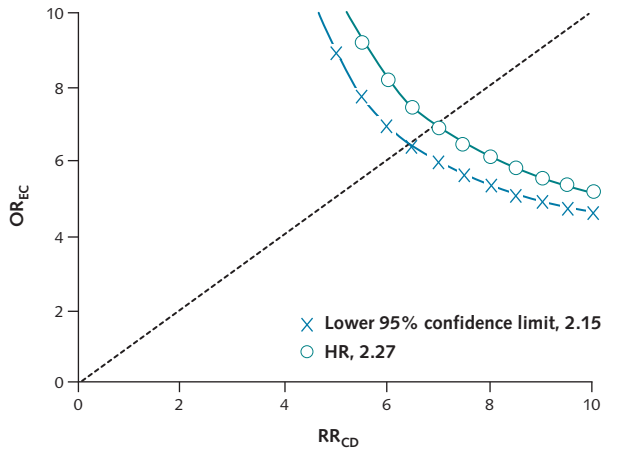
HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.
* Adjusted for age, sex, year of inclusion, hypertension, chronic kidney disease, history of alcohol misuse, liver failure, previous bleeding, and stroke.
† Aspirin or clopidogrel.

Appendix Table 7. HRs for Serious Bleeding, by Antithrombotic Therapy and NSAID Dosage*

NSAID†	Adjusted HR (95% CI)			
	No Treatment	Single Antiplatelet‡	Oral Anticoagulant	Oral Anticoagulant + Single Antiplatelet
Rofecoxib				
≤25 mg	2.98 (2.01–4.41)	4.21 (3.24–5.46)	3.66 (2.43–5.52)	2.24 (1.07–4.70)
>25 mg	4.15 (1.55–11.07)	4.08 (1.94–8.57)	–	–
Celecoxib				
≤200 mg	1.98 (1.27–3.07)	2.09 (1.50–2.90)	1.39 (0.77–2.50)	1.91 (1.03–3.56)
>200 mg	–	2.39 (1.39–4.13)	–	–
Diclofenac				
≤100 mg	2.20 (1.67–2.90)	3.19 (2.62–3.88)	2.57 (1.97–3.35)	2.76 (2.01–3.81)
>100 mg	6.09 (4.14–8.95)	5.29 (3.75–7.45)	6.33 (4.04–9.94)	6.42 (3.86–10.67)
Ibuprofen				
≤1200 mg	1.99 (1.62–2.45)	1.54 (1.28–1.85)	3.05 (2.51–3.70)	1.41 (1.04–1.93)
>1200 mg	3.40 (2.53–4.58)	1.72 (1.26–2.33)	4.96 (3.56–6.92)	2.00 (1.13–3.52)
Naproxen				
≤500 mg	2.03 (0.76–5.40)	1.57 (0.75–3.29)	3.09 (1.29–7.43)	–
>500 mg	4.46 (2.59–7.69)	2.84 (1.61–5.00)	5.30 (3.01–9.34)	–

HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.
* Only includes estimates for >3 events.
† Reported dosages are daily totals.
‡ Aspirin or clopidogrel.

Appendix Figure. **Estimation of effect of unmeasured confounders.**



"OR_{EC}" denotes the association between the confounder and NSAID use, and "RR_{CD}" denotes the association between the confounder and the outcome. The blue line indicates the magnitude needed for an unmeasured confounder to render the results statistically insignificant at a given OR_{EC} and RR_{CD}. The green line indicates the corresponding magnitude of an unmeaured confounder needed to nullify the results. The estimated HR for bleeding with NSAID therapy compared with no NSAID therapy (reference) is 2.27 (95% CI, 2.15 to 2.40). The blue line shows that an unmeasured confounder should be 6 times more prevalent among patients exposed to NSAIDs and be associated with a 6-fold increase in risk for bleeding to explain the effect of NSAID therapy compared with no NSAID therapy. HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.