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a nationwide study

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Risk of gastrointestinal bleeding associated with oral anticoagulation and non-steroidal anti-inflammatory drugs in patients with atrial fibrillation: a nationwide study

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Abstract

Aims: Non-vitamin K antagonist oral anticoagulants (NOACs) are displacing Vitamin K antagonists (VKAs) for stroke prophylaxis in patients with atrial fibrillation (AF). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) could increase gastrointestinal bleeding (GIB) risks among these patients. The aim of this study was to examine the risk of GIB among Danish AF patients taking oral anticoagulants (OACs) and NSAID.

Methods and **results:** Using nationwide administrative registries, we determined concomitant NSAID use among anticoagulant-naïve patients with AF initiating OACs between August 2011 and June 2017. We calculated short-term absolute risks differences and hazard ratios (HRs) for GIB based on multiple adjusted cause-specific Cox regressions with time-dependent NSAID treatment.

Among 41,183 patients (median age 70 years (IQR 64-78); 55% men), 21% of patients on NOACs and 18% on VKA were co-prescribed NSAIDs. The differences in absolute risk (95% Confidence Interval (CI)) of GIB within 14 days of commencing concomitant NSAID therapy (*versus* no concomitant NSAID therapy) were 0.10% (0.04%-0.18%) for NOACs and 0.13% (0.03%-0.24%) for VKA. NOACs overall were associated with less GIB than VKA (HR 0.77 [95% CI 0.69-0.85]). Compared with OACs alone, concomitant NSAIDs doubled the GIB risk associated with NOACs overall (HR 2.01 [95% CI 1.40-2.61] and with VKA (HR 1.95 [95% CI 1.21-2.69]).

Conclusion: Among this nationwide AF population taking OACs, concomitant NSAID therapy increased the short-term absolute risk of GIB. NOACs alone were associated with lower GIB risks than VKA but concomitant NSAIDs abolished this advantage. The findings align with post-hoc analyses from randomized studies. Physicians should exercise appropriate caution when prescribing NSAIDs for patients with AF taking NOACs or VKA.

Key words: atrial fibrillation, NSAID, antithrombotic treatment, prognosis

Introduction

For decades, vitamin K antagonists (VKAs), commonly warfarin, have been the preferred treatment for stroke prophylaxis in patients with atrial fibrillation (AF).[1] More recently, the non-vitamin-K-antagonist oral anticoagulants (NOACs) are available as alternatives. In Denmark, dabigatran, a direct thrombin inhibitor, was marketed for AF in August 2011 followed by the Factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, in February 2012, January 2013 and June 2016 respectively. Unlike VKAs, NOACs do not need frequent monitoring with blood tests. Their uptake has been rapid.[2, 3] While they have similar or safer overall bleeding risk profiles compared with VKAs, some have been associated with significantly more gastrointestinal bleeding than warfarin.[4-9]

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective, widely-used analgesics. Much attention has been given to their gastrointestinal safety and consequently, the incidence of NSAID-associated upper gastrointestinal bleeding has fallen.[10-12] Despite this, the case-fatality rate has not declined.[13] When co-prescribed with warfarin for cardiovascular patients, NSAIDs have been associated with a substantial independent risk of bleeding, even with short term use (<14 days).[14, 15] Although NSAIDs are discouraged in people with cardiovascular disease, pain is common and in the absence of more effective, safer anti-inflammatory analgesics, they are frequently prescribed.[14, 16, 17] Although NSAID is a well-recognized risk factor for bleeding in patients with AF, and included in the HASBLED score, the risk of gastrointestinal bleeding associated with concomitant NOAC and NSAID prescribing has not been investigated. As both drug groups are in widespread use, any risk is of considerable public health concern. We therefore examined the risk of gastrointestinal bleeding associated with NSAID therapy added to a VKA or NOAC among patients with AF in a nationwide cohort.

Methods

Data sources

In Denmark, each resident is registered with a unique, permanent identification number that enables individual-level linkage between several nationwide administrative registries. Four were linked at individual patient level in this study. The Danish National Patient Registry holds data on all hospital admission since 1978. Each admission is registered with one main discharge diagnosis and, if appropriate, one or more supplementary diagnoses using the International Classification of Diseases (ICD-8 until 1994; ICD-10 from 1994).[18] The civil registration registry records vital status data. The National Prescription Registry holds information on the date of dispensing, quantity, strength, and formulation of all prescriptions dispensed from Danish pharmacies since 1995 and is based on the Anatomical Therapeutic Chemical (ATC) system. Pharmacies must register each drug dispensing in the prescription registry for cost reimbursement ensuring complete registration.[19] 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 (20 tablets). All other NSAIDS analysed were available by prescription only. The ATC and ICD codes are reported in Supplementary Table 1.

Study population and follow up

We identified a cohort of oral anticoagulant (OAC)-naïve patients aged 30-95 years with AF on the day they claimed a first-time prescription for VKA (i.e. warfarin or phenprocoumon), dabigatran, rivaroxaban, or apixaban between August 22nd, 2011 and June 30th 2017.[20] The date of first-time OAC prescription claim defined the inclusion day. We defined doses of apixaban 5mg twice daily, dabigatran 150mg twice daily and rivaroxaban 20mg once daily as standard dosage and corresponding doses of 2.5mg, 110mg and 15mg as reduced dosage. The exclusion criteria were:

history of valvular disease (e.g. mitral stenosis); total hip or knee arthroplasties within five weeks before inclusion day; pulmonary embolism or deep vein thrombosis within six months before inclusion day; or two prescriptions of different OACs claimed at inclusion. Very few patients claimed edoxaban which was also excluded. The diagnosis of AF in the National Patient Registry is validated with a positive predictive value of 99%. [21]

NSAID Treatment

We identified all claimed prescriptions for the NSAIDs most commonly prescribed in Denmark: celecoxib, diclofenac, ibuprofen, and naproxen. Patient exposure was calculated by estimating a daily dose after comparing the accumulated dose and the elapsed time from consecutive prescriptions for each drug. Ongoing exposure was then calculated by dividing the number of tablets dispensed by the estimated average dosage. If only one prescription was registered for a patient, a standard dose, defined as the minimal recommended dose, was used to estimate the daily dose. We defined exposure as the time during which patients had medication available and discontinuation as the time at which patients had no more medication available. The method has been described previously.[22-24]

For most patients, treatment regimens changed during the study period. The NSAID exposure was therefore created as time-varying covariates. Patients were allowed in only one NSAID drug exposure group at a time but could change groups according to claimed prescriptions. To characterize the study population according to NSAID use, we also defined use as any prescription within 180 days from OAC initiation.

Comorbidity and concomitant pharmacotherapy

Comorbidities were defined from ICD codes recorded within 10 years prior to inclusion day. Concomitant pharmacotherapy was identified by ATC codes of prescriptions dispensed 180 days before inclusion day (Supplementary Table 1). The CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age >=75 years, Diabetes, Stroke/Transient ischemic attack (TIA), Vascular disease, Age 65-74 years, Female sex) score was defined from the registries as described previously.[25] The score accurately predicts stroke risk in AF populations.[22] Similarly, bleeding risk was defined using a modified HAS-BLED (Uncontrolled hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile international normalized ratio (INR), Elderly [>=65 years], Drugs [NSAIDs, antiplatelet agents, alcohol intake]) score.[25] Labile INR' was omitted, because INR values were not recorded in the registries. NSAIDs were also omitted as this was a main explanatory variable. Antiplatelet treatment at baseline was defined by prescription of acetylsalicylic acid or non-acetylsalicylic acid (clopidogrel, ticagrelor, prasugrel, dipyramadol) agents in the 6-months prior to inclusion.

Outcome

The primary outcome of gastrointestinal bleeding was defined as hospitalization for bleeding gastrointestinal ulcer, hematemesis, melena, or unspecified gastrointestinal bleeding from the Danish National Patient Registry.[26] The register do not provide data on bleeding severity other than fatal and non fatal. A fatal gastrointestinal bleed was defined if the patient died the same day as hospitalization or within 30 days. Occurrence and type of bleeding as recorded in hospital databases have shown a positive predictive value of 89%-99%.[27]

Statistical analysis

For each year during the study period (2011-2017), the rates of (concomitant) use of NSAID before and after the date of OAC initiation were calculated as number of NSAID users per 100 person-years within 180 days before and after OAC initiation.

For the main analysis, patients were included between January 1, 2012 and December 31, 2015 and followed for 2 years until June 30, 2017 or until the occurrence of gastrointestinal bleeding, death, switch to another OAC, or OAC discontinuation (defined as 30 days after unavailability of tablets). The restriction of the study period (2012-2015) was used to guarantee that all OACs were on the market and prescribed sufficiently to allow an analysis. Baseline was set as the OAC treatment start date (inclusion day).

Multiple Cox regression was used to associate current treatment regime with the rates of gastrointestinal bleeding where concomitant NSAID therapy was treated as a time-varying covariate. A second Cox regression model was used to associate the current treatment regime with the hazard rate of the competing risk (all-cause death without bleeding). We adjusted both models for year, age (grouped), sex, and all the individual components in the modified HASBLED model: chronic kidney disease, alcohol abuse, hypertension, previous bleeds, concomitant aspirin/anti-platelet treatment, stroke and abnormal liver function. We reported hazard ratios (HRs) with 95% confidence intervals (CIs). Based on the Cox regression models for bleeding and death, we also calculated the patient-specific absolute risks of gastrointestinal bleeding during a 14-day period of concomitant NSAID therapy (versus no concomitant NSAID therapy) see supplementary Figure 1 for the formula.[28] We reported the differences in absolute 14-day risks (ARD) for the periods 90-104 days and 365-379 days after inclusion day as average treatment effects, among all patients.

Confidence intervals for ARDs were obtained based on 1,000 bootstrap data sets.

As sensitivity analyses, we included all patients with OAC initiation in the period August 22, 2011 through June 30, 2017 and performed analyses for standard and reduced NOAC dosages when NSAID therapy was added. The level of statistical significance was set at 5%. Data management and statistical analyses were performed using SAS 9.4,(SAS Institute), Stata 11.0 (StataCorp) and R [R Foundation for Statistical Computing; https://www.R-project.org].

Ethics

In Denmark by law, retrospective registry studies do not require ethics approval. The Danish Data Protection Agency approved this study (No 2007-58-0015; GEH-2014-014, I-Suite 02732) and provided the data in anonymized form.

Results

During the observation period (Figure 1), NSAID use decreased during the 180 days following OAC initiation compared with the same period prior to initiation (Figure 2). NOACs displaced VKA as the anticoagulants of choice among patients with AF (Figure 3A). By 2017 some 90% of those newly-initiated OACs were prescribed a NOAC compared with 10% prescribed VKA. Co-prescribing of NSAIDs with OACs declined slightly over time, but compared with patients taking VKA, greater proportions taking NOACs were co-prescribed a NSAID, mean 18% *versus* 21% in 2016 (Figure 3B).

In total, 41,183 patients with AF in the period January 1, 2012 until December 31, 2015 were included in the study (Figure 1). The mean age was 70.2 years (standard deviation 11.1, median age 70 years, interquartile range 64-78)) and 54.6% were men. Some 16,722 (40.6%) used VKA, 7,158 (17.4%) apixaban, 5,665 (13.7%) rivaroxaban, and 11,638 (28.3%) dabigatran. The proportions of patients prescribed reduced NOAC dosages were 36%, 27%, and 39% for apixaban, rivaroxaban and dabigatran, respectively. During the study period 3,317 (8.1%) died while 5,450 (13.2%) switched to another OAC and 14,204 (34.5%) discontinued OAC treatment.

Gastrointestinal Bleeding

There were 1,642(4.0%) gastrointestinal bleeding events among the study cohort during follow-up of which 213 (13,0%) were fatal during hospitalization. Ninety days after the inclusion, the differences in absolute risk of GIB within 14 days with *versus* without concomitant NSAID therapy were 0.10 (0.04-0.18) for NOAC and 0.13(0.03-0.24) for VKA. (Figure 4)

Compared with VKA alone, NOACs overall were associated with lower rates of gastrointestinal bleeding (HR 0.78 [95%CI 0.70-0.86]) but concomitant NSAID therapy significantly increased the

rates in both cases: NOACs overall, HR 2.01 [95% CI 1.40-2.61]; VKA, HR 1.95 [95% CI 1.21-2.69].

Compared with the individual OAC treatments alone, concomitant NSAIDs conferred a significantly elevated HR of gastrointestinal bleeding for apixaban (HR 2.98[95%CI 1.51-4.44]) and VKA (HR 1.95 [95%CI 1.21-2.69]), with similar trends also for dabigatran (HR 1.52 [95%CI 0.76-2.28] and rivaroxaban (HR 1.94 [95%CI 0.77-3.12]) (Figure 4).

Supplemental analyses

For the period August 22, 2011 through June 30, 2017, we included 60,523 patients with 2,164 gastrointestinal bleeding events. For individual OAC regimens, concomitant NSAID therapy was associated with significantly elevated HRs for apixaban (HR 2.88 [95% CI 1.90-4.35]), rivaroxaban (HR 1.64 [95% CI 1,00-2.45]), dabigatran (HR 1.61 [95% CI 1.02-2.55])), and VKA (HR 2.08 [95% CI 1.49-2.91]) compared with each OAC on its own. Analyses for NSAIDs added to standard or reduced NOAC dosages had similar results to the main analyses (please see Supplemental Table 2) We made a stratified analyses with and without antiplatelets agents. The results remained the same (please see Supplemental Table 3). Furthermore we made a stratified analysis if PPI use was present at baseline (Please see Supplemental Table 4).

Discussion

Our Danish nationwide study including 41,183 OAC-naïve patients with AF initiating VKA or NOAC treatment found that concomitant NSAID therapy was associated with a doubling of the risk of gastrointestinal bleeding compared with an OAC alone. While significant the added risk was also modest for a typical couse of therapy of two weeks as shown in figure 4.

People with AF have increased risk of stroke and thromboembolism.[29] The risk is reduced with anticoagulation but at the cost of increased bleeding risks. While NOACs are associated with lower overall rates of bleeding than warfarin, the randomized studies found this was due mainly to decreased intracerebral bleeding and there was no clear advantage in respect of gastrointestinal bleeding.[4-6] Both Kent *et al* and Davidson *et al* found in post-hoc analyses of RE-LY and EINSTEIN study data that use of NSAIDs among patients taking OACs was associated with increased risk of major bleeding, including gastro-intestinal bleeding, compared with non-use.[30,31] Our observational study showed that NOACs were associated with less gastrointestinal bleeding than VKA but concomitant NSAIDs abolished this advantage.[30,31] Unlike warfarin, antidotes for NOAC-associated bleeding are agent-specific; idarucizumab for dabigatran reversal is approved by US and European medicines regulators, while andexanet alpha is approved in the US for apixaban- and rivaroxaban-associated bleeding and is awaiting approval in Europe.[32, 33] Nevertheless, in Denmark as in other countries, NOACs are increasingly the preferred anti-coagulation option in newly diagnosed AF.[3]

The absolute risk with dabigatran was 0.05 (0.02-0.15). It is lower than apixaban and rivaroxaban. Dabigatran has previously been showed to have a higher risk of GI bleeding, The reason we found a lower risk might be the fact that people with risk of GI bleeding would be prescribed with a reduced

dose and one of the other NOACs. (Supplemental table 2). Previous studies have found same results with reduce dosis of Dabigatran.

We have previously shown that NSAIDs co-prescribed with warfarin confer a substantial independent risk of bleeding in AF patients.[14] The current study, which includes a more contemporary AF population, shows that the risk extends to NOACs. Despite this, NSAID prescribing was consistently higher among patients on NOACs than among those on VKA.

Non-variceal upper gastrointestinal bleeding and mortality rates have fallen over the past twenty years, attributed partly to more judicious use of NSAIDs, but the case fatality rate has remained constant at around 5%-6%.[13,29] This appears to be related to pre-existing co-morbidities as well as to bleeding events acutely. In this study among patients at risk of bleeding owing to factors including anticoagulant use, older age, and multiple co-morbidities, 13% of those experiencing gastrointestinal bleeding died during hospitalization. Patients who were prescribed concomitant NSAIDs had significantly greater risk of associated bleeding compared with those prescribed an OAC without a concomitant NSAID. The finding that NSAIDs were co-prescribed to 14.6% of people taking OACs and that those taking NOACs had higher rates of co-prescribing than those taking VKA is therefore of substantial public health concern given the widespread use of both OACs and NSAIDs and the age and co-morbidity profiles of the patients.

NSAID co-prescribing may reflect misconceptions about the relative safety of NOACs and warfarin and application of overall bleeding risk data for NOACs to individual bleeding sites. Treatment information for both prescribers and patients does not emphasise gastrointestinal (or other) bleeding risks potentially associated with NOAC and NSAID co-prescribing. In the US, Food and Drug

Administration (FDA) summaries of product characteristics (SpCs) for NOACs note (Sections 5 and 7) that 'drugs affecting haemostasis may increase risk of bleeding' and include 'NSAIDs', some SpCs specifying 'chronic' NSAID use only (apixaban and dabigatran).[34-37] Patient Information Leaflets list drugs where concomitant use increases bleeding risk. All include NSAIDs as a group but provide no examples of named agents and 'long-term or chronic' use, as opposed to any use, is specified for apixaban and dabigatran.

The European Medicines Agency (EMA) SpCs for NOACs (Sections 4.4, 4.5) issue general cautions on 'care' when prescribing other medicinal products affecting haemostasis. For both apixaban and rivaroxaban, the SpC advises that "Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid)", and for dabigatran, notes that 'chronic use' but not short-term peri-operative use of NSAIDs with dabigatran increased bleeding risk.[38-41] Patient Information Leaflets counsel patients to 'tell your doctor or pharmacist' about multiple concomitant medicines including 'anti-inflammatory or pain-relieving' treatments, naming two examples, naproxen and acetylsalicylic acid.

In contrast, warfarin SpCs and Patient Information Leaflets include considerably stronger warnings about NSAID-associated bleeding risks and name commonly used NSAIDs.[42-43]

In the context of one in six AF patients initiating NOACs being prescribed concomitant NSAIDs within two years and the associated doubling of gastrointestinal bleeding risks found among the cohort studied here, it seems prudent to urgently strengthen concomitant medication cautions for prescribers and patients alike so that they are at least equivalent to those for warfarin.

Limitations

The main limitation of this study was the observational design. There is a lack of information about important clinical parameters serum creatinine, haemoglobin, INR, and body mass index. In the nationwide prescription registry, all Danish pharmacies are required to register all dispensed prescriptions, ensuring complete registration. Not all prescription NSAIDs were examined, but rather only those NSAIDS that were "most commonly" prescribed in Denmark. The only NSAID available in Denmark without a prescription is ibuprofen. Patients who used OTC ibuprofen only would be classified as nonusers, because they do not claim a prescription in the study period. However, we believe this potential misclassification had only a small, if any, influence on the findings. Furthermore, if there was a significant effect of OTC use on our results, this would influence the results by moving the risk estimates toward the null and hence dilutes any association between exposure and outcome. We did not have information on whether patients stopped taking OACs when treated with NSAIDs but given treatment guidelines, this was unlikely. We selected 14-day windows following prescription dispensings to be as sure as possible that the patients were likely to be taking NSAID treatment. Furthermore, the time-frame of 14 days allowed comparison of all the individual groups in the same way. We could not exclude possible effects of unmeasured confounders. Among potential confounders, data were unavailable on serum creatinine, haemoglobin, INR, and body mass index. We did not have information about the NSAID treatment indication, but as NSAIDs are not indicated for heart disease, this was likely to be for non-cardiac disease.

Another limitation is the effect of information bias. The patients do not necessarily take their medications consecutively, leading to the fact that the prescription may run longer and the patients therefore are exposed later than the database might indicate. There would be no measurable consequences for the rest of the population, because data from individuals taking therapy without

being identified as being on a prescription would be diluted in the data from the much larger population not on therapy.

We defined discontinuation as no consecutive dispensed prescription of the initiated OAC within 30 days after the end of a package. Discontinuation or treatment switching might arise due to side effects or unexpected outcomes that could under- or over-estimate the associated risk of gastrointestinal bleeding. We stopped following patients who discontinued or switched OAC treatment and thereby tried to overcome the associated problems. The definition of fatal events in our data set was hospitalization with gastrointestinal bleeding and death from any cause within 30 days. Indeed, any hospitalization is associated with increased mortality in studies such as ours and the possibility exit that patients could have been hospitalized for more than one condition (e.g. admitted with pneumonia/sepsis, then developing gastrointestinal bleeding in the intensive care unit – predicted mortality for such a patient would be quite high). Compared to the randomized trials, we did not have the possibility to adjudicate events through assessment of charts, procedures or other follow-up. Together with inclusion of non-selected individuals (compared to the often lower risk and homogenous inclusion in trials), we believe this readily explain the difference of the case-fatality rate between trials and our observational study.

Conclusions

Among Danish AF patients prescribed NOAC treatment, concomitant NSAID therapy was associated with a doubling of the risk of gastrointestinal bleeding compared with NOAC treatment alone. This aligns with findings from post-hoc analyses of data from large randomised trials that evaluated NOACs, RE-LY and EINSTEIN.

In our study, patients prescribed NOACs were more likely than those prescribed VKA to be co-prescribed NSAIDs. As patients with AF taking OACs are already at increased risk of gastrointestinal bleeding compared with background rates in the population at large, further unintended or un-necessary increase in their risks is a public health concern. Given trends towards increasing use of NOACs rather than VKA in AF, prescribers should be reminded of current evidence that NOACs are not superior to warfarin in respect of gastrointestinal bleeding risks and should exercise high levels of caution when prescribing NSAIDs for AF patients taking NOACs. Strengthening of prescribing and patient information regarding the risks of NOAC-NSAID co-prescribing are likely to be of public health benefit.

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http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

40. European Medicines Agency. Rivaroxaban
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf

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Table 1 Study population characteristics of the individual treatment groups without and with concomitant NSAID therapy at the date of first-time OAC prescription

	VKA	VKA+NSAID	Apixaban	Apixaban+ NSAID	Rivaroxaban	Rivaroxaban+ NSAID	Dabigatran	Dabigatran+NSAID
Characteristic	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total patients	16024	698	6850	308	5433	232	11092	546
Reduced dosage	-	-	2512(36.7%)	83(27.0%)	1443(26.6%)	66(28.5%)	4362(39.3%)	185 (33.88)
Age, median (IQR)	71 (64, 78)	69 (63, 77)	72 (65, 80)	68 (62, 77)	71 (64, 80)	70 (63, 76)	69 (63, 77)	67 (61, 75)
Sex	9196 (57.4%)	418 (59.9%)	3420 (49.9%)	173(56.2%)	2738 (50.4%)	122 (52.6%)	6163 (55.6%)	326 (59.7%)
Year								
2012	4792 (29.9%)	238 (34.1%)	0 (0.0%)	0 (0.0%)	329 (6.1%)	19 (8.2%)	3371 (30.4%)	162 (29.7%)
2013	4406 (27.5%)	179 (25.6%)	487 (7.1%)	27 (8.8%)	1289 (23.7%)	48 (20.7%)	3680 (33.2%)	176 (32.2%)
2014	3652 (22.8%)	155 (22.2%)	2298 (33.5%)	102 (33.1%)	1304 (24.0%)	55 (23.7%)	3014 (27.2%)	149 (27.3%)
2015	3174 (19.8%)	126 (18.1%)	4065 (59.3%)	179 (58.1%)	2511 (46.2%)	110 (47.4%)	1027 (9.3%)	59 (10.8%)
CHA2DS2-VASc								
High (>1)	12685 (79.2%)	547 (78.4%)	5609 (81.9%)	238 (77.3%)	4346 (80.0%)	183 (78.9%)	8299 (74.8%)	404 (74.0%)
Int (1)	2217 (13.8%)	105 (15.0%)	880 (12.8%)	51 (16.6%)	787 (14.5%)	39 (16.8%)	1850 (16.7%)	88 (16.1%)
Low (0)	1122 (7.0%)	46 (6.6%)	361 (5.3%)	19 (6.2%)	300 (5.5%)	10 (4.3%)	943 (8.5%)	54 (9.9%)
Modified Hasbled								

High (>2)	6624 (41.3%)	265 (38.0%)	2858 (41.7%)	116 (37.7%)	2142 (39.4%)	87 (37.5%)	3710 (33.4%)	183 (33.5%)
Int (2)	7796 (48.7%)	360 (51.6%)	3411 (49.8%)	164 (53.2%)	2828 (52.1%)	123 (53.0%)	6009 (54.2%)	287 (52.6%)
Low (0-1)	1604 (10.0%)	73 (10.5%)	581 (8.5%)	28 (9.1%)	463 (8.5%)	22 (9.5%)	1373 (12.4%)	76 (13.9%)
Hypertension	10348 (64.6%)	483 (69.2%)	4380 (63.9%)	205 (66.6%)	3449 (63.5%)	159 (68.5%)	6599 (59.5%)	339 (62.1%)
Stroke	2270 (14.2%)	93(13.3%)	1421 (20.7%)	49 (15.9%)	984 (18.1%)	29 (12.5%)	1662 (15.0%)	64 (11.7%)
Cronic kidney disease	1308 (8.2%)	44 (6.3%)	322(4.7%)	13 (4.2%)	199 (3.7%)	12 (5.2%)	210 (1.9%)	10 (1.8%)
Vascular diease	2308 (14.4%)	75 (10.7%)	703 (10.3%)	31 (10.1%)	481 (8.9%)	20 (8.6%)	999 (9.0%)	41 (7.5%)
Prior Bleeding	1973 (12.3%)	77 (11.0%)	908 (13.3%)	42 (13.6%)	605 (11.1%)	21 (9.1%)	1186 (10.7%)	54 (9.9%)
Liver failure	258 (1.6%)	17(2.4%)	99 (1.4%)	3(1.0%)	66 (1.2%)	3 (1.3%)	122 (1.1%)	6 (1.1%)
Alcohol	495 (3.1%)	26(3.7%)	239 (3.5%)	9 (2.9%)	171 (3.1%)	8 (3.4%)	347 (3.1%)	25 (4.6%)
Peripheral arterial disease	690 (4.3%)	19 (2.7%)	232 (3.4%)	10 (3.2%)	179 (3.3%)	7 (3.0%)	265 (2.4%)	14 (2.6%)
Antiplatelet	7742 (48.3%)	307(44.0%)	3048 (44.5%)	136(44.2%)	2474 (45.5%)	103 (44.4%)	4680 (42.2%)	226 (41.4%)
ADP receptor antagonists	2178 (13.6%)	72 (10.3%)	959 (14.0%)	40 (13.0%)	710 (13.1%)	19 (8.2%)	1200 (10.8%)	50 (9.2%)
Aspirin	6848 (42.7%)	282 (40.4%)	2461 (35.9%)	119 (38.6%)	2054 (37.8%)	94 (40.5%)	4059 (36.6%)	201 (36.8%)
Proton pump inhibitor	3687 (23.0%)	248 (35.5%)	1614 (23.6%)	99 (32.1%)	1181 (21.7%)	89(38.4%)	2064 (18.6%)	168 (30.8%)

Legend: Study population characteristics of the individual OACs groups with and without NSAID. Numbers and percentages of first-time initiators of vitamin K antagonists (VKA), dabigatran, rivaroxaban, and apixaban.

Figure 1 Selection of the study population

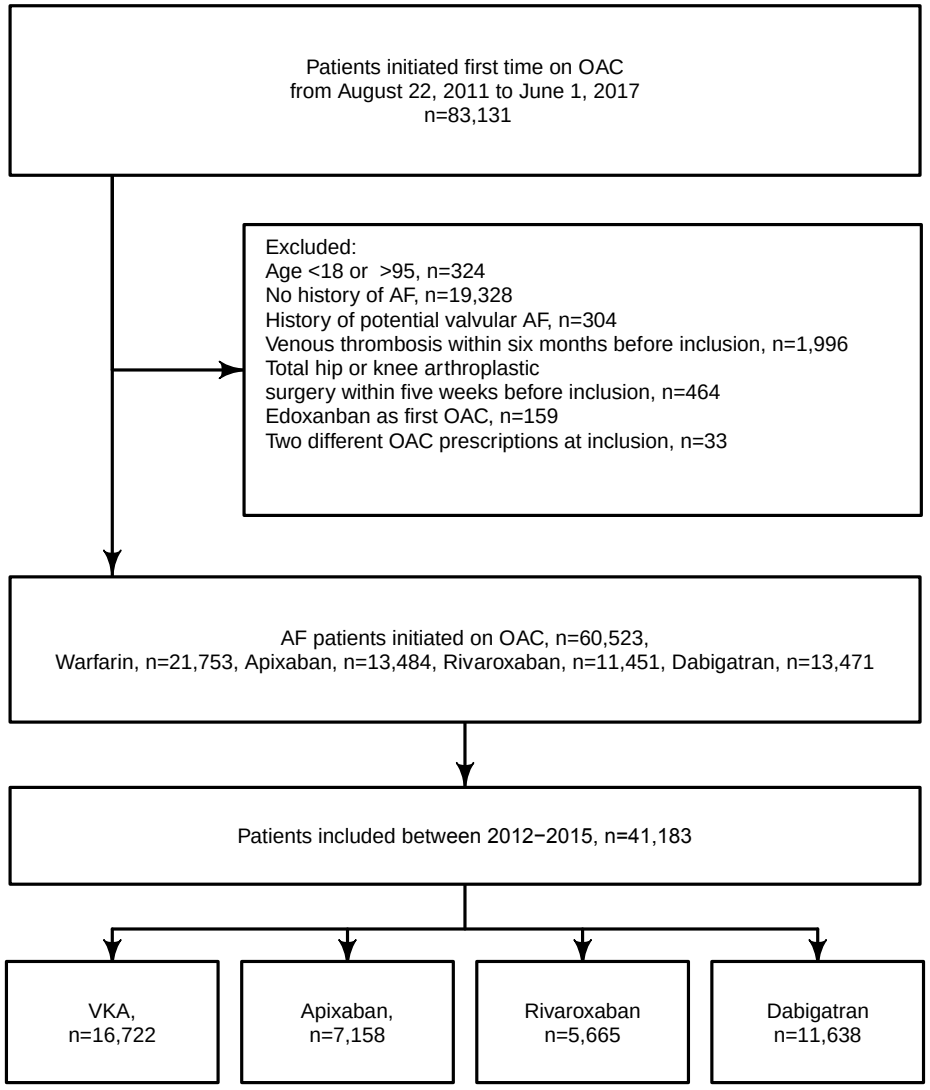


Figure 2 Rates of NSAID usage as concomitant therapy per 100 person years during the 180 days before and the 180 days following OAC initiation.

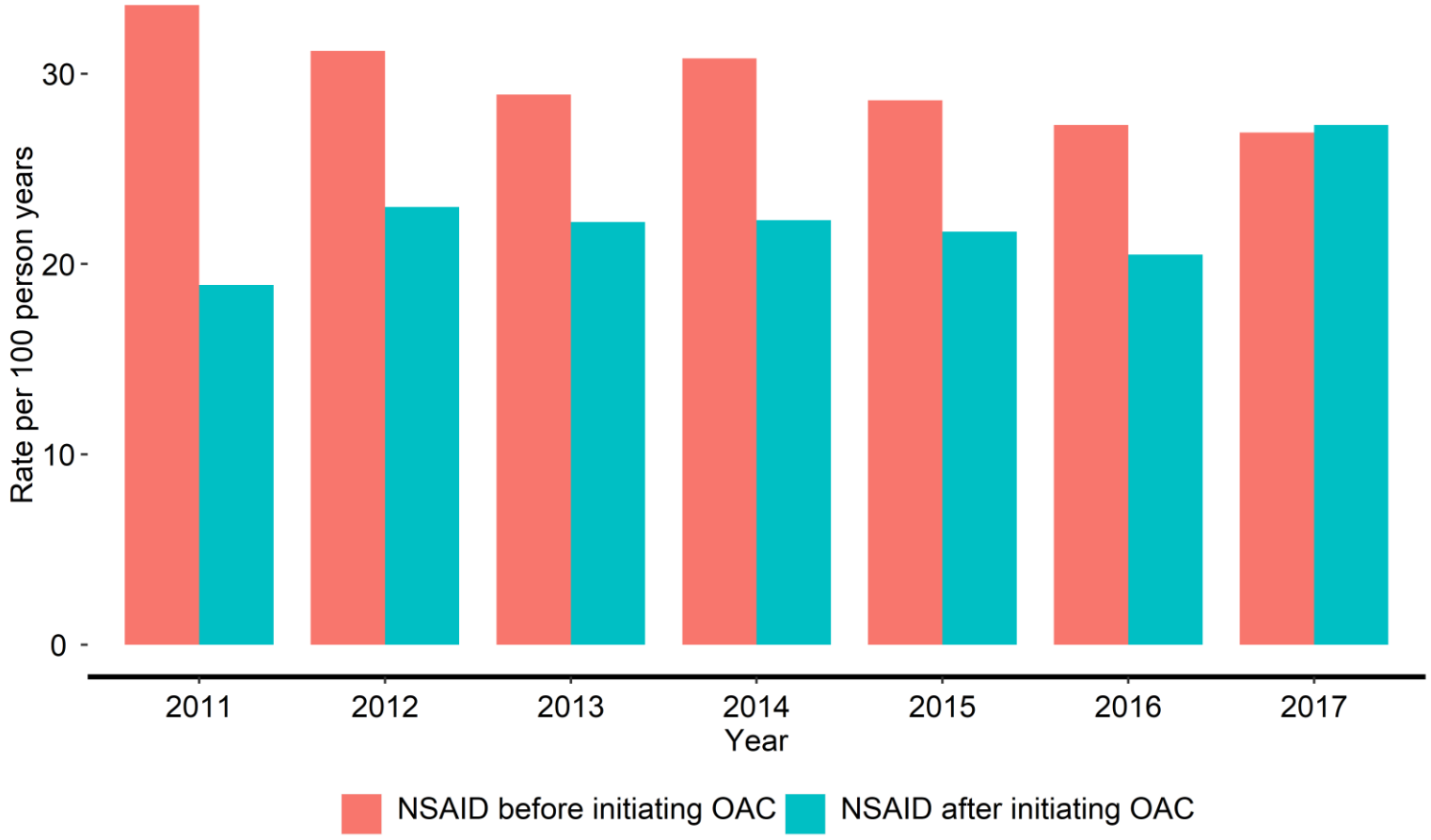


Figure 3A Percentage of VKA and NOAC initiation according to calendar year.

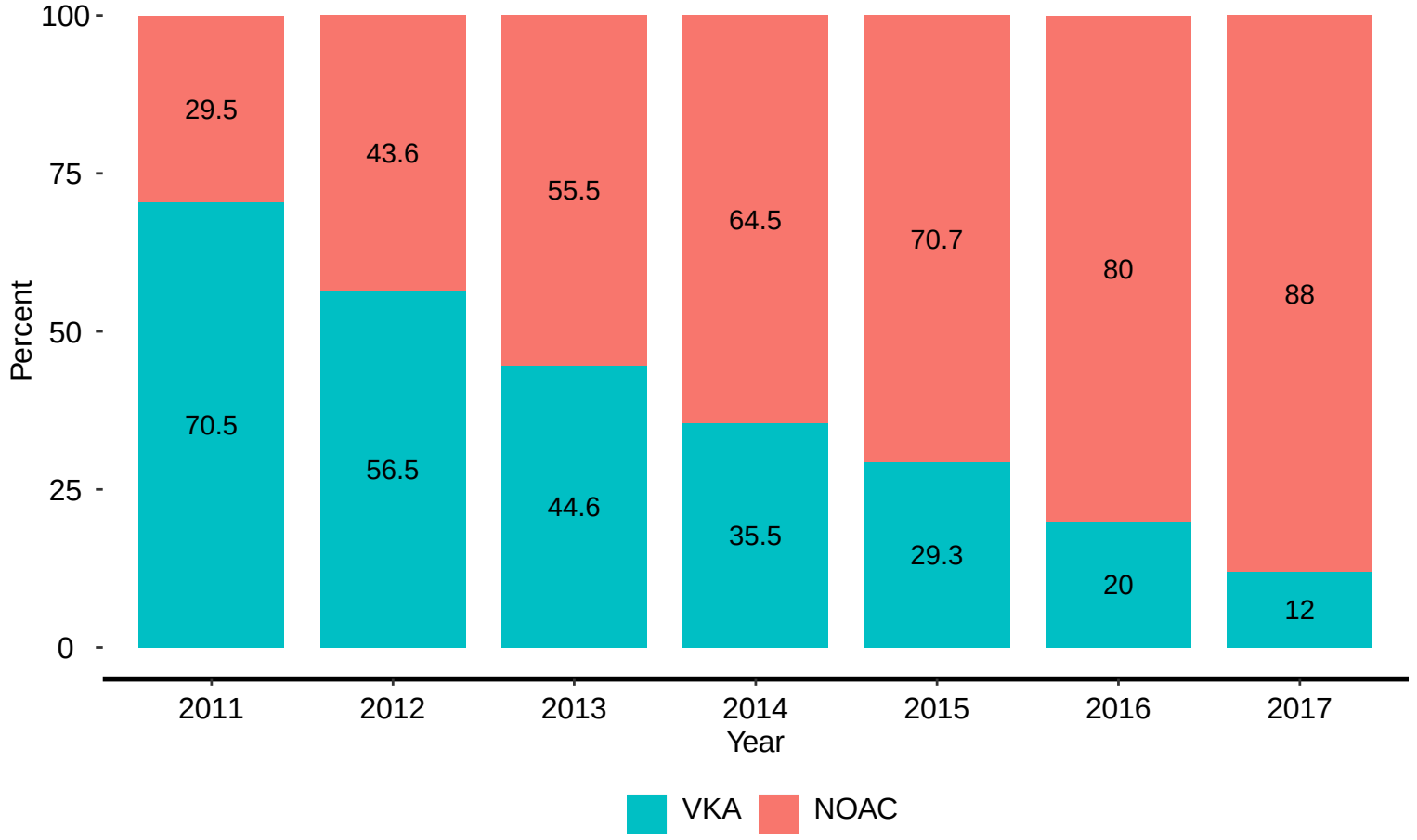


Figure 3B Rates of NSAID usage as concomitant therapy per 100 person years during the first 180 days following VKA or NOAC initiation.

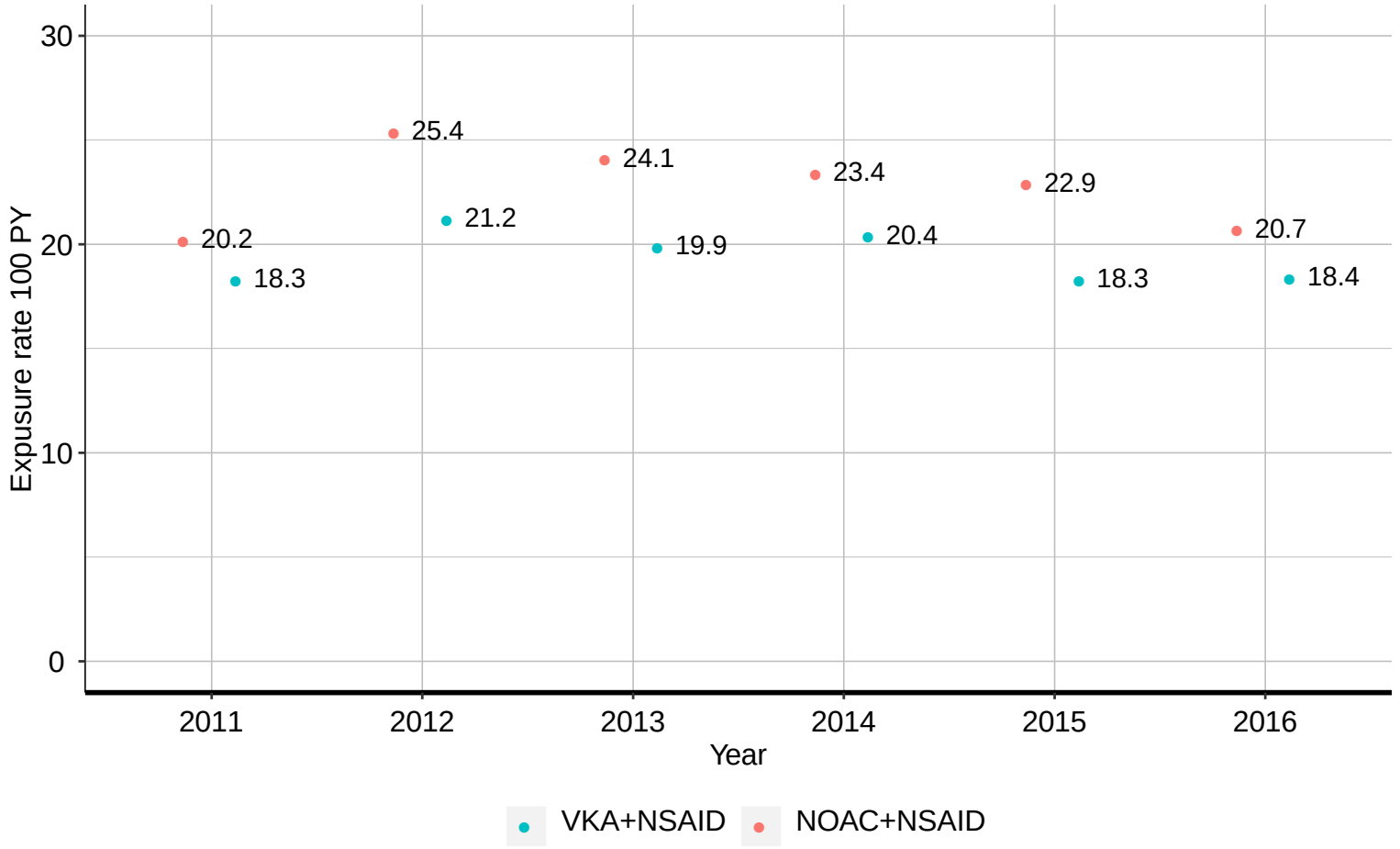
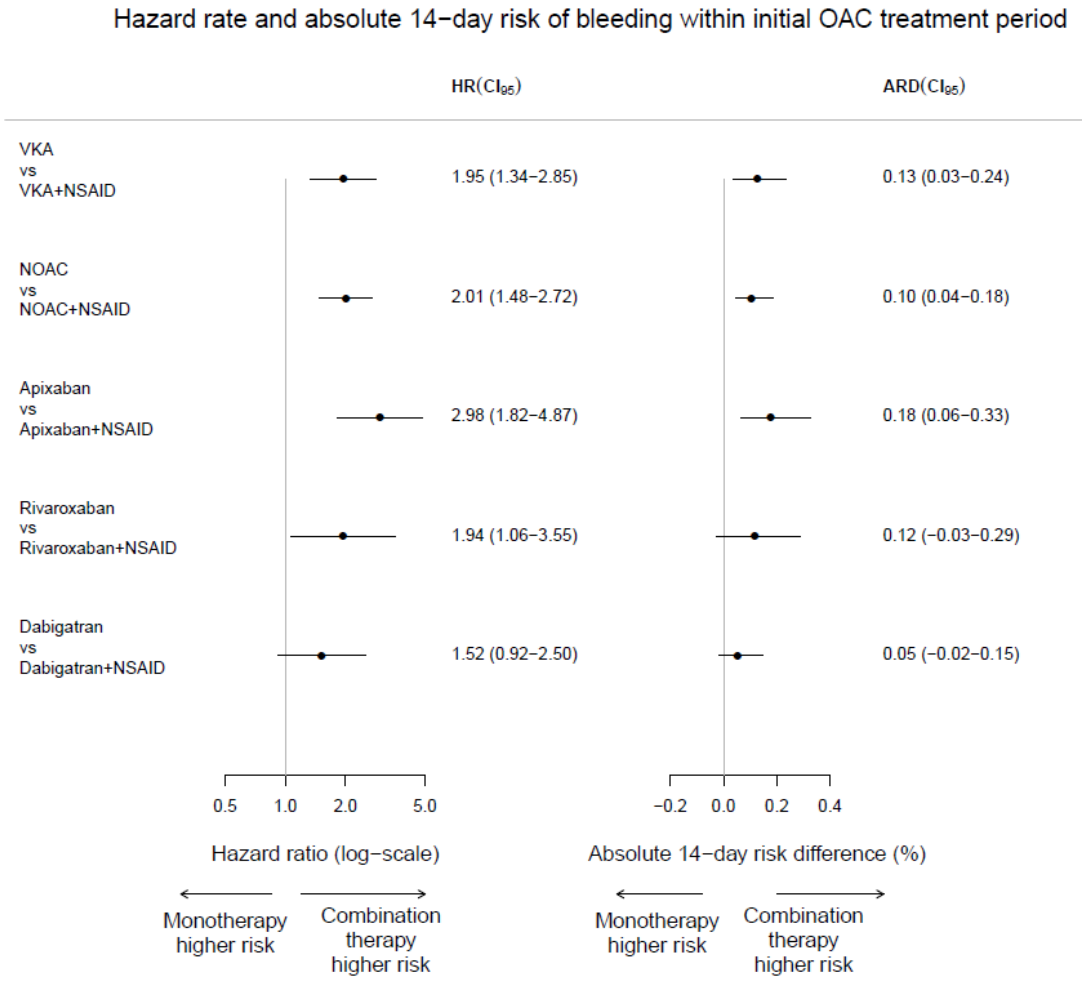


Figure 4 Hazard ratios (HR) and absolute 14-day absolute risk differences (ARD) of gastrointestinal bleeding under concomitant NSAID therapy relative to OAC therapy without NSAID in patients with atrial fibrillation (AF) adjusted for age, sex, bleeding risk factors incorporated in the HAS-BLED score. Abbreviations: NSAID, non-steroidal anti-inflammatory drug; VKA, vitamin K antagonists, NOAC, non-vitamin K antagonist oral anticoagulants; CI, confidence interval. Reference is the individual OACs treatment without NSAIDs (Vertical line indicates reference level).



Supplementary Table 1

Population		
atrial fibrillation	*Defined from diagnosis of atrial fibrillation with the absence of diagnosis codes of valvular atrial fibrillation and mitral- or aortic valve surgery.*	Presence of: ICD8: 42793, 42794. ICD10: I48. Absence of: ICD8: 4240, 4241, 39500- 39502, 39508, 39509, 39600-39604, 39608, 39609. ICD10: I05, I06, I080A, I081A, I082A, I083A, Z952, Z954. NCSP: KFKD, KFKH, KFMD, KFMH, KFGE, KFJF.
Vitamin K antagonist	*Defined from ATC-code.*	ATC: B01AA03
Dabigatran	*Defined from ATC-code.*	ATC: B01AE07.
Rivaroxaban	*Defined from ATC-code.*	ATC: B01AF01.
Apixaban	*Defined from ATC-code.*	ATC: B01AF02.
Non-steroidal anti-inflammatory drugs	*Defined from ATC-code*:	ATC M01A but excluding glucosamine (M01AX05), Including celecoxib (M01AH01), naproxen (M01AE02), diclofenac (M01AB05), ibuprofen (M01AE01)
Hip or knee replacement surgery	*Defined from surgical procedure performed.*	NCSP: KNFB, KNFC, KNGB, KNGC.
Deep venous thrombosis	*Defined from diagnosis.*	ICD10: I801-I803, I808, I809, I821-I823, I828, I829
Pulmonary embolism	*Defined from diagnosis.*	ICD10: I26.
Comorbidities and outcomes		
Stroke	*Defined from diagnosis of ischemic stroke, transient ischemic attack, or systemic thromboembolism.*	ICD10: I63, I64, I74, G458, G459.

Peripheral artery disease		ICD10: I70
Hypertension	*Defined from combination treatment with at least two classes of antihypertensive drugs: adrenergic α-antagonists, non-loop diuretics, vasodilators, beta-blockers, calcium channel blockers and renin-angiotension system inhibitors.*	ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Chronic kidney disease	*Defined from diagnosis of chronic glomerulonephritis, chronic tubulointestinal nephropathy, diabetic, and hypertensive nephropathy among others.*	ICD10: E102, E112, E132, E142, I120, M300, M313, M319, M321B, N02-N08, N11, N12, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168, Q61, Q613, Q615, Q619.
Abnormal liver function	*Defined from diagnosis of liver chronic liver disease, cirrhosis and hepatitis.*	ICD10: B15-B19, C22, D684C, I982, K70-K77, Q618A, Z944.
Bleeding	*Defined from diagnosis of intracranial bleeding, major gastrointestinal bleeding, respiratory or urinary tract bleeding, and bleeding due to anaemia.*	ICD10: D500, D62, G951A, H052A, H313, H356, H431, H450, I312, I60-I62, I850, I864A, J942, K228F, K298A, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K661, K638B, K638C, K838F, K868G , K920, K921, K922, N02, R04, R31, S064, S065, S066, S368D.
Alcohol abuse	*Defined from alcohol-related diagnosis codes or at least one dispensed prescription of an alcohol antagonist drug used to treat chronic*	ICD10: E244, E52, F10, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721.

	alcoholism.	ATC: N07BB.
Concomitant medication		
ADP receptor antagonists	*Defined from ATC-code.*	ATC: B01AC04, B01AC22, B01AC24
Proton pump inhibitors	*Defined from ATC-code.*	ATC: A02BC
Outcomes		
Gastrointestinal bleeding	*Defined from*	ICD10: K250, K254, K260, K264, K270, K280, K920-K922,

Supplementary Table 2

Hazard ratio of gastrointestinal bleeding according to OAC treatment and concomitant NSAID according to dose

	Apixaban		Apixaban+NSAID		Rivoxaban		Rivoxaban+NSAID		Dabigatran		Dabigatran+NSAID	
	Reduced dose (2.5 mg BID)	Standard dose (5 mg BID)	Reduced dose (2.5 mg BID)	Standard dose (5 mg BID)	Reduced dose (15 mg OD))	Standard dose (20 mg OD))	Reduced dose (15 mg OD))	Standard dose (20 mg OD))	Reduced dose (110 mg BID)	High dose (150 mg BID)	Reduced dose (110 mg BID)	High dose (150 mg BID)
Hazard ratio (95% CI)	Ref	Ref	4.28 (2.17-8.43)	2.19 (1.07-4.47)	Ref	Ref	2.45(0.99-6.03)	1.64(0.72-3.70)	Ref	Ref	1.65 (0.50-3.22)	1.49 (0.69-3.17)

Supplementary Table 3

Hazard ratio of gastrointestinal bleeding according to OAC treatment and concomitant NSAID stratified by any antiplatelet agents

Any antiplalets				
18716 patients, 875 events				
		HR	low	high
	VKA	1.98	1.20	3.27
	NOAC	2.17	1.45	3.25
	Apixaban	3.52	1.78	6.94
	Rivaroxaban	1.68	0.69	4.12
	Dabigatran	1.79	0.97	3.28
No antiplatelet				

22467 patients, 767 events				
	VKA	1.92	1.08	3.43
	NOAC	1.84	1.16	2.92
	Apixaban	2.54	1.25	5.19
	Rivaroxaban	2.25	0.99	5.11
	Dabigatran	1.13	0.47	2.76

Supplementary Table 4

Hazard ratio of gastrointestinal bleeding according to OAC treatment and concomitant NSAID stratified with baseline PPI

PPI				
9150 patienter, 416 events				
		HR	low	high
	VKA	1.65	0.84	3.23
	NOAC	1.45	0.79	2.66
	Apixaban	1.62	0.51	5.17
	Rivaroxaban	1.83	0.66	5.03
	Dabigatran	1.10	0.40	2.99
NO PPI				
32033 patients, 1226 event				

	VKA	2.11	1.33	3.34
	NOAC	2.27	1.60	3.22
	Apixaban	3.63	2.11	6.26
	Rivaroxaban	1.91	0.90	4.07
	Dabigatran	1.72	0.97	3.07

Supplementary Figure 1

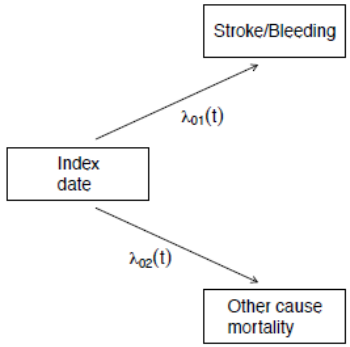
Multiple Cox regression for hazard rate of bleeding:

$$\hat{\lambda}_1(t|A(t),X) = \hat{\lambda}_{01}(t)e^{\hat{\beta}_1 A(t)+\hat{\beta}_2 X_1+\cdots+\hat{\beta}_p X_p}$$

A(t) concomitant NSAID treatment at time t
X OAC treatment and other covariates
t time on study

Multiple Cox regression for hazard rate of all-cause mortality:

$$\hat{\lambda}_2(t|A(t),X) = \hat{\lambda}_{02}(t)e^{\hat{\gamma}_1 A(t)+\hat{\gamma}_2 X_1+\cdots+\hat{\gamma}_p X_p}$$



Predicted outcome status 14 days after landmark date s (Benichou & Gail, 1990)

a=1 NSAID
a=0 no NSAID

$$\hat{Y}_i(a) = \int_s^{s+14\text{ days}} \underbrace{\exp\left\{-\int_0^t \left[\hat{\lambda}_1(u|a,X_i)+\hat{\lambda}_2(u|a,X_i)\right]\mathrm{d}u\right\}}_{\text{event-free until t}} \underbrace{\hat{\lambda}_1(t|a,X_i)\mathrm{d}t}_{\text{event of type 1 at t}}$$

$$\widehat{\mathrm{ATE}} = \frac{1}{n}\sum_{i=1}^{n}[\hat{Y}_i(1)-\hat{Y}_i(0)] \qquad \text{Average treatment effect}$$