CLINICAL RESEARCH STUDY

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Concomitant Use of Direct Oral Anticoagulants with Antiplatelet Agents and the Risk of Major Bleeding in Patients with Nonvalvular Atrial Fibrillation

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ABSTRACT

PURPOSE: Patients with nonvalvular atrial fibrillation commonly have comorbidities requiring concurrent use of oral anticoagulants and antiplatelets. There are no real-world data on the comparative safety of concomitant antithrombotic treatments in the era of direct oral anticoagulant (DOACs). Thus, we compared the incidence of intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding between concomitant DOAC-antiplatelet use and concomitant vitamin K antagonist (VKA)-antiplatelet use in patients with nonvalvular atrial fibrillation.

METHODS: Using computerized health care databases from Québec, we conducted a cohort study among patients newly diagnosed with nonvalvular atrial fibrillation between January 2011 and March 2014. Cox proportional hazards models yielded hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for disease risk score, of the study outcomes comparing current concomitant use of DOACs with ≥1 antiplatelet vs current concomitant use of VKAs with ≥1 antiplatelet.

RESULTS: A total of 5301 patients initiated concomitant DOAC-antiplatelet use, while 9106 patients initiated concomitant VKA-antiplatelet use. During a median follow-up of 1.6 months, concomitant DOAC-antiplatelet use was associated with a similar risk of gastrointestinal bleeding (HR 1.08; 95% CI, 0.81-1.45), but with a decreased risk of intracranial hemorrhage (HR 0.46; 95% CI, 0.24-0.91) and other major bleeding (HR 0.68; 95% CI, 0.51-0.91) compared with concomitant VKA-antiplatelet use.

CONCLUSIONS: Concomitant DOAC-antiplatelet use was associated with a similar risk of gastrointestinal bleeding, and a lower risk of intracranial hemorrhage and other major bleeding than concomitant VKA-antiplatelet use. These findings could inform physician decision-making in patients requiring concomitant treatment with oral anticoagulants and antiplatelets.

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BACKGROUND

Direct oral anticoagulants (DOACs) are increasingly being used for ischemic stroke prevention among patients with nonvalvular atrial fibrillation,[1,2] partly because of their favorable efficacy and safety compared with vitamin K antagonists (VKAs).[3] However, the safety of DOACs in patients with nonvalvular atrial fibrillation requiring additional use of antiplatelet agents remains uncertain. This is important, as up to 30% of patients with nonvalvular atrial fibrillation may receive concomitant treatments of oral anticoagulants with antiplatelets due to comorbid cardiovascular conditions.[4-7] While concomitant use of VKAs with antiplatelets has previously been shown to increase the risk of bleeding compared with VKAs alone,[8,9] data are lacking on the comparative safety of concomitant use of antithrombotic drugs in the era of DOACs.

CLINICAL SIGNIFICANCE

- Direct oral anticoagulants with antiplatelets are associated with a similar risk of gastrointestinal bleeding compared with vitamin K antagonists and antiplatelets.
- Direct oral anticoagulants with antiplatelets are associated with a decreased risk of intracranial hemorrhage and other major bleeding compared with vitamin K antagonists and antiplatelets.
- There were no duration—response relations for the 3 bleeding outcomes.
- Age, sex, or baseline bleeding risk did not modify the associations.

In a meta-analysis of randomized controlled trials (RCTs) assessing the efficacy of DOACs in nonvalvular atrial fibrillation, use of acetylsalicylic acid (ASA) with DOACs was associated with a similar risk of major bleeding (hazard ratio [HR] 0.83; 95% confidence interval [CI], 0.69-1.01), but a decreased risk of intracranial hemorrhage (HR 0.38; 95% CI, 0.26-0.56), compared with use of ASA with VKAs.[7] However, the analysis was limited to use of ASA at randomization not accounting for use during follow-up.[7] Moreover, 2 RCTs evaluating concomitant use of DOACs with antiplatelets restricted inclusion to patients with nonvalvular atrial fibrillation undergoing coronary intervention.[10,11] Finally, a recently published cohort study addressing the safety of such regimes in real-world clinical practice had methodological limitations such as inclusion of prevalent users and did not report results on specific types of major bleeding.[12]

Thus, to address this important safety issue, we conducted a population-based study to compare the incidence of intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding between concomitant DOAC-antiplatelet use and concomitant VKA-antiplatelet use in patients with nonvalvular atrial fibrillation.

METHODS

Data Sources

This study was conducted by linking 3 computerized health care databases from the Canadian province of Québec: *Régie de l'assurance maladie du Québec* (RAMQ), *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MEDÉCHO), and the *Institut de la statistique du Québec* (ISQ).[13] The RAMQ databases collect information on demographics, medical services (coded using the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] or enhanced version of ICD-10 for Canada ICD-10-CA), and dispensed outpatient prescriptions. Under the universal health care program, medical services are covered for all Québec residents, while coverage in the Public Prescription Drug Insurance Plan is limited to residents (and their children) with no private drug insurance plans, those at least 65 years of age, and recipients of financial assistance.[14] RAMQ data quality has been previously documented.[15,16] MEDÉCHO contains records of all hospitalizations occurring in Québec and includes date and type of admission and discharge, as well as primary and secondary diagnoses (coded using ICD-10-CA). Finally, ISQ contains vital statistics including date and cause of death. The study protocol was approved by the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada. No informed consent was required.

Base Cohort of Patients with Incident Nonvalvular Atrial Fibrillation

Using the databases above, we identified all patients at least 18 years of age with a first inpatient or outpatient diagnosis of atrial fibrillation between January 1, 2011 (when the first DOAC, dabigatran, was approved for stroke prevention in nonvalvular atrial fibrillation in Québec) and March 31, 2014. All patients were required to have been covered by the RAMQ Public Prescription Drug Insurance Plan for at least 1 year prior to the diagnosis of atrial fibrillation. We restricted inclusion to patients with nonvalvular atrial fibrillation by excluding patients with a history of mitral or aortic stenosis or valvular repair, and those with a history of hyperthyroidism, at any time prior to the diagnosis of atrial fibrillation. Finally, we excluded patients dispensed VKAs or DOACs in the year prior to the nonvalvular atrial fibrillation diagnosis to maximize the inclusion of new users during the study period.

Study Cohort of Concomitant Oral Anticoagulant-Antiplatelet Users

Using the base cohort defined above, we identified all patients initiating concomitant use of an oral anticoagulant

(DOAC [dabigatran, rivaroxaban, or apixaban] or VKA) with at least one antiplatelet agent (ASA, dipyridamole, clopidogrel, prasugrel, or ticagrelor) during the study period. Thus, concomitant users comprised 3 types of patients: 1) those on antiplatelets with a prescription overlapping a new prescription for an oral anticoagulant; 2) those on an oral anticoagulant with a prescription overlapping a new prescription for at least one antiplatelet; and 3) patients initiating treatment with an oral anticoagulant and at least one antiplatelet on the same day (Supplementary Figure 1, available online). Cohort entry was defined as the first day of concomitant use during the study period. We excluded patients with any bleeding-related hospitalization in the 3 months prior to cohort entry, to exclude events related to precohort entry antithrombotic exposure. Patients were followed until an event (described in detail below), discontinuation of concomitant use (described in detail below), end of registration with the Public Prescription Drug Insurance Plan, death, or end of study period (December 31, 2014), whichever occurred first.

Exposure Groups

We compared patients initiating concomitant use of a DOAC with at least one antiplatelet with patients initiating concomitant use of a VKA with at least one antiplatelet. The latter group served as reference as this represented a clinically relevant comparator, while minimizing potential confounding by indication.[1] An *as-treated* exposure definition was used where patients were considered continuously exposed to concomitant use if the prescription durations of the drugs of interest were overlapping each other. We allowed for a 30-day grace period in the event of nonoverlapping prescriptions.

Bleeding Outcomes

We conducted 3 analyses; for intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding separately (ICD-10 codes in Supplementary Table 1, available online). The bleeding outcomes were defined by inpatient diagnoses (captured in MEDÉCHO in primary or secondary position), or bleeding-related deaths (captured in MEDÉCHO or ISQ).

Disease Risk Score

To control for confounding, we calculated disease risk scores (DRS) using a historical cohort from the same data source.[17] This historical cohort comprised patients newly diagnosed with nonvalvular atrial fibrillation between January 1, 2007 and December 31, 2010 who were on concomitant VKA-antiplatelet use. The DRS included the following variables measured at cohort entry: age, sex, alcohol-related disorders, hypertension, ischemic stroke or transient ischemic attack, congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, renal or liver disease, all diagnosed at any time prior to cohort entry. We also considered time from nonvalvular atrial fibrillation diagnosis to initiation of oral anticoagulation, cancer (other than nonmelanoma skin cancer) diagnosed in the year prior to cohort entry, and history of major bleeding 3 to 15 months prior to cohort entry. Moreover, the model included use of nonsteroidal antiinflammatory drugs, selective serotonin reuptake inhibitors, proton pump inhibitors, and H_2 blockers in the year prior to cohort entry, because these drugs have been associated with bleeding. Finally, we measured the number of nonantithrombotic drugs in the year prior to cohort entry as a proxy for overall health. For each bleeding outcome, we fitted a Cox proportional hazards model to the historical cohort, which was then applied to the study cohort to estimate the relative hazard of bleeding for each cohort member.[17]

Statistical Analysis

Crude incidence rates and rate differences for the bleeding outcomes with 95% CIs based on the Poisson distribution were calculated for each exposure group. We used Cox proportional hazards models to estimate HRs and 95% CIs for each bleeding outcome (intracranial hemorrhage, gastrointestinal bleeding, other major bleeding) associated with concomitant DOAC-antiplatelet use compared with concomitant VKA-antiplatelet use. The models were adjusted for DRS by including an interaction term between DRS modeled as a categorical variable (quintiles for intracranial hemorrhage and deciles for gastrointestinal bleeding and other major bleeding) and DRS as a continuous variable, as well as year of cohort entry.

Secondary Analyses

We conducted 7 secondary exploratory analyses. First, we repeated the primary analyses for the individual DOACs (dabigatran, rivaroxaban, and apixaban). Second, to assess a possible duration−response relation between concomitant DOAC-antiplatelet use and the incidence of the bleeding outcomes, we estimated HRs for 3 prespecified duration categories (<3, 3-6, and >6 months). Third, we assessed whether the risk of the bleeding outcomes associated with concomitant DOAC-antiplatelet use varies among patient subgroups (age ≤75 vs >75 years, males vs females, or a modified HAS-BLED [uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history or predisposition, age >65 years, alcohol-related disorders] score[18] of 0-2 vs 3-7). Fourth, we assessed the association between concomitant DOAC-antiplatelet use and risk of genitourinary bleeding, a common complication of antithrombotic treatment.[19] Fifth, we assessed the risk of the bleeding outcomes associated with concomitant DOAC-ASA use vs concomitant VKA-ASA use. This analysis was limited to patients using ASA as the only antiplatelet at cohort entry and censored upon addition or switch to another antiplatelet during follow-up. Sixth, we assessed the risk of the bleeding outcomes in patients on DOACs with at least 2 antiplatelets compared with patients on VKAs with at least 2 antiplatelets. Finally, we assessed whether the risk of the bleeding outcomes differed between

patients entering the study cohort upon addition of an oral anticoagulant, an antiplatelet, or both.

Sensitivity Analyses

We conducted 6 sensitivity analyses to assess the robustness of our findings. First, to assess potential exposure misclassification, we repeated the primary analyses using a 15-day grace period between successive prescriptions. Second, we used a stricter outcome definition considering only primary diagnoses for hospitalized bleeding or fatal bleeding events. Third, to assess potential informative censoring, as discontinuation of antithrombotic treatment could be related to the outcome, we repeated the primary analyses using an *intention-to-treat* approach, where exposure is defined based on the drug used at cohort entry, and limiting follow-up to 6 months. Fourth, we excluded patients with a history of both VKA and DOAC use between nonvalvular atrial fibrillation diagnosis and cohort entry. Fifth, we repeated the primary analyses after accounting for competing risk due to death.[20] Finally, we censored on the first major bleeding event during follow-up, thus not allowing patients to contribute events to multiple types of bleeds. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 5301 patients initiated concomitant DOAC-antiplatelet use and 9106 patients initiated concomitant VKA-antiplatelet use during the study period (Figure 1).

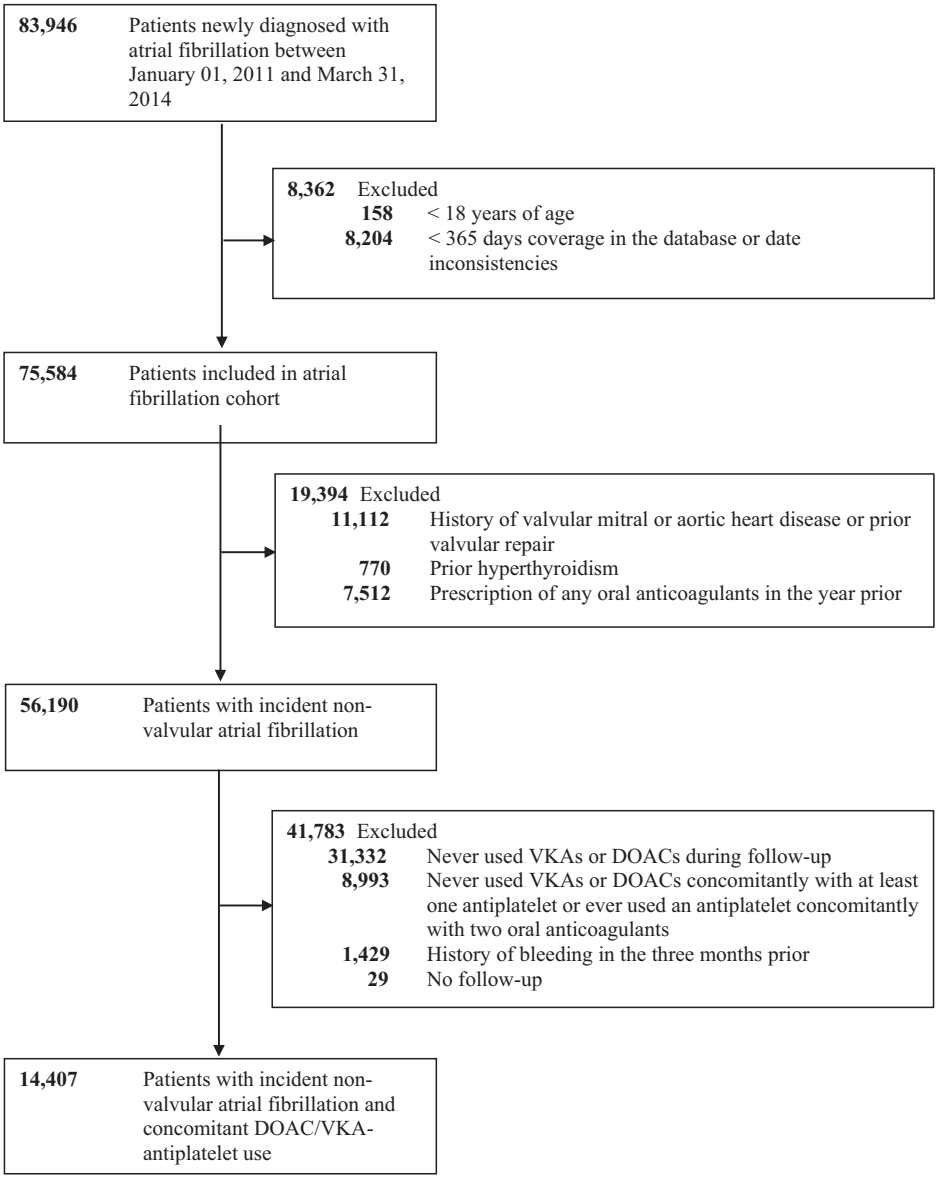

Figure 1 Flowchart describing the construction of base and study cohorts.
DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

The median duration of follow-up was 1.4 months for concomitant DOAC-antiplatelet use and 1.7 months for concomitant VKA-antiplatelet use (1.6 months overall), generating a total of 14,751 person-years. This follow-up period was primarily driven by discontinuation of antiplatelets (60%) (Supplementary Table 2, available online). During the follow-up period, 65 patients had an intracranial hemorrhage, 253 had a gastrointestinal bleeding, and 308 had other major bleeding episodes.

Table 1 presents the characteristics of the nonvalvular atrial fibrillation patients on concomitant DOAC-antiplatelet use vs concomitant VKA-antiplatelet use at cohort entry. Patients on concomitant DOAC-antiplatelet use were less likely to have renal or vascular disease or congestive heart failure than patients on concomitant VKA-antiplatelet use, and they also had slightly lower HAS-BLED scores. In both groups, most patients were on single antiplatelet treatment (92% in the DOAC group vs 86% in the VKA group) and the most common antiplatelet was ASA (94% in the DOAC group vs 93% in the VKA group).

Table 2 shows the results related to concomitant DOAC-antiplatelet use and the risk of the bleeding outcomes (18,21). Concomitant DOAC-antiplatelet use was associated with a similar risk of gastrointestinal bleeding (HR 1.08; 95% CI, 0.81-1.45), but with a decreased risk of intracranial hemorrhage (HR 0.46; 95% CI, 0.24-0.91) and other major bleeding (HR 0.68; 95% CI, 0.51-0.91), compared with concomitant VKA-antiplatelet use. Cumulative incidence curves for the bleeding outcomes are presented in Supplementary Figures 2-**4**, available online.

Drug-specific analyses revealed similar associations for the 3 DOACs, although these were based on fewer events (Supplementary Table 3, available online). We observed no duration−response relations for the bleeding outcomes

Table 1 Baseline Demographics and Clinical Characteristics of the Cohort Stratified by Concomitant Use of Antithrombotic Drugs at Cohort Entry

Characteristic	Concomitant DOAC-Antiplatelet Use	Concomitant VKA-Antiplatelet Use
Total	5301	9106
Age, y (mean, SD)	75.5 (9.1)	78.0 (9.0)
Male, n (%)	2819 (53.2)	4709 (51.7)
Time from NVAF diagnosis to VKA/DOAC initiation, d (mean, SD)	77.0 (180.2)	38.6 (116.3)
History of alcohol-related disorders, n (%)	210 (4.0)	427 (4.7)
History of arterial hypertension, n (%)	4544 (85.7)	8337 (91.6)
History of cancer, n (%)	787 (14.9)	1399 (15.4)
History of congestive heart failure, n (%)	1043 (19.7)	2804 (30.8)
History of coronary artery disease, n (%)	2577 (48.6)	5588 (61.4)
History of diabetes mellitus, n (%)	1685 (31.8)	3577 (39.3)
History of liver disease, n (%)	269 (5.1)	676 (7.4)
History of peripheral vascular disease, n (%)	556 (10.5)	1718 (18.9)
Prior ischemic stroke or transient ischemic attack, n (%)	486 (9.2)	1105 (12.1)
Prior major bleeding*	70 (1.3)	171 (1.9)
History of renal disease, n (%)	457 (8.6)	2210 (24.3)
CHA_2DS_2-VASC score, mean (SD)†	3.7 (1.5)	4.3 (1.5)
Modified HAS-BLED score, mean (SD)†	1.4 (0.8)	1.7 (1.0)
Number of antiplatelets at cohort entry, mean (SD)	1.1 (0.3)	1.1 (0.4)
One, n (%)	4886 (92.2)	7862 (86.3)
Two or more, n (%)	415 (7.8)	1244 (13.7)
Class of antiplatelets at cohort entry, n (%)		
Acetylsalicylic acid	4972 (93.8)	8487 (93.2)
$P2Y_{12}$ inhibitors	744 (14.0)	1863 (20.5)
H_2 blockers, n (%)	85 (1.6)	185 (2.0)
Nonsteroidal anti-inflammatory drugs, n (%)	947 (17.9)	1527 (16.8)
Proton pump inhibitors, n (%)	2752 (51.9)	5577 (61.3)
Selective serotonin reuptake inhibitors, n (%)	457 (8.6)	901 (9.9)
Number of non-antithrombotic drugs, mean (SD)	11.5 (6.0)	13.7 (6.6)

CHA_2DS_2-VASc = congestive heart failure, arterial hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, female sex; DOAC = direct oral anticoagulant; HAS-BLED = abnormal renal or liver function, previous stroke or transient ischemic attack, bleeding history or predisposition, age >65 years, alcohol-related disorders or drugs; NVAF = nonvalvular atrial fibrillation; SD = standard deviation; VKA = vitamin K antagonist.

*Assessed 3-15 months prior to cohort entry.

†We calculated a CHA_2DS_2-VASc[21] score and a modified HAS-BLED[18] score for each patient, defining uncontrolled arterial hypertension as intake of two or more antihypertensive drugs in the year prior to cohort entry.

Table 2 Crude and Adjusted Hazard Ratios for the Association Between the DOAC-Antiplatelet Concomitant Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation

	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Rate Difference (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage							
Current concomitant VKA-antiplatelet use	9106	54	3508	1.5 (1.2-2.0)		[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	11	1461	0.8 (0.4-1.4)	−0.3 (-1.6-1.1)	0.47 (0.25-0.91)	0.46 (0.24-0.91)
Gastrointestinal bleeding							
Current concomitant VKA-antiplatelet use	9106	181	3462	5.2 (4.5-6.1)		[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	72	1448	5.0 (3.9-6.3)	−0.8 (-1.4−0.2)	0.87 (0.66-1.14)	1.08 (0.81-1.45)
Other major bleeding							
Current concomitant VKA-antiplatelet use	9106	246	3421	7.2 (6.3-8.2)		[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	62	1450	4.3 (3.3-5.5)	−2.9 (-4.3−1.5)	0.56 (0.43-0.74)	0.68 (0.51-0.91)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.

*Per 100 person-years.

†Adjusted for disease risk score and calendar year.References:Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093-1100. [18] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-272. [21]

(Supplementary Table 4, available online), and age, sex, or HAS-BLED score did not modify the associations (Supplementary Tables 5-7, available online). Concomitant DOAC-antiplatelet use was associated with a trend toward an increased risk of genitourinary bleeding compared with concomitant VKA-antiplatelet use (HR 1.42; 95% CI, 0.88-2.27), with the difference being driven by rivaroxaban and apixaban (Supplementary Table 8, available online). Comparing concomitant DOAC-ASA use vs concomitant VKA-ASA use, or concomitant use of a DOAC with at least 2 antiplatelet agents vs concomitant use of a VKA with at least 2 antiplatelet agents yielded results similar with those of the primary analysis (Supplementary Tables 9, 10, available online). Finally, we observed no effect modification for the bleeding outcomes after stratifying patients based on how they entered the cohort (Supplementary Table 11, available online). The results of the sensitivity analyses were consistent with those of the primary analysis (summarized in Figure 2 and presented in detail in Supplementary Tables 12-17, available online).

DISCUSSION

Our study assessed the risk of intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding associated with concomitant DOAC-antiplatelet use in patients with nonvalvular atrial fibrillation. Compared with concomitant VKA-antiplatelet use, concomitant DOAC-antiplatelet use was associated with a similar risk of gastrointestinal bleeding (HR 1.08; 95% CI, 0.81-1.45), but with a decreased risk of intracranial hemorrhage (HR 0.46; 95% CI, 0.24-0.91) and other major bleeding (HR 0.68; 95% CI, 0.51-0.91). The findings of the primary analyses remained consistent in several sensitivity analyses.

Our results on intracranial hemorrhage are congruent with a recent meta-analysis of RCTs, which showed that in patients using ASA at baseline, DOACs were associated with a decreased risk compared with VKAs (HR 0.38; 95% CI, 0.26-0.56). Importantly, the incidence rates of intracranial hemorrhage in our study were approximately twofold higher than the ones reported in the trials comparing different DOACs with VKAs in monotherapy.[3] This increase in the absolute risk of intracranial hemorrhage combined with the strong reduction in the relative risk associated with concomitant DOAC-antiplatelet use highlight the importance of choosing the appropriate oral anticoagulant in patients with nonvalvular atrial fibrillation requiring additional use of antiplatelets.

Our results on gastrointestinal bleeding showing a similar risk among concomitant DOAC-antiplatelet use and concomitant VKA-antiplatelet use are opposed to the previously reported increased risk with DOACs in monotherapy compared with VKAs in monotherapy.[3] A possible explanation could be the preferential concomitant prescribing of VKAs and antiplatelets instead of DOACs and antiplatelets in high-risk patients, as the higher prevalence of proton-pump inhibitors in the VKA

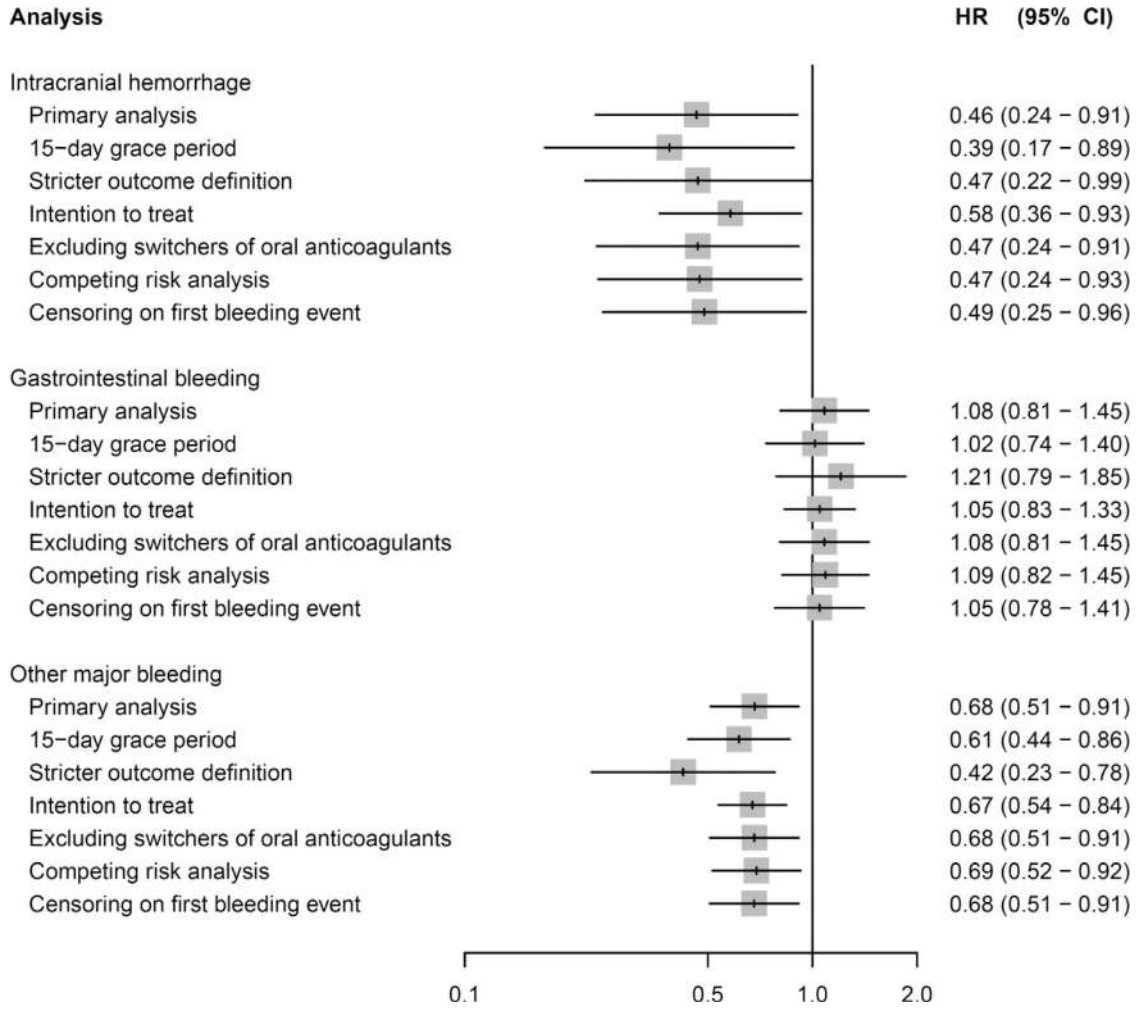

Figure 2 Forest plot summarizing the results of the primary analysis and sensitivity analyses, showing adjusted hazard ratios and 95% confidence intervals for the association between DOAC-antiplatelet concomitant use and risk of the three bleeding outcomes.
CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio.

group alludes. However, the pharmacologic properties of the different antithrombotic medications could also account for this phenomenon.[22] Indeed, while bleeding episodes related to VKAs and antiplatelets usually occurs in the upper gastrointestinal tract, bleeding episodes related to dabigatran and rivaroxaban, the 2 most prevalent DOACs in our cohort, originate more often in the lower gastrointestinal tract.[22] Thus, the common localization of VKA and antiplatelet-related gastrointestinal bleeding could lead to a higher additive risk due to concomitant antiplatelet use with VKAs than with DOACs.

Recently, 2 RCTs compared the risk of major bleeding between concomitant DOAC-antiplatelet use and concomitant VKA-antiplatelet use,[10,11] while a third one is ongoing.[23] Although they have considerably expanded our knowledge about concomitant antithrombotic treatment, a direct comparison with our study is challenging. First, these trials were restricted to nonvalvular atrial fibrillation patients undergoing coronary intervention.[1,24] Second, while trial participants randomized to VKAs received dual antiplatelet treatment, patients randomized to DOACs received either single antiplatelet treatment[10,11] or dual antiplatelet treatment with a low-dose DOAC.[11] Finally, effect estimates for intracranial hemorrhage and gastrointestinal bleeding were based on very few events[10] or were not reported.[11] Nevertheless, the lower risk of major bleeding among concomitant DOAC-antiplatelet use shown in the RCTs is congruent with our findings.

Our study has several strengths. First, the use of an *as-treated* exposure definition for both oral anticoagulants and antiplatelets allowed us to assess concomitant use with high precision. This is particularly important in drug−drug interaction studies aiming to investigate the effects associated with the *concurrent* use of 2 or more medications. Second, the population-based setting and the few exclusion criteria applied during study cohort assembly make the results of this study highly

generalizable. Finally, we defined bleeding events based on related hospitalization or death likely maximizing the sensitivity and specificity of this outcome definition.

Our study also has some limitations. First, given its observational nature, residual confounding is possible. To mitigate this potential bias, we adjusted for DRS, including 18 clinically important risk factors. Of note, adjustment had only a minor effect on the point estimates of the bleeding outcomes. Second, the median follow-up in our study was short (1.6 months). However, this was expected given current recommendations limiting concomitant use of oral anticoagulants with antiplatelets to few months for most patients.[1,24] Finally, our drug-specific analyses should be interpreted cautiously given the low number of exposed events.

In summary, the results of this population-based study indicate that compared with concomitant VKA-antiplatelet use, concomitant DOAC-antiplatelet use is associated with a similar risk of gastrointestinal bleeding, but a lower risk of intracranial hemorrhage and other major bleeding. These findings could help physician decision-making in patients requiring concomitant treatment with oral anticoagulants and antiplatelets.

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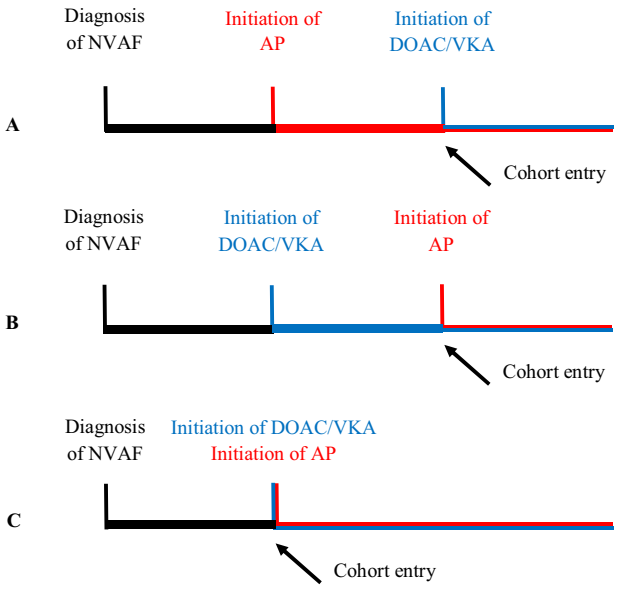
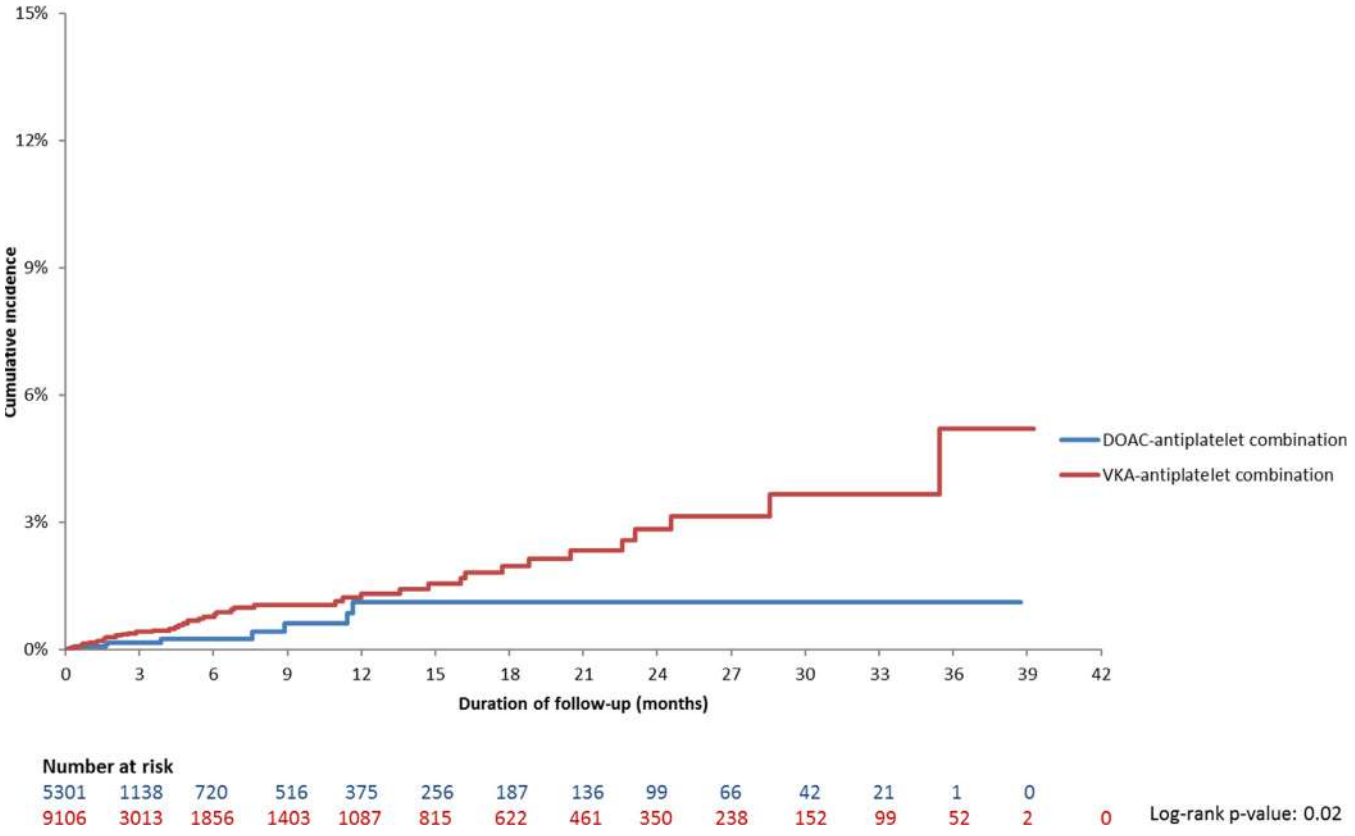
Authorship: LA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

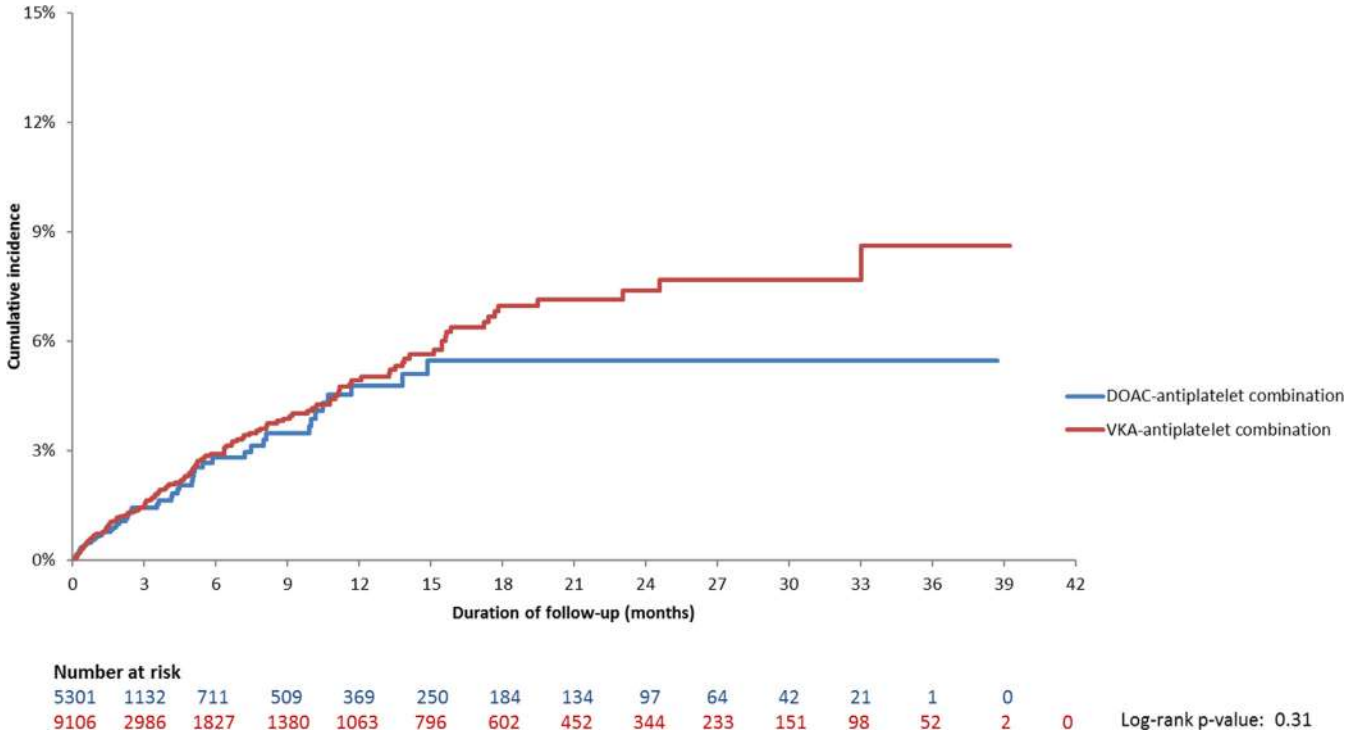


Supplementary Figure 1 Diagram depicting cohort entry with different patterns of initiation of concomitant use of antithrombotic drugs. The black line represents person-time prior to cohort entry spanning from the diagnosis of nonvalvular atrial fibrillation to the initiation of the first antithrombotic drug (either an antiplatelet or an oral anticoagulant). The blue line represents person-time prior to cohort entry exposed to an oral anticoagulant (either a vitamin K antagonist [VKA] or a direct oral anticoagulant [DOAC]). Red line represents person-time prior to cohort entry exposed to at least one antiplatelet. Cohort entry corresponded to the initiation of DOAC-antiplatelet or VKA-antiplatelet concomitant use. Red-and-blue line represents person-time after cohort entry. Scenario **A** corresponds to cohort entry upon addition of a DOAC or a VKA to at least one antiplatelet, scenario **B** corresponds to cohort entry upon addition of at least one antiplatelet to a DOAC or a VKA, and scenario **C** corresponds to cohort entry upon concomitant initiation of a DOAC or a VKA and at least one antiplatelet.

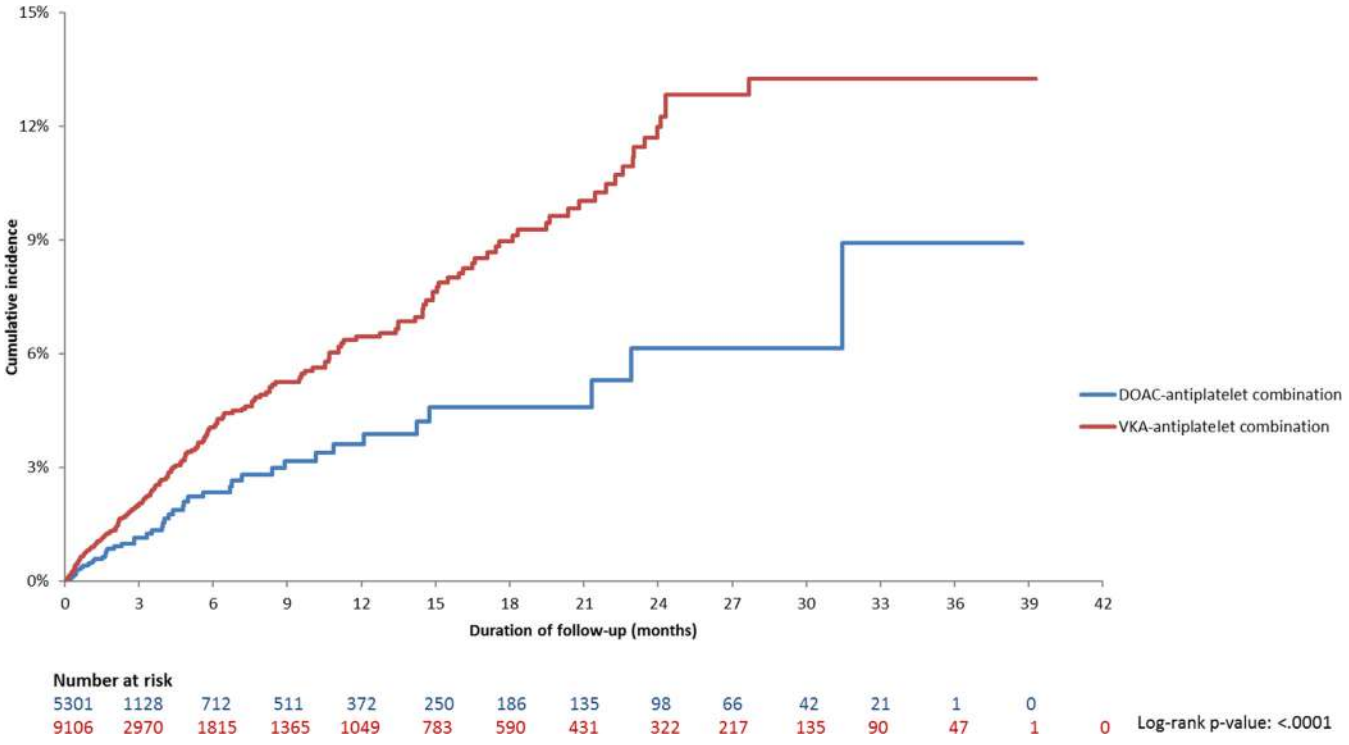
AP = antiplatelet; DOAC = direct oral anticoagulant; NVAF = nonvalvular atrial fibrillation; VKA = vitamin K antagonist.



Supplementary Figure 2 Cumulative incidence of intracranial hemorrhage among concomitant DOAC-antiplatelet and VKA-antiplatelet users. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.



Supplementary Figure 3 Cumulative incidence of gastrointestinal bleeding among concomitant DOAC-antiplatelet and VKA-antiplatelet users. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.



Supplementary Figure 4 Cumulative incidence of other major bleeding among concomitant DOAC-antiplatelet and VKA-antiplatelet users. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

Supplementary Table 1 ICD-10 Codes for Different Types of Major Bleeding

Type of Bleeding	ICD-10 Code	Description
ICH	I60	Subarachnoid
	I61	Intracerebral
	I620	Subdural
	I621	Nontraumatic extradural (acute)
	I629	Unspecified intracranial hemorrhage (nontraumatic)
	I690	Sequelae of subarachnoid hemorrhage
	I691	Sequelae of intracerebral hemorrhage
	I692	Sequelae of intracranial hemorrhage
	S0636	Traumatic hemorrhage of cerebrum
	S064	Epidural hemorrhage
	S065	Subdural (traumatic)
	S066	Subarachnoid (traumatic)
GIB	I850	Esophageal varices with bleeding
	K920	Hematemesis
	K921	Melena
	K922	Gastrointestinal hemorrhage (unspecified)
	K226	Gastro-esophageal laceration-hemorrhage syndrome
	K228	Hemorrhage of esophagus NOS
	K250	Acute gastric ulcer with hemorrhage
	K252	Acute gastric ulcer with hemorrhage/perforation
	K254	Chronic gastric ulcer with hemorrhage
	K256	Chronic gastric ulcer with hemorrhage/perforation
	K260	Acute duodenal ulcer with hemorrhage
	K262	Acute duodenal ulcer with hemorrhage/perforation
	K264	Chronic duodenal ulcer with hemorrhage
	K266	Chronic duodenal ulcer with hemorrhage/perforation
	K270	Acute peptic ulcer with hemorrhage
	K272	Acute peptic ulcer with hemorrhage/perforation
	K274	Chronic peptic ulcer with hemorrhage
	K276	Chronic peptic ulcer with hemorrhage/perforation
	K280	Acute gastrojejunal ulcer with hemorrhage
	K282	Acute gastrojejunal ulcer with hemorrhage/perforation
	K284	Chronic gastrojejunal ulcer with hemorrhage
	K286	Chronic gastrojejunal ulcer with hemorrhage/perforation
	K290	Acute hemorrhagic gastritis
	K2921	Alcoholic gastritis (with hemorrhage)
	K2961	Other gastritis with bleeding
	K2971	Gastritis (unspecified with bleeding)
	K2991	Gastroduodenitis (unspecified with bleeding)
	K2981	Duodenitis (with hemorrhage)
	K3181	Angiodysplasia of stomach and duodenum with hemorrhage
	K5521	Angiodysplasia of colon with hemorrhage
	K5711	Diverticulosis of small intestine without perforation or abscess with bleeding
	K5713	Diverticulitis of small intestine without perforation or abscess with bleeding
	K5731	Diverticulosis of large intestine without perforation or abscess with bleeding
	K5733	Diverticulitis of large intestine without perforation or abscess with bleeding
	K625	Hemorrhage of anus and rectum
	K661	Hemoperitoneum
Other	D683	Hemorrhagic disorder due to circulating anticoagulants
	D699	Unspecified hemorrhagic conditions
	H0523	Orbital hemorrhage
	H113	Conjunctival hemorrhage
	H313	Choroidal hemorrhage and rupture
	H356	Retinal hemorrhage
	H431	Vitreous hemorrhage
	H44819	Hemophthalmos, unspecified eye

Supplementary Table 1 (*Continued*)

Type of Bleeding	ICD-10 Code	Description
	H450	Vitreous hemorrhage in diseases classified elsewhere
	H922	Otorrhagia
	I230	Hemopericardium as current complication following acute myocardial infarction
	I312	Hemopericardium NEC
	J942	Hemothorax
	M250	Hemarthrosis
	M7981	Nontraumatic hematoma of soft tissue
	N02	Recurrent and persistent hematuria
	N421	Congestion and hemorrhage of prostate
	N836	Hematosalpinx
	N837	Hematoma of broad ligament
	N857	Hematometra
	N897	Hematocolpos
	N92	Excessive, frequent and irregular menstruation
	N93	Other abnormal uterine and vaginal bleeding
	N950	Postmenopausal bleeding
	R04	Hemorrhage from respiratory passages
	R31	Unspecified hematuria
	R233	Spontaneous ecchymoses
	R58	Hemorrhage NEC
	T810	Hemorrhage and hematoma complicating a procedure NEC
	T792	Traumatic secondary and recurrent hemorrhage and seroma, initial encounter

GIB = gastrointestinal bleeding; ICD = International Classification of Diseases; ICH = intracranial hemorrhage; NEC = not elsewhere classified NOS = not otherwise specified.

Supplementary Table 2 Reasons for Censoring

	Type of Bleeding Event		
Reasons for Censoring	Intracranial Hemorrhage	Gastrointestinal Bleeding	Other Major Bleeding
Total number	14,407	14,407	14,407
Discontinuation of concomitant use, n (%)			
DOAC/VKA	2947 (20.5)	2861 (19.9)	2859 (19.8)
Antiplatelet	8591 (59.6)	8529 (59.2)	8518 (59.1)
Both	3 (0.02)	3 (0.02)	3 (0.02)
Switch of use, n (%)			
From DOAC to VKA	1 (0.01)	1 (0.01)	1 (0.01)
From VKA to DOAC	1 (0.01)	1 (0.01)	1 (0.01)
End of registration, n (%)	29 (0.2)	28 (0.2)	27 (0.2)
Death, n (%)	427 (3.0)	424 (2.9)	416 (2.9)
End of study period, n (%)	2136 (14.8)	2108 (14.6)	2084 (14.5)

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

Supplementary Table 3 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Drug-Specific Analysis)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9106	54	3508	1.5 (1.2-2.0)	[Reference]	[Reference]
Current concomitant dabigatran-antiplatelet use	2575	9	927	1.0 (0.4-1.8)	0.63 (0.31-1.28)	0.64 (0.32-1.30)
Current concomitant rivaroxaban-antiplatelet use	2207	1	446	0.2 (0.01-1.3)	0.13 (0.02-0.97)	0.12 (0.02-0.88)
Current concomitant apixaban-antiplatelet use	519	1	58	1.7 (0.04-9.6)	0.90 (0.12-6.64)	0.72 (0.09-5.61)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9106	181	3462	5.2 (4.5-6.1)	[Reference]	[Reference]
Current concomitant dabigatran-antiplatelet use	2575	44	918	4.8 (3.5-6.4)	0.91 (0.66-1.27)	1.10 (0.79-1.54)
Current concomitant rivaroxaban-antiplatelet use	2207	26	442	5.9 (3.8-8.6)	0.89 (0.59-1.35)	1.18 (0.75-1.87)
Current concomitant apixaban-antiplatelet use	519	2	58	3.5 (0.4-12.5)	0.45 (0.11-1.81)	0.54 (0.13-2.24)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9106	246	3421	7.2 (6.3-8.2)	[Reference]	[Reference]
Current concomitant dabigatran-antiplatelet use	2575	30	922	3.3 (2.2-4.7)	0.45 (0.31-0.66)	0.54 (0.37-0.80)
Current concomitant rivaroxaban-antiplatelet use	2207	28	442	6.3 (4.2-9.2)	0.77 (0.52-1.14)	1.01 (0.66-1.56)
Current concomitant apixaban-antiplatelet use	519	4	58	6.9 (1.9-17.7)	0.74 (0.28-2.01)	0.96 (0.34-2.66)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 4 Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Duration-Response Analysis)

Exposure	< 3 Months HR (95% CI)	3-5.9 Months HR (95% CI)	≥6 Months HR (95% CI)	*P* for Interaction
Intracranial hemorrhage				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.37 (0.15-0.92)	0.35 (0.04-2.82)	0.63 (0.22-1.87)	.73
Gastrointestinal bleeding				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.09 (0.75-1.57)	1.18 (0.61-2.29)	0.90 (0.48-1.70)	.83
Other major bleeding				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.67 (0.46-0.97)	0.84 (0.43-1.64)	0.62 (0.34-1.12)	.77

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.

Supplementary Table 5 Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Interaction with Age)

Exposure	≤75 Years of Age HR (95% CI)	>75 Years of Age HR (95% CI)	*P* for Interaction
Intracranial hemorrhage			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.23 (0.05-0.99)	0.63 (0.30-1.33)	.22
Gastrointestinal bleeding			
Current concomitant VKA-antiplatelet use	1.00 [Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.32 (0.86-2.04)	0.94 (0.64-1.37)	.22
Other major bleeding			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.78 (0.52-1.18)	0.61 (0.41-0.91)	.38

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.

Supplementary Table 6 Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Interaction with Sex)

Exposure	Female HR (95% CI)	Male HR (95% CI)	*P* for Interaction
Intracranial hemorrhage			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.66 (0.24-1.80)	0.37 (0.15-0.88)	.38
Gastrointestinal bleeding			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.34 (0.88-2.03)	0.93 (0.63-1.36)	.19
Other major bleeding			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.53 (0.32-0.89)	0.77 (0.54-1.09)	.24

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.

Supplementary Table 7 Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Interaction with HAS-BLED* Score)

Exposure	HAS-BLED Score 0-2 HR (95% CI)	HAS-BLED Score 3-7 HR (95% CI)	*P* for Interaction
Intracranial hemorrhage			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.62 (0.31-1.24)	—	.98
Gastrointestinal bleeding			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.25 (0.91-1.73)	0.72 (0.36-1.46)	.16
Other major bleeding			
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.68 (0.49-0.94)	0.79 (0.42-1.49)	*0.69*

CI = confidence interval; DOAC = direct oral anticoagulant; HAS-BLED = uncontrolled arterial hypertension, abnormal renal function, abnormal liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years old, alcohol-related disorders or drugs; HR = hazard ratio; VKA = vitamin K antagonist.

*We used a modified HAS-BLED score including uncontrolled arterial hypertension, abnormal renal or liver function, previous stroke or transient ischemic attack, bleeding history or predisposition, age >65 years, and alcohol-related disorders, because all patients were exposed to antiplatelets, and international normalized ratio values were not available. We defined uncontrolled arterial hypertension as intake of ≥2 antihypertensive drugs in the year prior to cohort entry.

Supplementary Table 8 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Genitourinary Bleeding Among Patients with Nonvalvular Atrial Fibrillation

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Current concomitant VKA-antiplatelet use	9106	59	3484	1.7 (1.3-2.2)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	29	1458	2.0 (1.3-2.9)	1.15 (0.74-1.81)	1.42 (0.88-2.27)
DOAC types						
Current concomitant VKA-antiplatelet use	9106	59	3484	1.7 (1.3-2.2)	[Reference]	[Reference]
Current concomitant dabigatran-antiplatelet use	2575	14	925	1.5 (0.8-2.5)	0.90 (0.50-1.62)	1.04 (0.58-1.87)
Current concomitant rivaroxaban-antiplatelet use	2207	13	445	2.9 (1.6-5.0)	1.67 (0.90-3.08)	2.81 (1.35-5.81)
Current concomitant apixaban-antiplatelet use	519	2	58	3.4 (0.4-12.4)	1.87 (0.45-7.81)	3.57 (0.78-16.38)

CI = confidence interval; DOAC = direct oral anticoagulants; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 9 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-ASA Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-ASA use	7243	41	2568	1.6 (1.2-2.2)	[Reference]	[Reference]
Current concomitant DOAC-ASA use	4557	9	1181	0.8 (0.4-1.5)	0.47 (0.23-0.97)	0.47 (0.22-0.99)
Gastrointestinal bleeding						
Current concomitant VKA-ASA use	7243	121	2543	4.8 (4.0-5.7)	[Reference]	[Reference]
Current concomitant DOAC-ASA use	4557	54	1171	4.6 (3.5-6.0)	0.89 (0.65-1.23)	1.15 (0.82-1.62)
Other major bleeding						
Current concomitant VKA-ASA use	7243	155	2522	6.1 (5.2-7.2)	[Reference]	[Reference]
Current concomitant DOAC-ASA use	4557	48	1173	4.1 (3.0-5.4)	0.63 (0.45-0.87)	0.75 (0.54-1.06)

ASA = acetylsalicylic acid; CI = confidence interval; DOAC = direct oral anticoagulants; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 10 Crude and Adjusted Hazard Ratios for the Association Between Concomitant Use of a DOAC with Multiple Antiplatelets and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant use of a VKA with multiple antiplatelets	1244	8	767	1.0 (0.5-2.1)	[Reference]	[Reference]
Current concomitant use of a DOAC with multiple antiplatelets	415	0	209	-	-	-
Gastrointestinal bleeding						
Current concomitant use of a VKA with multiple antiplatelets	1244	52	749	7.0 (5.2-9.1)	[Reference]	[Reference]
Current concomitant use of a DOAC with multiple antiplatelets	415	16	206	7.8 (4.4-12.6)	1.04 (0.59-1.82)	1.13 (0.63-2.04)
Other major bleeding						
Current concomitant use of a VKA with multiple antiplatelets	1244	76	737	10.3 (8.1-12.9)	[Reference]	[Reference]
Current concomitant use of a DOAC with multiple antiplatelets	415	11	208	5.3 (2.6-9.5)	0.49 (0.26-0.93)	0.56 (0.29-1.07)

CI = confidence interval; DOAC = direct oral anticoagulants; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 11 Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Nonvalvular Atrial Fibrillation (Interaction with the Way Patients Entered the Cohort)

Exposure	Addition of Antiplatelets HR (95% CI)	Addition of an Oral Anticoagulant HR (95% CI)	Concomitant Initiation of an Oral Anticoagulant and Antiplatelets HR (95% CI)	*P* for Interaction
Intracranial hemorrhage				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	0.61 (0.06-5.85)	0.46 (0.23-0.92)	—	.97
Gastrointestinal bleeding				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.66 (0.44-6.22)	1.03 (0.76-1.40)	1.65 (0.54-5.06)	.58
Other major bleeding				
Current concomitant VKA-antiplatelet use	[Reference]	[Reference]	[Reference]	
Current concomitant DOAC-antiplatelet use	1.96 (0.65-5.87)	0.63 (0.46-0.86)	0.78 (0.23-2.62)	.14

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.

Supplementary Table 12 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (15-Day Grace Period)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	8814	40	2568	1.6 (1.1-2.2)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5144	7	1157	0.6 (0.2-1.3)	0.39 (0.18-0.88)	0.39 (0.17-0.89)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	8814	147	2541	5.8 (4.9-6.8)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5144	58	1148	5.1 (3.8-6.5)	0.82 (0.60-1.11)	1.02 (0.74-1.40)
Other major bleeding						
Current concomitant VKA-antiplatelet use	8814	187	2517	7.4 (6.4-8.6)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5144	47	1151	4.1 (3.0-5.4)	0.52 (0.38-0.72)	0.61 (0.44-0.86)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 13 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (Stricter Outcome Definition)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9106	40	3508	1.1 (0.8-1.6)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	9	1461	0.6 (0.3-1.2)	0.51 (0.25-1.06)	0.47 (0.22-0.99)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9106	74	3488	2.1 (1.7-3.3)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	34	1457	2.3 (1.6-3.3)	1.00 (0.66-1.50)	1.21 (0.79-1.85)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9106	77	3481	2.2 (1.8-2.8)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	13	1461	0.9 (0.5-1.5)	0.39 (0.22-0.70)	0.42 (0.23-0.78)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 14 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (Intention-to-Treat)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9106	91	7579	1.2 (1.0-1.5)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	24	3763	0.6 (0.4-1.0)	0.53 (0.34-0.83)	0.58 (0.36-0.93)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9106	266	7477	3.6 (3.1-4.0)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	115	3717	3.1 (2.6-3.7)	0.84 (0.68-1.05)	1.05 (0.83-1.33)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9106	385	7422	5.2 (4.7-5.7)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	108	3722	2.9 (2.4-3.5)	0.54 (0.44-0.67)	0.67 (0.54-0.84)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 15 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (Excluding Patients with a Switch Between a VKA and a DOAC Prior to Cohort Entry)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9092	54	3503	1.5 (1.2-2.0)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5248	11	1444	0.8 (0.4-1.4)	0.48 (0.25-0.92)	0.47 (0.24-0.91)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9092	180	3458	5.2 (4.5-6.0)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5248	70	1432	4.9 (3.8-6.2)	0.85 (0.65-1.13)	1.08 (0.81-1.45)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9092	245	3416	7.2 (6.3-8.1)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5248	61	1433	4.3 (3.3-5.5)	0.56 (0.42-0.74)	0.68 (0.51-0.91)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 16 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (Competing Risk)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9106	54	3508	1.5 (1.2-2.0)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	11	1461	0.8 (0.4-1.4)	0.48 (0.25-0.92)	0.47 (0.24-0.93)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9106	181	3462	5.2 (4.5-6.1)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	72	1448	5.0 (3.9-6.3)	0.88 (0.67-1.15)	1.09 (0.82-1.45)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9106	246	3421	7.2 (6.3-8.2)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	62	1450	4.3 (3.3-5.5)	0.57 (0.43-0.75)	0.69 (0.52-0.92)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.

Supplementary Table 17 Crude and Adjusted Hazard Ratios for the Association Between Concomitant DOAC-Antiplatelet Use and the Risk of Bleeding Outcomes Among Patients with Non-valvular Atrial Fibrillation (Censoring on First Bleeding Event)

Exposure	Patients	Events	Person-Years	Incidence Rate* (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)†
Intracranial hemorrhage						
Current concomitant VKA-antiplatelet use	9106	51	3378	1.5 (1.1-2.0)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	11	1438	0.8 (0.4-1.4)	0.49 (0.25-0.94)	0.49 (0.25-0.96)
Gastrointestinal bleeding						
Current concomitant VKA-antiplatelet use	9106	178	3378	5.3 (4.5-6.1)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	70	1438	4.9 (3.8-6.2)	0.85 (0.64-1.12)	1.05 (0.78-1.41)
Other major bleeding						
Current concomitant VKA-antiplatelet use	9106	240	3378	7.1 (6.2-8.1)	[Reference]	[Reference]
Current concomitant DOAC-antiplatelet use	5301	61	1438	4.2 (3.2-5.5)	0.57 (0.43-0.75)	0.68 (0.51-0.91)

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; VKA = vitamin K antagonist.
*Per 100 person-years.
†Adjusted for disease risk score and calendar year.