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Major bleeding risk associated with oral anticoagulant in real clinical practice.

A multicentre 3-year period population-based prospective cohort study

Short running title: Major bleeding risk and oral anticoagulant

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Abstract (245 words)

AIMS

The objective was to compare major bleeding risk of DOACs (per type and dose) with VKAs,

irrespective of indication, using real-world data.

METHODS

A population-based prospective cohort study, using the French national health data system

(SNIIRAM), identified 47,469 adults living within five well-defined geographical areas, who

were new users of oral anticoagulants in the period 2013-2015: 20,205 VKA users, 19,579

rivaroxaban users, 4,225 dabigatran users and 3,460 apixaban users. From all emergency

departments within these areas, clinical data for all adults referred for bleeding was

collected and medically validated. The databases were linked for common key variables. The

main outcome measure was major bleeding: intracranial haemorrhage, major

gastrointestinal bleeding and other major bleeding events. Hazard ratios were derived from

adjusted Cox proportional hazard models. We used propensity score weighting as a

sensitivity analysis, with separate analyses according to indications (atrial fibrillation or

venous thromboembolism).

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RESULTS

Compared to VKAs, high and low-dose DOACs were associated with a reduced risk of intracranial haemorrhage (adjusted hazard ratio 0.55, 95% confidence interval 0.37 to 0.82 and 0.54, 0.26 to 1.12 respectively), and a reduced risk of other major bleeding events (0.41, 0.29 to 0.58 and 0.41, 0.22 to 0.79 respectively), irrespective of duration and indication. Neither DOAC dose evidenced any significant difference from VKAs in terms of risk of major gastrointestinal bleeding.

CONCLUSIONS

There is a clear benefit of using DOACs with regard to intracranial haemorrhage. The study provides new insight into major gastrointestinal and other major bleeding events.

STATEMENT1: WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Meta-analyses of randomized trials have identified higher rates of gastrointestinal bleeding for DOACs compared to warfarin.

- All DOACs significantly reduce the risk of intracranial bleeding compared to adjusted-dose warfarin.

- Observational studies on real-world data, mostly based on reimbursement claims, have been inconsistent and generally imprecise.

STATEMENT2: WHAT THIS STUDY ADDS

- This study included new users of oral anticoagulants, irrespective of indication, thus broadening the view on safety issues.

- The medical validation of all bleeding events supports the validity of the results.

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- DOACs were associated with a decreased risk of other (non-gastrointestinal non-intracranial) major bleeding events among patients, irrespective of duration, dose and indication, compared to VKAs.

Introduction

Anticoagulants have demonstrated significant benefits in preventing venous or arterial thrombotic events, especially for stroke, atrial fibrillation (AF), venous thromboembolism (VTE) and in presence of mechanical heart valves [1]. These drugs are commonly prescribed, and their long-term use has been on the increase , particularly among the elderly. Bleeding is the most well-known and feared complication of anticoagulants. Numerous studies on drug-induced adverse events have reported anticoagulants as the first medication class involved in resort to emergency departments and hospitalization among adults [2], mostly for haemorrhage, and particularly intracranial haemorrhage (ICH), which results in substantial morbidity and mortality [3].

Direct oral anticoagulants (DOACs), including direct thrombin inhibitors and factor Xa inhibitors, are now available for the prevention of stroke and systemic embolism. Pivotal randomised clinical trials (RCTs) have reported a very considerable reduction in the relative risk of ICH, ranging from 23% for rivaroxaban [4] to almost 70% for dabigatran etexilate 110 mg twice daily [5]. Major gastrointestinal (GI) bleeding under DOACs has been either as frequently observed as with warfarin [5,6] or more frequently observed [4,5] than with warfarin.

Real-world data on bleeding risk is needed, particularly as the selection criteria applied to RCTs may have artificially improved the picture. Trial patients often have a lower risk of bleeding than do those in ordinary practice, because trials often exclude patients with the

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highest risk. It is important to know whether the bleeding event rates observed in RCTs are reflected in routine clinical practice, and whether there are differences across the different DOACs for bleeding risk.

Several analyses using large reimbursement claims databases have yielded reassuring findings in line with those from RCTs: a lower rate of ICH with both doses of dabigatran [7-18], with rivaroxaban [16,18-20] and with apixaban [13,16,18,20], similar [7,8,10,11,14,17,18] or higher rates of GI bleeding associated with dabigatran [7,8, 9,12,13,21] or rivaroxaban [18,22] compared to warfarin; and lower rates of GI bleeding associated with apixaban [13,18]. Data on dabigatran from the US is also reassuring, bearing in mind that the FDA has not authorised the 110 mg dose for AF patients [10,12,17,21,23-27].

Meta-analyses [28-31] of these observational studies on real-world data, mostly based on reimbursement claims, concluded to heterogeneity across studies. Assessing bleeding from reimbursement claims is liable to be influenced by variability in coding and misclassification, which could bias relative risk estimates. In addition, most studies focused on patients with non-valvular AF. Only three studies have provided data for a wider population [23,25,32]. We conducted a population-based cohort study within well-defined areas, including new users of oral anticoagulants, collecting data prospectively and medically validating all major bleeding events over a three-year period. Our main objective was to compare major bleeding risk per type and dose of DOACs with VKAs, whatever the indication.

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Methods

Study design and participants

We conducted a prospective population-based cohort study using the French national health insurance database (SNIIRAM). We were provided access to a subset of all adult subjects (> 18 years) living within five well-defined areas, with at least one reimbursement for an oral anticoagulant (dabigatran, rivaroxaban, apixaban or VKA) in 2013-2015. In order to medically validate all bleeding events occurring in this cohort, we linked these individuals to an ad-hoc data collection from all emergency departments, either public or private, located in these five areas. The areas were defined using lists of postcodes around five large French cities (Angers, Brest, Grenoble, Nantes and Rennes, all with a university hospital, covering slightly more than 3 million inhabitants). This list comprises all municipalities in which inhabitants are referred in case of need to one of the participating emergency services . The study received regulatory approval (CNIL, DR-2013-488, with subsequent substantial changes DR-2016-489).

Firstly, the SNIIRAM anonymously and comprehensively links a healthcare reimbursement database (DCIR) to the French hospital discharge database (PMSI): the DCIR contains anonymous individual data on all reimbursements for health expenditure, including drugs; the database does not provide any direct information on the medical indication for each reimbursement; the PMSI provides hospital discharge diagnoses (ICD-10 code) as well as details of medical acts.

Secondly, an ad-hoc data collection from emergency departments gathered clinical data for all adult subjects referred for bleeding between January 1, 2013 and December 31, 2015, focusing on oral anticoagulants, the type of bleeding, and also collecting demographics (month and year of birth, gender) and date of hospital admission. To identify patients

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referred for bleeding, the first step was a search based on carefully-chosen haemorrhage-related diagnostic codes or the implementation of specific emergency therapies (red blood transfusion, platelet transfusion, vitamin K, protamin sulfate, prothrombin complex concentrate and FEIBA). This search was applied to the electronic health records from emergency departments. A pilot study found good sensitivity for the computer search [33]. In each area, a referent expert medical doctor checked all records identified for oral anticoagulant exposure and severe bleeding criteria (see below for details).

Thirdly, the SNIIRAM sample and the ad-hoc data collection sample were linked using common key variables (date of birth (month, year), gender, date of hospital entry and discharge, type of oral anticoagulant, and care facility involved). Pairs were defined from emergency department stays identified in the SNIIRAM subset, matched on the key variables to a bleeding event in the ad-hoc data collection (see reference [34] for matching details).

Outcomes

We anticipated that the estimates for associations between anticoagulant and major bleeding could be heterogeneous across the three types of major bleeding, and we therefore defined three classes for the primary outcome: ICH, GI bleeding and other major bleeding events. Major bleeding was defined from at least one of the following criteria: unstable haemodynamics (systolic arterial pressure < 90 mmHg or mean arterial pressure < 65 mm Hg) or haemorrhagic shock, uncontrollable bleeding, need for transfusion or haemostatic procedure (embolization, endoscopic procedure, surgery). The location or the symptoms then defined the type: ICH for intracranial haemorrhage, acute GI bleeding, and other major bleeding in life-threatening locations - intraspinal, intraocular, retroperitoneal,

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pericardial, thoracic, intra-articular, or intramuscular haematoma with compartment syndrome. We also considered epistaxis with at least two procedures of nasal packing, and hematuria when bleeding lasted more than 12 hours despite bladder washing as "other" major bleeding events. There was a slight alteration with respect to the International Society on Thrombosis and Haemostasis (ISTH) classification of major bleeding events [35] because in our dataset no information was available on haemoglobin levels.

The secondary outcome was all-cause mortality.

Main exposure: oral anticoagulant

Only "new users", defined as having had no oral anti-coagulant exposure in 2012, were analysed.

The indication for anticoagulant prescription was derived from the main discharge diagnosis and/or medical acts performed in the 30 days before the first observed issue of anticoagulant (Table S1 for code definitions). "Medical acts" include imagery procedures such as Doppler ultrasonography (of the lower limb for a suspicion of deep vein thrombosis, echocardiography), CT scan, MRI; and therapeutic procedures (thrombectomy, fibrinolysis, thrombo-aspiration, transcutaneous cardio-version, plaster cast, osteosynthesis, orthopaedic surgery, valve surgery, vascular by-pass, angioplasty, coronary surgery).

For patients who were not hospitalised and had no "medical act" within a month of the start of OACs, the indication was not determined, and classified as 'unknown'. For the at-risk cohort identified through the SNIIRAM database, we classified person-month exposure to dabigatran, rivaroxaban, apixaban or VKAs on the basis of their issue dates. Exposure groups and index dates were defined at first dispensation. We differentiated high-dose (dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg per day) and low-dose (dabigatran

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220 mg or rivaroxaban 10 mg or apixaban 5 mg per day). For DOACs, they are prescribed at fixed doses and the quantity dispensed by pharmacists is limited by law to 30 days, so the number of days of supply was established as [last issue date minus first issue date] plus 30 days. For VKAs, computing supply was not straightforward as we lacked information on dosing instructions. The number of days of supply was established as [last issue date minus first issue date] plus 60 days; we checked that there was at least one INR measure within the previous two months.

Patients were censored in case of discontinuation of oral anticoagulants (using the end date of supply as previously described) or switch (from VKAs to DOACs or vice versa), or date of dose change for DOACs (from high-dose to low-dose or vice-versa), or death, or major bleeding event (as previously defined), or moving outside the area, or end of follow-up, whichever occurred first.

The main exposure was further subdivided according to whether the anticoagulant drug was prescribed alone or in combination with an antiplatelet drug (aspirin, clopidogrel, ticagrelor, or prasugrel) and according to the duration of use (under 6 months, 6 to 12 months or over one year).

Statistical analysis

Patient characteristics and descriptive incidence rates were explored first. Co-morbidities (Table S1 for code definitions) and co-medication (listed in Table 1) were retrieved from SNIIRAM. We calculated a modified HAS-B(L)ED score (adapted from Pister et al. [36]) as a measure of bleeding risk and a co-morbidity score (Charlson's index adapted by Bannay et al. [37], see Tables S2 and S3 for definitions of scores). Crude incidence rates (IR) were calculated for the first bleeding episode per 10,000 person-months according to the type of

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bleeding, the type of oral anticoagulant (VKAs, DOAC high-dose or DOAC low-dose), and the duration of use (under 6 months, 6 to 12 months or over one year) and the HAS-B(L)ED score level.

Cox proportional hazard regression analyses were conducted for each type of bleeding event to determine hazard ratios for DOACs (high-dose or low-dose) versus VKAs, both unadjusted and adjusted on known patient characteristics: gender, modified HAS-B(L)ED score, and co-morbidities using the modified Charlson index. For each particular type of bleeding event, censoring occurred when death or any other type of bleeding event occurred, whichever first.

For each outcome we tested interactions between exposure and gender, modified HAS-B(L)ED score (<2, 2 and ≥3), and the modified Charlson index (four classes). We also tested interaction with time. Subgroup analyses were performed for some components of the HAS-BLED score: firstly, a concomitant antiplatelet regimen defined as any antiplatelet agents dispensed at least once concomitantly with oral anticoagulant after the index date, and secondly age (under or over 65 years).

As a secondary analysis, Cox proportional hazard regression models were run to estimate overall survival for DOACs (high-dose or low-dose) versus VKAs.

We conducted four sensitivity analyses to assess the robustness of our findings. First, we restricted the study population to patients without a presumed orthopaedic indication and ran the same Cox model used in the main analysis. Second, we performed separate analyses for the two main indications, AF or stroke, and acute venous thromboembolism. We regenerated the probability of treatment, DOACs (high-dose or low dose) versus VKAs in the AF or stroke population, and DOACs (high-dose) versus VKAs in the acute venous thromboembolism population using logistic regression models (a multinomial regression in

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the AF or stroke population) using 22 pre-specified variables (listed in Tables S4 and S5 along with standardized differences). We then used the stabilized inverse probability of treatment weighting (SIPTW) based on the propensity score [38] as weights in Cox proportional hazard regression models. The weights were truncated by resetting the value of weights greater (or lower) than the 99th (1st) percentile to the value of the 99th (1st) percentile [39]. Covariate balance between the weighted cohorts was assessed using standardized mean differences. To estimate the impact of absolute risks, we calculated the numbers needed to harm using weighted hazard ratios [40]. Third, adjusted Cox proportional hazard regression models were run to compare different DOACs, using apixaban as a reference. Fourth, we identified any hospitalisation that occurred outside the pre-specified area, with ICD-10 codes as primary discharge diagnoses that could be related to major bleeding, using a published list: [41] indeed, some subjects can experience bleeding while on holiday or travelling (i.e. only temporarily outside the area), and therefore their bleeding event cannot be medically validated from chart review. Cox proportional hazard regression analyses were run using a modified dataset including these events. All statistical tests were two-tailed and P-values <0.05 were considered significant. Statistical analyses were performed using SAS software 9.4 (SAS Institute, Cary, N.C., USA). Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY

Results

Cohort characteristics

A cohort generation flowchart is presented in Fig 1: 47,469 patients who had started anticoagulants between 2013 and 2015 (new users) were eligible for inclusion. Baseline characteristics in relation to the type of oral anticoagulant first prescribed are presented in

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Table 1. The mean age was 70 years (median, 73 years, Q1-Q3, 62-82) and 51% were males.

In all, 52% were diagnosed with AF, leaving 48% of the patients prescribed anticoagulants

for other indications: mostly a diagnosis of venous thromboembolism (VTE) (22%) or VTE

prevention following lower limb orthopaedic surgery (13%).

Patients treated with rivaroxaban or dabigatran at high doses were younger, and more likely

to be male. Patients treated with any of the DOACs whatever the dose had lower co-

morbidity (modified Charlson index) and bleeding risk (modified HAS-B(L)ED) than patients

treated with VKAs.

The median follow-up time was different between VKA, 234 days (25th, 75th percentile;

116, 510), high-dose, DOAC 163 days (67, 412), and low-dose DOAC, 60 days (60, 119).

The moment of censoring and the numbers and reasons involved are described in Figure S1

and Table S6.

The end of follow-up and treatment discontinuation were the most common reasons for

censoring. End of follow-up was the first reason among Apixaban users (74% for high dose

and 62% for low dose), which could be explained by the fact it was the last to join the

market. Discontinuation ranked ahead of end of follow-up for low-dose Dabigatran and low-

dose Rivaroxaban; this is intuitive, as low doses are associated with short-term treatment.

Differences in follow-up or treatment discontinuation timing across anticoagulant classes

could bias estimates if there was an interaction with time. We checked for an interaction of

this nature and did not detect any significant interaction.

We observed that switching and dose change (for DOACs) were uncommon except for high-

dose Dabigatran .

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Lower limb orthopaedic surgery was the presumed indication observed for 5829 (60%) out of 9605 patients with low-dose DOAC. In this context, the duration of treatment is short (2 weeks for knee replacement and 5 weeks for hip replacement).

Incidence rates

A total of 573 (1.2%) patients experienced a first major bleeding episode. The fatality rate was 56/573 = 9.77%. Table S7 shows the number of bleeding events according to bleeding site and indication (panel A), and anticoagulant drug (panel B). Nearly all major bleeding events (98%) occurred among patients for whom an anticoagulant was prescribed for AF or VTE.

The crude incidence rates for all major bleeding were higher during the first 6 months of therapy than during the '6-12 months' period, overall (S2 Figure). There was a statistically significant linear association between HAS-B(L)ED and all major bleeding.

Among VKA users, the rates were higher for all bleeding sites, with higher HAS-B(L)ED scores (Table S8). Incidence rates for ICH and other major bleeding events were lower among DOAC users than VKA users irrespective of the DOAC dose (high or low).

We also observed 2196 deaths. The incidence rate per 100 person-years (95%CL) was 9.05 (8.63 to 9.49) for VKA, 2.25 (2.01 to 2.51) for high-dose DOAC, and 4.28 (3.71 to 4.94) for low-dose DOAC.

Bleeding risk and anticoagulant exposure

Forest plots showing adjusted HRs for each first bleeding episode and all-cause mortality for DOACs compared to VKAs are presented in Fig 2. There were no interactions for any bleeding outcome between anticoagulant exposure and gender, modified HAS-B(L)ED score,

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or modified Charlson's index. The tests for interaction with time were all non-significant (p value > .15). Proportional hazard assumptions held true. All results were therefore derived from Cox multivariate proportional models including gender, modified HAS-B(L)ED score, and modified Charlson's index. Compared to VKAs, DOACs, either high or low-dose, were associated with a reduced risk of ICH and other major bleeding events, as well as with all-cause mortality. We observed consistent results across the different types of other major bleeding events (Figure S3). There was no obvious heterogeneity across the different types of DOACs in relation to any major bleeding outcome, or all-cause mortality (Figure S4). There was no statistically significant association between DOACs (whether low or high-dose) and major GI bleeding compared to VKAs (Figure 2 and S5).

There were no relevant interactions for any bleeding outcome or for all-cause mortality between anticoagulant exposure and concomitant antiplatelet drug use or age (elderly people > 65 years, HASB(L)ED score level) (data not shown).

Sensitivity analyses

The results of the sensitivity analyses are summarized in Figures 2, 3 and S6. Restricting the study population to patients without presumed orthopaedic indications led to estimates close to the null, but still statistically significant for other major bleeding and all-cause mortality; very few events were lost (3 GI bleedings and 9 deaths) but person-time at risk decreased by 30% (Figure 2). Analyses were then conducted in sub-cohorts of new anticoagulant users with AF (n = 24,505) or VTE (n = 10,380). Using the SIPTW, the weighted cohorts were well balanced across all covariates (Tables S4 and S5).

Forest plots showing the weighted HRs for each bleeding event and all-cause mortality for DOACs compared to VKAs, are provided in Fig 3. Among patients with AF, DOACs were

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associated with a lower risk of other major bleeding events, and better overall survival than VKAs. Neither dose showed significant differences from VKAs in terms of ICH risk or GI bleeding risk. The same pattern was observed among patients with VTE.

Forest plots showing adjusted HRs for all-cause mortality for dabigatran, rivaroxaban or VKAs, using apixaban as a reference, are provided in Figure S6. Among patients with AF, high-dose apixaban was associated with better overall survival than VKAs and rivaroxaban. A re-analysis including 93 major bleeding events occurring outside the study region did not change the hazard ratios (data not shown).

Numbers-needed-to-harm

Figure S7 shows the numbers-needed-to-harm to assess the risk of DOACs in comparison with VKAs. Overall, the number-needed-to-harm (to observe one extra ICH or any other major non-GI bleeding event) remained fairly high.

Discussion

This population-based cohort study was based not only on an administrative healthcare database, but also on a prospective clinical data collection with medical validation of all bleeding events. It showed a decreased risk of ICH, other major non-GI bleeding events, and all-cause mortality associated with the use of DOACs, whether low- or high-dose, irrespective of duration and indication, compared to VKAs. Neither DOAC dose differed significantly from VKAs in terms of GI bleeding risk. Among patients with AF, high-dose apixaban was associated with better overall survival than VKAs or rivaroxaban. Our findings for new anticoagulant users generally, whatever the indication, provide more generalisable evidence than findings from subsets of patients with only AF or VTE.

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Strengths. Our large comprehensive study is unique by its ability to directly compare different DOACs, including the different doses, encompassing all indications, in the exploration of an important and common safety outcome. This minimizes a bias that affects the external validity of studies focusing on hospital data only, whereby patients diagnosed and managed in primary care are not included. Indeed, roughly the same numbers of patients without AF are also prescribed anticoagulants (note the 48% in our study). We thus enhanced representativeness. We hypothesised that bleeding risk related to oral anticoagulants was mostly related to patient characteristics, not to the indication for anticoagulant use.

The other strength of our study is that it retrieves and links data from a prospective multi-centre clinical study and data from a public healthcare system database that covers all residents within the defined area. As a result, the overall dataset gave us a complete picture of all hospitalizations and prescriptions dispensed, as well as the medical validation of bleeding events. On the one hand, this complete data coverage within the defined area eliminates a potential selection and recall bias, which is a problem in hospital-based observational studies; on the other hand, the clinical data enhances the validity of outcome measurements, minimising classification bias, which is a problem in administrative databases. There is indeed a risk of misclassification related to coding errors at the time of hospital admissions; this may not be very likely for serious conditions like bleeding. However, the absence of validation could lead to overestimating incidence rates for major GI bleeding or urogenital bleeding [42].

We adopted a new-user design capturing all events after the start of treatment. We ran a Cox proportional hazard model as the main analysis, adjusting for all available confounding

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factors, and we also undertook a sensitivity analysis using stabilized inverse probability of treatment weighting using a propensity score, which showed similar results.

Limitations. Exposure in our study was based on reimbursement claims data. We studied drug exposure on the basis of pharmacy dispensations but had no information on patients' actual intake. The lack of information on patient adherence could have led to incorrect estimations of exposure, but the clinical validation of major bleeding made it possible to check that patients were still receiving anticoagulants at the time of bleeding. Bleeding events could be more likely to be detected among patients prescribed VKAs than among those taking DOACs, introducing a surveillance bias, because of the regular monitoring required for VKA users. As major bleeding requires hospital referral, it is less likely to be missed among patients taking DOACs. This limitation does not apply to deaths. Although we extensively adjusted for baseline differences, which should have helped to reduce the possible indication bias, it is unlikely that we captured the full extent of different prescribing behaviours, and some unmeasured, residual confounding factors could still be present. Our study lacked certain patient characteristics (such as smoking and weight - but we think they are not really confounders), or time-within-therapeutic-range for patients receiving VKAs.

Covering all indications and also including patients who received low-dose DOAC for brief thromboprophylaxis after orthopaedic surgery may have impacted the overall estimate. Sensitivity analyses, restricting the study population either to patients without a presumed orthopaedic indication, or to patients with AF, showed consistent estimates, closer to the null than that for the entire population, but still significant for other major bleeding.

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Discussion of main results in relation to other studies. In the comparison of our findings with pivotal outcome trials and observational studies, caution is required, as there are differences in the study populations, definitions of bleeding and healthcare systems, as well as other factors that are difficult to take into account. To facilitate comparison with other studies, we show analyses separately for patients with AF and VTE, and for high or low-dose DOAC.

Incidence rates for bleeding events for patients taking warfarin or VKAs highlight the way in which previous observational studies differ from ours, as incidence rates are linked to a number of risk factors. In other word, by comparing incidence rates among patients taking warfarin or VKAs, we thought we could compare background characteristics of the populations under study. Our findings were in line with Danish studies [43,44] as well as with a study in the UK [32] for GI bleeding rates and ICH rates, but our rates were much lower than those reported in studies using US insurance data [12,23,25].

Intracranial haemorrhage. A recent meta-analysis [30] of observational studies reported a large effect of all three DOACs studied on ICH, with relative reductions in incidence of 36% for rivaroxaban, 55% for apixaban, and 58% for dabigatran. There was significant heterogeneity for rivaroxaban. The studies included focused on patients with AF. However, a more recent study [32], not included in the meta-analysis, showed that the use of rivaroxaban was associated with a lower risk of ICH among patients without AF but not among patients with AF.

Gastrointestinal bleeding. In landmark trials [4–6], dabigatran and rivaroxaban were both associated with a higher rate of GI bleeding than warfarin, whereas apixaban had a lower rate. Since then, numerous post hoc analyses and meta-analyses of this data have concluded that DOACs were likely to involve a higher risk of GI bleeding compared to

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warfarin, which was related to the use of higher doses, particularly for dabigatran [45–49]. There was no standard definition of GI bleeding in the RCTs, limiting the interpretation of the data, collected as adverse events and coded as such. Moreover, the use of warfarin in the clinical trial setting is likely to be higher than its use in daily practice. Finally, patients enrolled in clinical trials are often not representative of real-world practice. Reports from observational studies using various large administrative datasets have reported contradictory findings [7,12,14,23,25,26,50], and all have had substantial limitations. Mainly, their data is conditional on the accuracy of administrative coding for diagnoses, and the primary outcome of GI bleeding was not reviewed. One study suggested that the risk of GI bleeding, validated by a manual chart review, was lower with the use of DOACs than with warfarin, irrespective of the indication [51]. More recently, a study in primary care setting reported that apixaban was associated with a decreased risk of GI bleeding, irrespective of indication [32]. Our study reported no significant difference for either high or low-dose DOACs compared to VKAs. It is worth noting that not all patients admitted for GI bleeding were categorised as having an outcome because our criteria for major bleeding were more stringent, based on clinical judgement and not solely relying on hospital referral.

Other major bleeding events. Few studies have reported on major bleeding events other than ICH and GI bleeding. In a multicenter prospective study, Becattini et al. reported heterogeneous results with significantly more frequent hematuria and upper airway bleeding events and less frequent retroperitoneal and soft/tissue hematomas with DOACs compared to VKAs [52]. A large real-world evaluation in the USA based on elderly Medicare patients with nonvalvular AF reported consistent results across all major bleeding events when comparing apixaban to warfarin, but it also reported some heterogeneity when comparing dabigatran (mostly high-dose) or rivaroxaban to warfarin [53]. A nationwide

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Norwegian registry study showed a statistically significant reduction in "other" major bleeding events when comparing dabigatran or apixaban (mostly high-dose for both) to warfarin [13]. A cohort of patients with nonvalvular AF from a large US commercial database combined with Medicare initiating dabigatran or warfarin treatment showed a statistically significant reduction for other major bleeding events with dabigatran [26]. Definition was based on an algorithm using administrative inpatient claims with either a primary or secondary diagnosis [13,26,53] and these studies reported higher incidence rates than our study. However, our main analysis, combining all DOACs, showed a similar pattern for "other" major bleeding events to that for ICH. In addition, we observed consistent results across the different types of bleeding.

Major bleeding and all-cause mortality.

A meta-analysis of DOAC trials found a 10% reduction in all-cause mortality with high-dose DOACs compared to warfarin [49]. However, mortality was not significantly different between rivaroxaban and warfarin [4], whereas the mortality reduction was significant for apixaban (11% reduction)[6] and of borderline significance for high-dose dabigatran [5]. A meta-analysis of observational studies identified 6 studies involving 319,486 patients that compared dabigatran to VKAs with regard to survival and concluded to a significant benefit with dabigatran, but with substantial heterogeneity across studies [30]. Only one study involving 41,785 patients reported better survival rates with apixaban than with VKAs [43]. There was no statistical difference between rivaroxaban and VKAs for death in two studies that included 51,795 patients [19,30]. There was again significant heterogeneity. Our analysis is in line with these observations, showing a differential effect of DOACs, with better overall survival with high-dose apixaban compared to rivaroxaban or warfarin,

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whereas there was no substantial difference between high-dose dabigatran and apixaban among patients with AF.

To conclude, our study in real-world practice confirms a clear benefit for DOACs with regard to ICH. It provides new insight into major GI and other major bleeding events, by integrating a medical validation of all bleeding events. While there is reassurance concerning the safety of DOACs for other major non-GI bleeding events, neither dose of DOACs differed significantly from VKAs for major GI bleeding. It is worth noting that incidence rates for major bleeding remained fairly low with DOACs and the numbers needed to observe one ICH or one other major bleeding event remained fairly large. Lastly, there was a substantial benefit of DOACs in relation to all-cause mortality.

Acknowledgement

Contributors

JB, EO, EN participated in the analysis and interpretation of the data and the drafting of the manuscript. JB and EO participated in the study concept and design. JB, EO, EN, FB, MM, LP, PMR, KL and LMS participated in the critical revision of the report. EN, FB participated in the statistical analyses.

Declaration of interests

We have no competing interests to declare.

Data access and cleaning methods

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The authors (JB, FB, EN and EO) had full access to all of the data (extracted from SNIIRAM

and clinical database) that was used to generate the study population. The database

extracted was stored locally in a dedicated and secure data centre: extraction was

performed by CNAMTS; csv data files were imported into the MySql database with a

physical data model consistent with the original SNIIRAM database design; investigators had

no direct access to SNIIRAM. Metrics and visual tools were used to check data completeness

and fit to expected data extraction: the metrics included the number of patients extracted

(compared to the expected number), and the stability of reimbursement frequencies over

time in order to validate data completeness at a population level.

Data sharing

The statistical code is available from the corresponding author. Under French law and

regulations, patient-level data from SNIIRAM cannot be made available.

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Table 1 Characteristics of subjects by drug exposure

Characteristics	VKA N = 20 205	Dabigatran Low N = 2 944	Dabigatran High N = 1 281	Rivaroxaban Low N =5 246	Rivaroxaban High N = 14 333	Apixaban Low N = 1 415	Apixaban High N =2 045
Age, median (Q1-Q3)	77 (64-85)	76 (65-83)	67 (60-74)	68 (60-76)	69 (58-79)	82 (74-86)	72 (64-78)
> 65 years	14616 (72.3)	2200 (74.7)	744 (58.1)	3028 (57.7)	8542 (59.6)	1224 (86.5)	1473 (72.0)
Gender, female	10354 (51.2)	1533 (52.1)	445 (34.7)	2892 (55.1)	6451 (45.0)	825 (58.3)	751 (36.7)
Presumed indication [a]							
AF or peripheral embolism or stroke	11535 (57.1)	1275 (43.3)	946 (73.8)	242 (4.6)	7774 (54.2)	913 (64.5)	1820 (89.0)
VTE	5662 (28.0)	-	53 (4.1)	-	4598 (32.1)	-	67 (3.3)
Lower limb orthopaedic surgery	218 (1.1)	1138 (38.7)	-	4371 (83.3)	-	320 (22.6)	-
Valvular heart disease	406 (2.0)	-	5 (0.4)	-	28 (0.2)	1 (0.1)	6 (0.3)
Other or unknown	2384 (11.8)	531 (18.0)	277 (21.6)	633 (12.1)	1933 (13.5)	181 (12.8)	152 (7.4)
Comorbidities [b]							
Diabetes mellitus	3204 (15.9)	327 (11.1)	178 (13.9)	503 (9.6)	1564 (10.9)	194 (13.7)	333 (16.3)
Coronary heart disease	2451 (12.1)	131 (4.4)	65 (5.1)	104 (2.0)	595 (4.2)	123 (8.7)	126 (6.2)
Hematologic or immune disease	1581 (7.8)	69 (2.3)	14 (1.1)	147 (2.8)	301 (2.1)	55 (3.9)	40 (2.0)
Medication use							
Lipid-lowering drug (last year)	8471 (41.9)	1135 (38.6)	466 (36.4)	1607 (30.6)	4718 (32.9)	567 (40.1)	949 (46.4)
Antiulcer agent (last year)	10626 (52.6)	1434 (48.7)	496 (38.7)	3291 (62.7)	6045 (42.2)	707 (50.0)	856 (41.9)
Antiplatelet agents (recent use)	6320 (31.3)	847 (28.8)	365 (28.5)	723 (13.8)	3579 (25.0)	536 (37.9)	729 (35.6)
NSAID (last year)	5000 (24.7)	1117 (37.9)	455 (35.5)	3341 (63.7)	4841 (33.8)	395 (27.9)	552 (27.0)
Modified HAS-B(L)ED score [c]							
0 – 1	8151 (40.3)	1399 (47.5)	751 (58.6)	2956 (56.3)	8614 (60.1)	547 (38.7)	1037 (50.7)
2	6661 (33.0)	1068 (36.3)	392 (30.6)	1560 (29.7)	4109 (28.7)	585 (41.3)	750 (36.7)
≥ 3	5393 (26.7)	477 (16.2)	138 (10.8)	730 (13.9)	1610 (11.2)	283 (20.0)	258 (12.6)

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Concomitant medications [d]							
Antiplatelet agents	5218 (25.8)	503 (17.1)	194 (15.1)	719 (13.7)	1848 (12.9)	241 (17.0)	265 (13.0)
NSAID	1549 (7.7)	394 (13.4)	187 (14.6)	1736 (33.1)	1683 (11.7)	132 (9.3)	143 (7.0)
Modified Charlson comorbidity index [e]							
0	10060 (49.8)	2105 (71.5)	937 (73.1)	4410 (84.1)	10629 (74.2)	870 (61.5)	1379 (67.4)
1-2	6244 (30.9)	617 (21.0)	275 (21.5)	721 (13.7)	2867 (20.0)	392 (27.7)	512 (25.0)
3-4	2705 (13.4)	182 (6.2)	63 (4.9)	78 (1.5)	593 (4.1)	121 (8.6)	118 (5.8)
≥ 5	1196 (5.9)	40 (1.4)	6 (0.5)	37 (0.7)	244 (1.7)	32 (2.3)	36 (1.8)

Values are numbers (percentages) unless stated otherwise; high: dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg per day; low: dabigatran 220 mg or rivaroxaban 10 mg or apixaban 5 mg per day; [a] based on hospital discharge main diagnosis (according to ICD-10 or medical act classification in the month before the index date; [b] based on hospital discharge diagnosis (according to ICD-10 or co-medications (ATC system) in the previous year, see table S1 for details; [c] The HAS-BLED score assigns points for the presence of hypertension, abnormal renal or liver function, stroke, bleeding history, age 65 years or older, and antiplatelet drug or alcohol use. Labile INR was excluded from our scoring; see table S2 for details; [d] at least one delivery concomitant with any anticoagulant; [e] as defined by Bannay et al, see table S3 for details; NSAID denotes non-steroidal anti-inflammatory drug; recent use was defined by at least 2 deliveries in the 3 months before index date
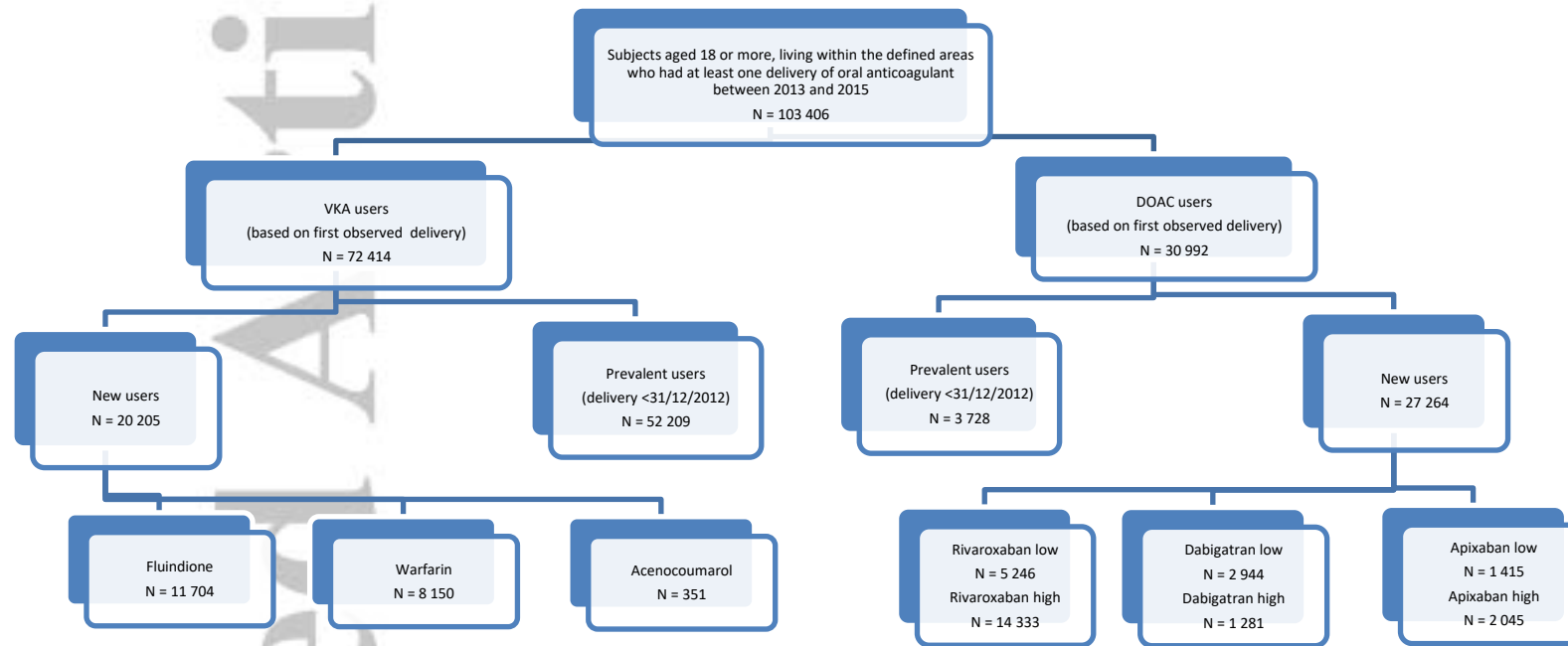
Figure 1. Study population
High denotes full dose (dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg per day) and low, reduced dose (dabigatran 220 mg or rivaroxaban 10 mg or apixaban 5 mg per day) ; VKA denotes Vitamin K antagonist and DOAC direct oral anticoagulants.

	Events (100p-yrs)		HR (CI 95%)
Intracranial bleeding			
VKA	105 (1.9)		1.00
DOAC low-dose			
All population	8 (0.4)		0.36 (0.18-0.76)
Restricted population	8 (0.3)		0.54 (0.26-1.12)
DOAC high-dose	35 (1.4)		0.55 (0.37-0.82)
GI bleeding			
VKA	126 (1.9)		1.00
DOAC low-dose			
All population	19 (0.4)		0.82 (0.50-1.35)
Restricted population	16 (0.3)		1.03 (0.61-1.75)
DOAC high-dose	57 (1.4)		0.94 (0.67-1.31)
Other major bleeding			
VKA	169 (1.9)		1.00
DOAC low-dose			
All population	10 (0.4)		0.27 (0.14-0.50)
Restricted population	10 (0.3)		0.41 (0.22-0.79)
DOAC high-dose	44 (1.4)		0.41 (0.29-0.58)
All-cause mortality			
VKA	1700 (1.9)		1.00
DOAC low-dose			
All population	186 (0.4)		0.61 (0.52-0.71)
Restricted population	177 (0.3)		0.81 (0.69-0.95)
DOAC high-dose	310 (1.4)		0.36 (0.32-0.41)

←Favors DOAC   Favors VKA→

0.1   0.5   0.8 1   2

Fig 2. Association estimates between each major bleeding event, all-cause mortality, and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA)

Fig 3. Association between each major bleeding event, all-cause mortality, and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA) for venous thromboembolism or stroke prevention with atrial fibrillation

Appendices

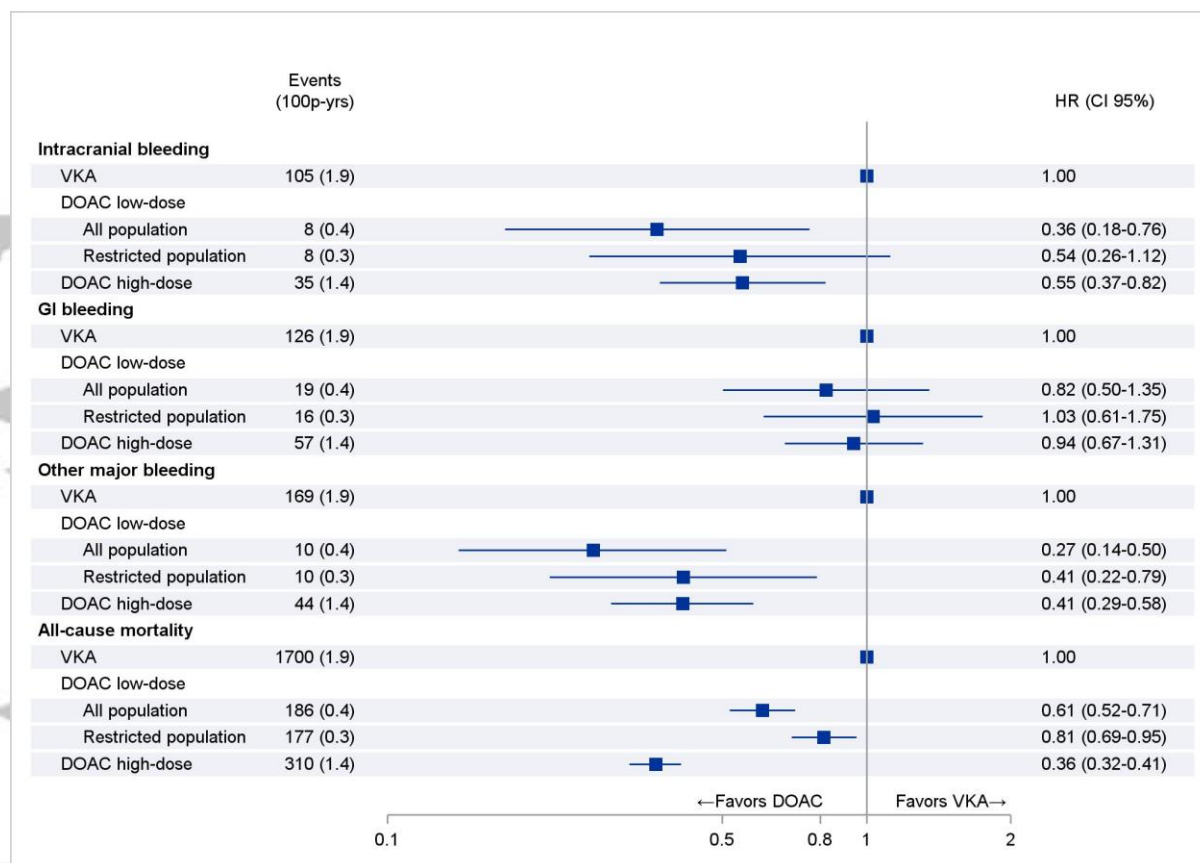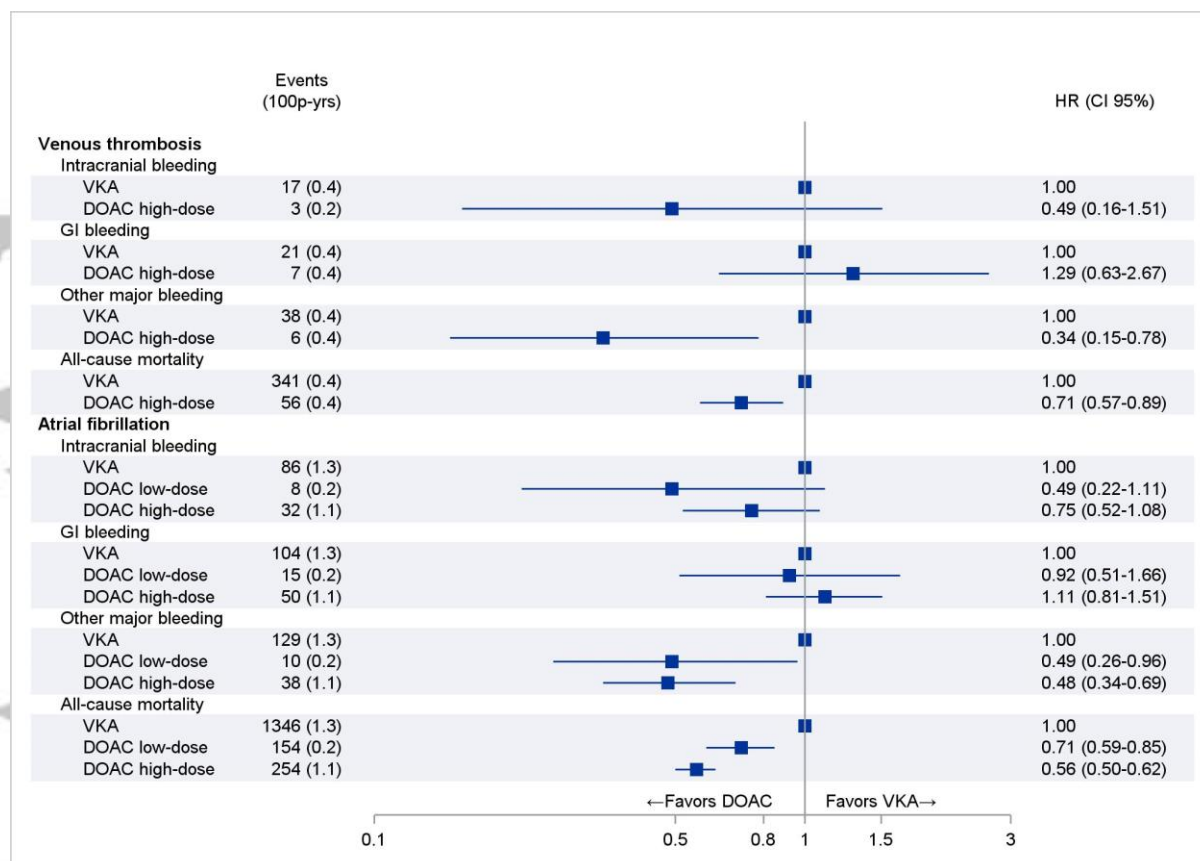Manuscript word count: 4754

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Supporting Information

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Table S1. Definition of presumed indication of oral anticoagulant, and co-morbidities

Conditions	ICD-10 code	"Medical act" code	ATC code
AF peripheral embolism ischemic stroke	I490x, R002x, I470x, I48x, I481x, I482x, I480x, I489x, I500x, I501x, I743x, I471x ,I495x, I509x, I742x, I110x, I498x, K550x, I499x, I479x, I745x, R000x, I744x, E059x, I740x, E058x, I748x,K551x, I132x, E055x, I130x, I741x, R008x, R4700x, I63x, G45x, I670x, I64x, I652x, I651x, I653x, I658x, I694x	DEMP001, DEMP002, YYYY490, DKRP004, DZQM002, DAQM003, DEQP001, EQRP002, GLRP004, DZQJ001, DEQP002, DZQJ008, DZQJ011, DZQJ010, DZQJ009, DEQP004, DEQP003, DZQM006, DEQP007, DZQM005, DZQJ001, DEQP005, DERP003, DZQJ008, DZQJ006, EEFA004, EEFA002, ECFA002, DERP004, DEQP001, EEFA001, EBQM002, EBQM001, ACQH003, EBQM003, ACQJ002, ACQN001, ACQJ001, ACQN004, EAQM003	
Venous thromboembolism	I26x, I801x, I802x, I803x, I808x, I809x, I81x, I822x, I823x, I829x, I636x, I676x, I828x, G08x, I800x, I820x, O871x, I821x, K751x, O223x	DHQH003, DHQM002, ECQH010, ECQH011, EFQM001, EJQH003, EJQM003, EJQM004, EJQM004, EJQP001, EMQH001, EQBP001, GFQL002, GFQL006, ZBQH001	
Lower limb orthopaedic surgery	T840x,Y831x, Z470x, Z966x	BFKA001, DBKA006, LFCA001, LHCA002, LHQH001, MBCA005, MDCA011, MDCB003, MEQH001, MGDA002, MGQH001, MHDB001 MHEP002, MHQH001, MZJB001, MZMP013, MZMP015, MZQH001, NAFA002, NBCA001, NBCA004 to NBCA006, NBCA010, NBCA014, NBCA015, NBCB003, NBCB004, NBFA003, NBMA002, NBMA003, NBPA011, NBPA016, NCCA002, NCCA004, NCCA007, NCCA012, NCCA014, NCCA017, NCCA018, NCCB006, NCEP002, NCFA006, NCPA001 to NCPA003, NCPA008, NCPA013 to NCPA0015, NDCA006, NDEP001, NDFA002, NDGA003, NDPA002 to NDPA004, NDPA011, NDPA013, NDPA014, NEEP002, NEFA004, NEFC001, NEJA001, NEKA001 to NEKA0021, NELA003, NEMA018, NEMA020, NEMA021, NFCA002, NFCA003, NFCC002, NFEA002, NFEC002, NFFA002, NFFA004, NFFC001 to NFFC004, NFJA001, NFJA002, NFJC002, NFKA001, NFKA002, NFKA004 to NFKA009, NFMA002, NFMA004, NFMC002, NFMC003, NFMP001, NFMP002, NFPA002, NFPC001, NFQC001, NFQH001 NFQP001, NFRP001, NGCA001, NGDA002, NGDA004, NGJA001, NGMP001, NGMP002, NGQH001, NHDA003 to NHDA005, NHFA001, NHMA002, NHMA008, NJCA001, NJEA002, NJEA003, NJFA005, NJMA002, NJMA004, NJPA018, NJPA025, NJPA029, NZJB001, NZMP003, NZMP006, NZMP008, NZMP014, NZQH002, PAGA009 to PAGA011, PAGB004, PAPA003, ZEMP006,	
Valvular heart disease	I05x, I080x, I081x, I083x, I342x, Z952x, Z953x, Z954x I350x, I340x, I351x, I352x, I330x, I361x, I060x,	YYYY108, YYYY118, DBMA011, DGKA025, DGKA011, DBKA011, DBQM001, DBKA006, YYYY062, DBMA002, DBMA003, DZQJ002, DBLF001, DBKA011, DBKA009	

.

	I341x, Q231x, I062x, I348x, I371x', I339x, I38x, I398x, I088x, I089x', I349x, I358x, I391x, Q224x, Q230x		
Diabetes	E10x, E11x, E12x, E13x, E14x	BGNA001, BGNP001, BGNP004, BGNP006, BGNP007, BGNP008	A10A, A10B
Ischemic heart disease	I20 to I25	DDAF001, DDAF003 to DDAF010, DDMA003 to DDMA009, DDMA011, DDMA012, DDMA013, DDMA015 to DDMA038, DDQH006, DDQH009 to DDQH015, DDAA002, DDFF001, DDFF002, DDPF002	
Hematologic or immune diseases	D50 to D89		
Lipid-lowering drug			C10AA, C10AB, C10AC01, C10AC02, C10BA02, C10BA05, C10AX, C10BX03
Antiulcer agent			A2B
Anti-platelet inhibitors			B01AC

ICD-10 stands for International Classification of Diseases, 10th revision; Medical Act classification is unique to France (CCAM nomenclature); "Medical acts" include imaging procedures such as Doppler ultrasonography (of the lower limb for a suspicion of deep vein thrombosis, echocardiography), CT scan, MRI; and therapeutic procedures (thrombectomy, fibrinolysis, thrombo-aspiration, transcutaneous cardio-version, plaster cast, osteo-synthesis, orthopaedic surgery, valve surgery, vascular by-pass, angioplasty, coronary surgery); ATC stands for Anatomical Therapeutic Chemical classification system.

Table S2. Items included in the modified HAS-BLED score

Letter	Original item	Modified item	New definition	ICD-10 code	Medical procedure	LTD	ATC	Score
H	Hypertension uncontrolled	Yes	Hospitalisation, LTD affiliation or treatment [a]	I10, I11, I15		severe arterial hypertension	C02, C03, C07-C09	1
A	Impaired renal and/or hepatic function	Yes	Hospitalisation, LTD affiliation	K70x, K713-5, K717, K721, K73, K74, Z49x, Z99x, I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N17x, N18x, N19, N250, Z490, Z492, Z940, Z992	JVJx	Liver cirrhosis, Severe chronic kidney disease		1 or 2
S	Previous history of stroke	No		G45x, I63x, I693				1
B	Previous history of bleeding	No		I312, I60-I62, I982, J942, K226, K252, K262, K270, K272, K280, K282, K290, K625, K661, K920-K922, M250, N939, R040-R043, R31, R58, S064-S066				1
L	Labile INR	Not used [b]						1
E	Age> 65 years (Elderly)	No						1
D	Drugs [c] /alcohol concomitantly	Yes	Hospitalisation related to alcohol abuse	E244x, F10x, G312x, G621x, G721x, I426x, K292x, K70x,K852x, K860x, O354x, R780x, Y90x, Z714x, Z721x,Z502x			B01AC, M01A[c]	1 or 2

The different criteria were assessed in the 12 months preceding inclusion date, i.e., the first observed antithrombotic delivery, except for antiplatelet agents and NSAID where the criteria were assessed between the first observed antithrombotic delivery and censure date.

Labile INR initially used in the original HAS-BLED score was not taken into account; this item does not make sense in new users or even in prevalent users of DOAC

The modified HAS-BLED score varies from 0 to 8.

Original items are those described by Pisters et al, Chest 2010; LTD stands for long-term disease registration; ATC stands for Anatomical Therapeutic Chemical Classification.

[a] at least two deliveries in the 12 months preceding inclusion date of a drug belonging to one of the following ATC classes: C02, C03, C07-C09;

[b] of note, this item is not relevant to new users of DOAC;

[c] antiplatelet agents (B01AC04-B01AC07, B01AC22-B01AC24, B01AC30 or B01AC56) or non-steroidal anti-inflammatory drugs (M01A, including M01AX02 (niflumic acid) and M01AX17 (nimesulide) but none of the other drugs labelled M01AX; at least one delivery concomitant with any anticoagulant.

Table S3. Modified Charlson Score (according to Bannay et al.[35])

Factors	Weight	ICD-10 code	Medical act code	ATC code
Congestive heart failure	2	I11.0, I13.0, I13.2, I50.x		
Peripheral vascular disease	1	I70x, I71x, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z95.9	DGAFx, DGCAx, DGFPx, DGKA004, EANF002, EBFAx, EBNF001, ECCA00-2, -3, -7, -9, ECFAx, ECJF001, ECKA002, ECMA001, ECNF002, ECPFx, EDAFx, EDCAx, EDEAx, EDFAx, EDJFx, EDKAx, EDMAx, EDNFx, EDPFx, EEAFx, EECAx, EEJF001, EENFx, EEPFx, ENAF00-1, -2, ENFAx, ENNFx,	
Cerebrovascular disease	1	G45.x, G46.x, H340, I60x-I69x		
Dementia	2	F00x–F03x, F051, G30x, G311		N06D [a]
CPD	1	I278, I279, J40x–J47x, J60x–J67x, J684, J701, J703		R03 [b]
Mild liver disease	2	B18x, K700–K703, K709, K713–K715, K717, K73x, K74x, K760, K762–K764, K768, K769, Z944		
Moderate or severe liver disease	2	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767		
Hemiplegia	1	G041, G114, G80-1, -2, G81x, G82x, G830–4, G839		
Moderate or severe renal disease	2	I120, I131, N032–N037, N052–N057, N18x, N19x, N250, Z490–Z492, Z940, Z992		
Any malignancy, leukemia and lymphoma	3	C00x–C26x, C30x–C34x, C37x–C41x, C43x, C45x–C58x, C60x–C76x, C81x–C85x, C88x, C90x–C97x		
Metastatic solid tumour	11	C77x–C80x		
AIDS/HIV	1	B20x–B22x, B24x, Z21		

The different criteria were assessed in the 12 months preceding inclusion date; [a] at least 3 deliveries; [b] at least 2 deliveries; CPD stands for chronic pulmonary disease; DGAF, EDAF, EEAF, and ENAF stand for intra-luminal dilation, DGCA, EDCA stand for vascular break and/or by-pass, DGFP, DGKA004, ECKA002, ECMA001, EDKA, and EDMA stand for vascular replacement, EANF002, EBNF001, ECNF002, EDNF, EENF, and ENNF stand for fibrinolysis, EBFA, ECFA, EDFA, and ENFA stand for thromboendarteriectomy, ECCA, EDEA, and EECA stand for by-pass, ECJF001, EDJF, and EEJF001 stand for thrombo-aspiration, ECPF, EDPF, and EEPF stand for recanalization.

.

Table S4. Baseline characteristics in unweighted and weighted cohorts of new users of DOAC or VKA for atrial fibrillation

	VKA	DOAC low-dose	DOAC high-dose	Before Weighting Standardised difference vs. VKA		After Weighting Standardised difference vs. VKA	
	N = 11 535	N = 2430	N = 10 540	DOAC low-dose	DOAC high-dose	DOAC low-dose	DOAC high-dose
Age, mean year	76.5	80.6	71.6	0.098	0.112	0.005	0.005
Gender, female	49.5	56.2	42.5	0.134	0.141	0.009	0.001
Myocardial infarction	3.36	1.32	0.81	0.120	0.177	0.001	0.002
Coronary heart disease	15.6	8.19	5.87	0.213	0.316	0.007	0.006
Diabetes mellitus	18.6	14.5	14.9	0.107	0.097	0.013	0.011
Heart failure	23.1	15.9	9.28	0.174	0.379	0.013	0.006
Hypertension	58.5	56.2	46.5	0.048	0.242	0.003	0.004
Peripheral vascular disease	9.90	3.79	2.89	0.216	0.286	0.000	0.024
Cerebrovascular disease	13.4	9.22	6.76	0.125	0.219	0.020	0.019
Stroke	10.0	6.91	5.63	0.104	0.161	0.013	0.020
Dementia	4.64	3.95	1.45	0.033	0.184	0.001	0.000
Chronic pulmonary disease	18.6	16.3	13.6	0.058	0.134	0.008	0.004
Mild liver disease	1.90	0.33	0.52	0.124	0.125	0.022	0.017
Moderate or severe liver disease	0.80	0.08	0.17	0.088	0.089	0.023	0.015
Impaired hepatic function	1.24	0.21	0.29	0.101	0.108	0.027	0.016
Hemiplegia	5.08	3.25	2.13	0.086	0.157	0.010	0.020
Renal disease	10.2	3.09	1.15	0.250	0.391	0.046	0.042
Impaired renal function	12.4	3.33	1.53	0.295	0.431	0.028	0.038
Malignancy	7.09	3.79	3.66	0.134	0.152	0.021	0.016
Metastatic solid tumour	1.52	1.03	0.72	0.041	0.075	0.005	0.012
AIDS/HIV	0.10	0.00	0.01	0.035	0.038	0.025	0.010
Previous bleeding	4.65	2.35	1.41	0.114	0.188	0.006	0.007

values are percentage otherwise stated; For age, the standardized difference is $d = \frac{(\bar{X_1}-\bar{X_2})}{\sqrt{\frac{s_1^2+s_2^2}{2}}}$ For a binary categorical baseline variable, the standardized difference is $d = \frac{(\hat{p_1}-\hat{p_2})}{\sqrt{\frac{[\hat{p_1}(1-\hat{p_1})+\hat{p_2}(1-\hat{p_2})]}{2}}}$ DOAC are

dabigatran, rivaroxaban or apixaban; VKA stands for vitamin K antagonist

Table S5. Baseline characteristics in unweighted and weighted cohorts of new users of DOAC high-dose or VKA for venous thromboembolism

	VKA N = 5 662	DOAC N = 4718	Standardised difference Before	After
Age, mean year	66.9	58.9	0.167	0.002
Gender, female	55.3	46.9	0.168	0.001
Myocardial infarction	0.62	0.21	0.062	0.002
Coronary heart disease	4.91	1.72	0.175	0.017
Diabetes mellitus	10.7	5.9	0.173	0.002
Hypertension	34.3	19.7	0.331	0.008
Heart failure	6.69	2.23	0.213	0.009
Peripheral vascular disease	4.50	1.61	0.165	0.001
Cerebrovascular disease	4.20	1.29	0.175	0.018
Stroke	2.33	0.66	0.135	0.007
Dementia	4.61	1.44	0.182	0.002
Chronic pulmonary disease	14.5	11.0	0.106	0.020
Mild liver disease	2.49	0.66	0.144	0.028
Moderate or severe liver disease	1.25	0.17	0.125	0.032
Impaired hepatic function	1.71	0.28	0.140	0.035
Hemiplegia	2.17	0.83	0.108	0.007
Renal disease	5.56	0.89	0.258	0.031
Impaired renal function	7.44	1.42	0.287	0.018
Malignancy	9.03	3.86	0.208	0.005
Metastatic solid tumour	2.61	0.76	0.141	0.004
AIDS/HIV	0.23	0.04	0.050	0.015
Previous bleeding	4.27	1.84	0.139	0.001

Values are percentage otherwise stated

For age, the standardized difference is $d = \frac{(\bar{X}_1 - \bar{X}_2)}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$

For a binary categorical baseline variable, the standardized difference is $d = \frac{(\hat{p}_1 - \hat{p}_2)}{\sqrt{\frac{[\hat{p}_1(1-\hat{p}_1) + \hat{p}_2(1-\hat{p}_2)]}{2}}}$

DOAC are dabigatran, rivaroxaban or apixaban; VKA stands for vitamin K antagonists.

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Table S6. Timing of censoring according to reason and anticoagulant

	Vitamin K Antagonists				Apixaban High-dose				Dabigatran High-dose				Rivaroxaban High-dose			
	N	q1	q2	q3	N	q1	q2	q3	N	q1	q2	q3	N	q1	q2	q3
Dose change					209	28	60	129	305	42	165	369	472	44	130	311
Discontinuation	6619	110	162	247	187	60	91	150	339	60	91	207	4996	60	108	182
Death	1700	60	154	359	13	37	81	141	14	106	370	616	283	45	135	351
End of follow-up	10183	184	420	705	1552	77	187	316	476	510	750	925	7327	115	322	660
Major bleeding	400	46	162	359	13	137	224	251	7	20	112	552	116	55	154	389
Moving outside	338	66	176	377	14	56	106	161	20	130	387	607	127	86	222	418
Switch	965	33	86	248	57	30	57	143	120	28	92	238	1012	19	59	181

	Apixaban Low-dose			Dabigatran Low-dose			Rivaroxaban Low-dose		
	N	q1	q2	q3	N	q1	q2	q3	N	q1	q2	q3
Dose change	115	17	29	60	115	17	69	327	216	14	41	180
Discontinuation	292	60	60	82	1464	60	60	60	4257	60	60	60
Death	43	21	70	149	114	54	236	478	29	33	58	225
End of follow-up	901	60	137	267	925	338	694	917	707	49	60	89
Major bleeding	6	136	161	446	28	22	125	603	3	1	1	24
Moving outside	6	64	143	307	24	68	217	405	6	29	35	378
Switch	52	21	52	106	274	43	144	292	28	11	39	169

q1 and q3 stand for 1st and 3rd quartile, respectively; q2 stands for median.

Table S7 Panel A. Total number of major bleeding events according to indication

Bleeding site	AF	VTE	Orthopaedic	Unknown	All
Intracranial haemorrhage (ICH)	126	20	2	-	148
Extra/subdural	47	6	2	-	55
Intracerebral	64	12	-	-	76
Other, intraventricular or unspecified	15	2	-	-	17
Gastrointestinal (GI) bleeding	169	28	4	1	202
Upper GI	29	9			38
Lower GI	140	19	4	1	164
Other major bleeding	177	44	2	-	223
Hematuria / genitourinary	49	8	-	-	57
Oropharynx	37	9	-	-	46
Muscle (include soft tissue)	54	16	2		72
Other	37	11	-	-	48
All	472	92	8	1	573

AF denotes atrial fibrillation, VTE acute venous thromboembolism

Table S7 Panel B. Total number of major bleeding events according to anticoagulant

Bleeding site	VKA	Dabigatran		Rivaroxaban		Apixaban		All
		High	Low	High	Low	High	Low	
Intracranial haemorrhage (ICH)	105	0	6	31	1	4	1	148
Extra/subdural	41		3	9	0	1	1	55
Intracerebral	54		2	18	1	1	0	76
Other, intraventricular or unspecified	10		1	4	0	2	0	17
Gastrointestinal (GI) bleeding	126	5	16	46	1	6	2	202
Upper GI	27	1	0	7	0	2	1	38
Lower GI	99	4	16	39	1	4	1	164
Other major bleeding	169	2	6	39	1	3	3	223
Hematuria / genitourinary	41	1	2	10	0	1	2	57
Oropharynx	30	1	0	14	1	0	0	46
Muscle (include soft tissue)	65	0	1	5	0	1	0	72
Other	33	0	3	10	0	1	1	48
All	400	7	28	116	3	13	6	573

.

Table S8. Crude incidence rates of bleeding events by anticoagulant exposure, dose and HAS-B(L)ED score level

			Vitamin K antagonist			DOAC		
			No of events	Person years	Incidence rate per 100 py (95% CI)	No of events	Person years	Incidence rate per 100 py (95% CI)
HAS-B(L)ED 0-1	Low dose	Intracranial haemorrhage				3	1760	0.17 (0.05 - 0.53)
		Gastrointestinal bleeding				11	1760	0.62 (0.35 - 1.13)
		Other major bleeding				4	1760	0.23 (0.09 - 0.61)
	High dose	Intracranial haemorrhage	26	6775	0.38 (0.26 - 0.56)	20	7068	0.28 (0.18 - 0.44)
		Gastrointestinal bleeding	31	6775	0.46 (0.32 - 0.65)	16	7068	0.23 (0.14 - 0.37)
		Other major bleeding	48	6775	0.71 (0.53 - 0.94)	15	7068	0.21 (0.13 - 0.35)
HAS-B(L)ED 2	Low dose	Intracranial haemorrhage				5	1731	0.29 (0.12 - 0.69)
		Gastrointestinal bleeding				3	1731	0.17 (0.06 - 0.54)
		Other major bleeding				7	1731	0.40 (0.19 - 0.85)
	High dose	Intracranial haemorrhage	42	6627	0.63 (0.47 - 0.86)	8	4792	0.17 (0.08 - 0.33)
		Gastrointestinal bleeding	33	6627	0.50 (0.35 - 0.70)	27	4792	0.56 (0.39 - 0.82)
		Other major bleeding	71	6627	1.07 (0.85 - 1.35)	33	4792	0.69 (0.49 - 0.97)
HAS-B(L)ED >2	Low dose	Intracranial haemorrhage				0	852	0.00 (0.00 - 0.43)
		Gastrointestinal bleeding				5	852	0.59 (0.24 - 1.41)
		Other major bleeding				2	852	0.23 (0.06 - 0.94)
	High dose	Intracranial haemorrhage	37	5386	0.69 (0.50 - 0.95)	7	1922	0.36 (0.17 - 0.76)
		Gastrointestinal bleeding	62	5386	1.15 (0.90 - 1.48)	14	1922	0.73 (0.43 - 1.23)
		Other major bleeding	67	5386	1.24 (0.98 - 1.58)	7	1922	0.36 (0.17 - 0.76)

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Figure S1. Figure Reason of censoring (expressed as percentage) across drug classes.
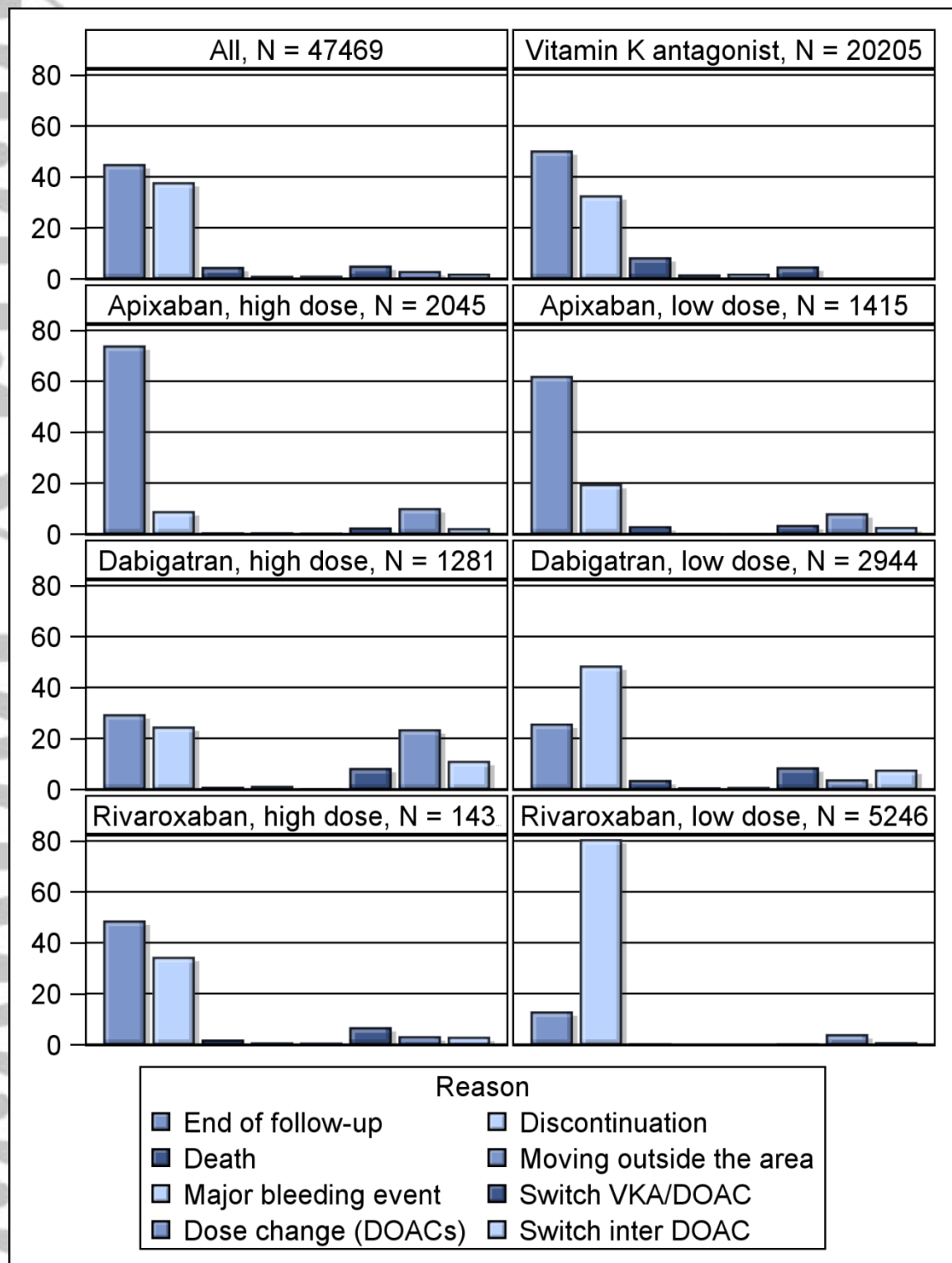
Figure S2. Crude incidence rates of bleeding according to HAS-(B)LED strata and time period
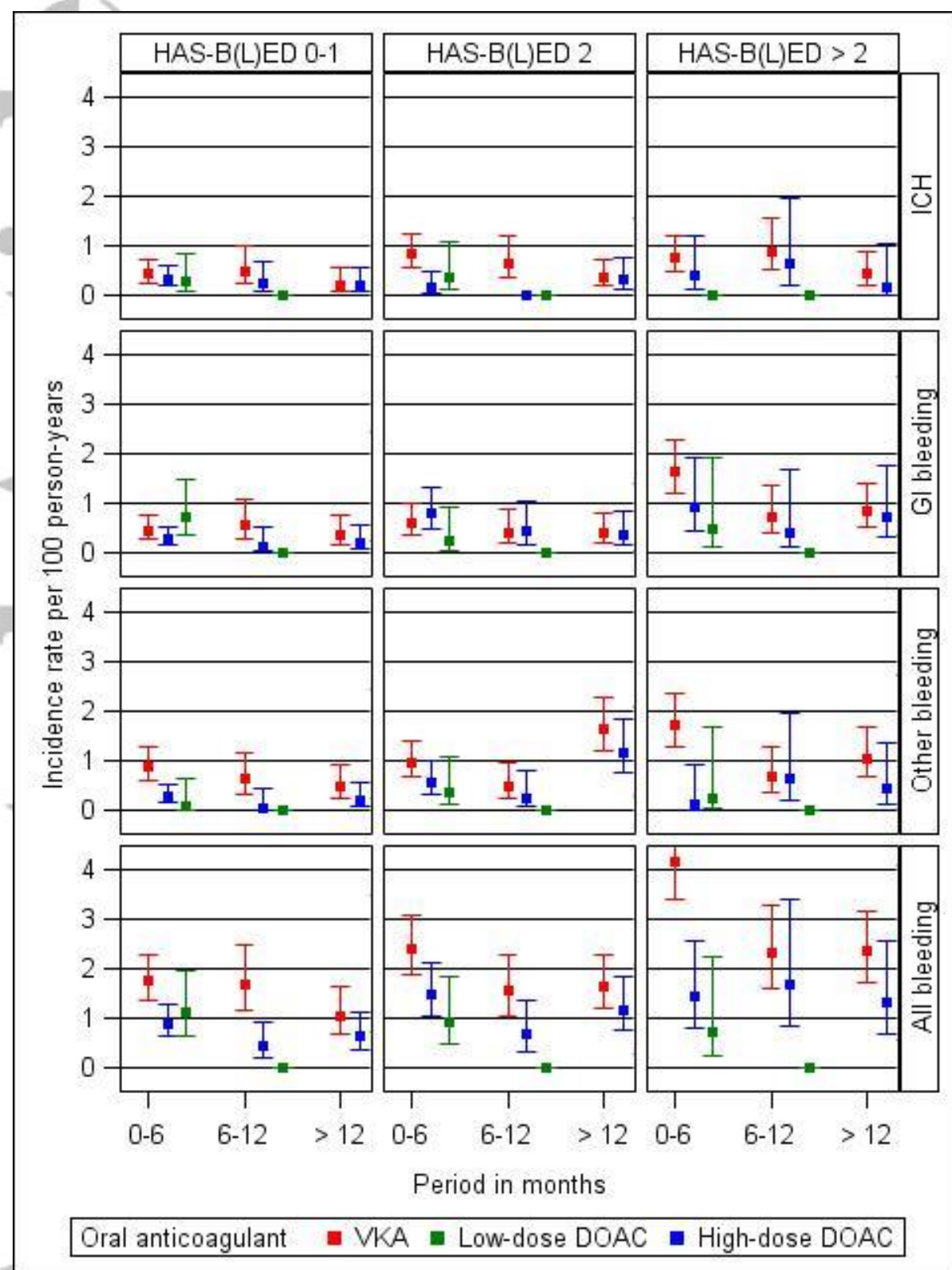
ICH denotes intracranial bleeding, and GI gastrointestinal; DOAC stands for direct oral anticoagulant; high-dose (dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg per day), low-dose (dabigatran 220 mg or rivaroxaban 10 mg or apixaban 5 mg per day)

Figure S3. Association estimates between different location of other major bleeding event, and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA)

	Events (100p-yrs)	HR (CI 95%)
Hematuria		
VKA	41 (1.9)	1.00
DOAC low-dose	4 (0.4)	0.49 (0.17-1.40)
DOAC high-dose	12 (1.4)	0.48 (0.24-0.93)
Oropharyngeal bleeding		
VKA	30 (1.9)	1.00
DOAC low-dose	1 (0.4)	0.17 (0.02-1.23)
DOAC high-dose	15 (1.4)	0.84 (0.44-1.62)
Muscular bleeding		
VKA	65 (1.9)	1.00
DOAC low-dose	1 (0.4)	0.07 (0.01-0.49)
DOAC high-dose	6 (1.4)	0.16 (0.07-0.37)
Other site		
VKA	33 (1.9)	1.00
DOAC low-dose	4 (0.4)	0.48 (0.17-1.39)
DOAC high-dose	11 (1.4)	0.45 (0.22-0.91)
All sites combined		
VKA	169 (1.9)	1.00
DOAC low-dose	10 (0.4)	0.27 (0.14-0.51)
DOAC high-dose	44 (1.4)	0.41 (0.29-0.58)

← Favors DOAC

0.01   0.1   1

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Figure S4. Association estimates between each major bleeding event, all-cause mortality, and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA)

	Events (100p-yrs)	HR (CI 95%)
Intracranial bleeding		
VKA	105 (1.9)	1.00
DOAC low-dose	8 (0.4)	0.36 (0.18-0.76)
Apixaban	1 (0.1)	0.28 (0.04-2.04)
Dabigatran	6 (0.2)	0.52 (0.23-1.18)
Rivaroxaban	1 (0.1)	0.02 (0.15-1.05)
DOAC high-dose	35 (1.4)	0.37 (0.55-0.82)
Apixaban	4 (0.1)	0.72 (0.26-1.98)
Dabigatran	0 (0.1)	
Rivaroxaban	31 (1.1)	0.59 (0.39-0.89)
GI bleeding		
VKA	126 (1.9)	1.00
DOAC low-dose	19 (0.4)	0.50 (0.82-1.35)
Apixaban	2 (0.1)	0.52 (0.13-2.11)
Dabigatran	16 (0.2)	1.33 (0.79-2.26)
Rivaroxaban	1 (0.1)	0.13 (0.02-0.95)
DOAC high-dose	57 (1.4)	0.94 (0.67-1.31)
Apixaban	6 (0.1)	0.48 (1.11-2.54)
Dabigatran	5 (0.1)	0.87 (0.35-2.15)
Rivaroxaban	46 (1.1)	0.92 (0.64-1.31)
Other major bleeding		
VKA	169 (1.9)	1.00
DOAC low-dose	10 (0.4)	0.27 (0.14-0.51)
Apixaban	3 (0.1)	0.56 (0.18-1.77)
Dabigatran	6 (0.2)	0.31 (0.14-0.69)
Rivaroxaban	1 (0.1)	0.08 (0.01-0.58)
DOAC high-dose	44 (1.4)	0.41 (0.29-0.58)
Apixaban	3 (0.1)	0.34 (0.11-1.06)
Dabigatran	2 (0.1)	0.19 (0.05-0.76)
Rivaroxaban	39 (1.1)	0.45 (0.31-0.64)
All-cause mortality		
VKA	1700 (1.9)	1.00
DOAC low-dose	186 (0.4)	0.61 (0.52-0.71)
Apixaban	43 (0.1)	0.85 (0.62-1.15)
Dabigatran	114 (0.2)	0.68 (0.56-0.83)
Rivaroxaban	29 (0.1)	0.32 (0.20-0.49)
DOAC high-dose	310 (1.4)	0.36 (0.32-0.41)
Apixaban	13 (0.1)	0.17 (0.10-0.30)
Dabigatran	14 (0.1)	0.17 (0.10-0.30)
Rivaroxaban	283 (1.1)	0.40 (0.35-0.46)

← Favors DOAC

0.01   0.1   1

.

Figure S5. Association estimates between major gastrointestinal bleeding and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA)

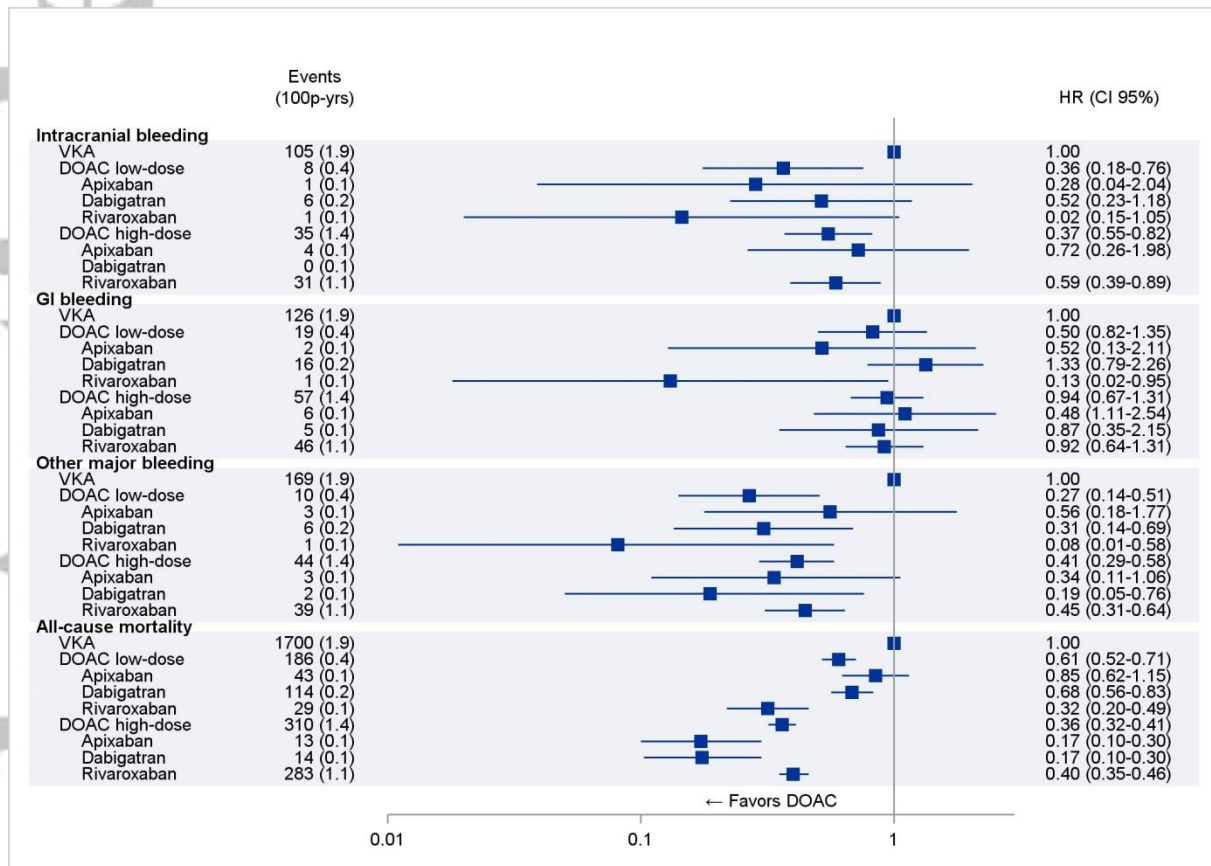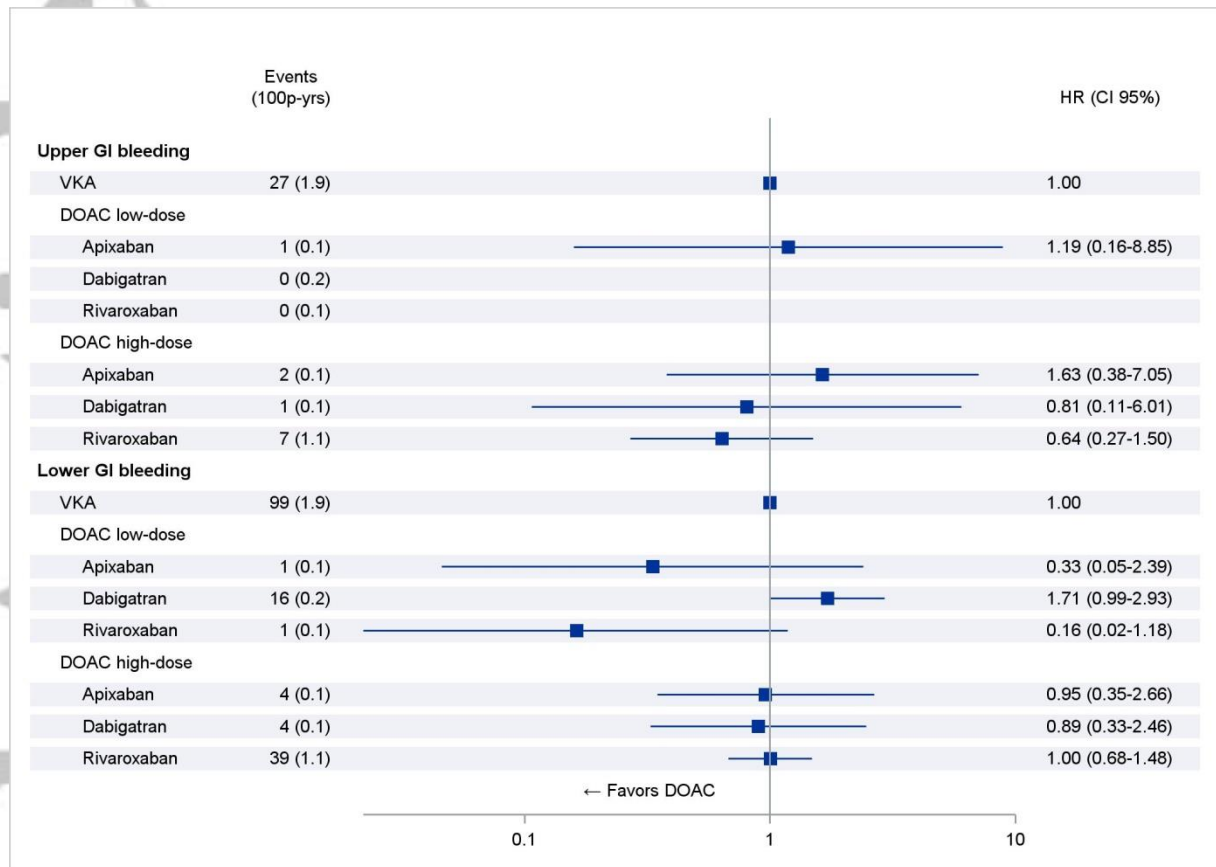|	Events (100p-yrs)		HR (CI 95%)
Upper GI bleeding			
VKA	27 (1.9)		1.00
DOAC low-dose			
Apixaban	1 (0.1)		1.19 (0.16-8.85)
Dabigatran	0 (0.2)		
Rivaroxaban	0 (0.1)		
DOAC high-dose			
Apixaban	2 (0.1)		1.63 (0.38-7.05)
Dabigatran	1 (0.1)		0.81 (0.11-6.01)
Rivaroxaban	7 (1.1)		0.64 (0.27-1.50)
Lower GI bleeding			
VKA	99 (1.9)		1.00
DOAC low-dose			
Apixaban	1 (0.1)		0.33 (0.05-2.39)
Dabigatran	16 (0.2)		1.71 (0.99-2.93)
Rivaroxaban	1 (0.1)		0.16 (0.02-1.18)
DOAC high-dose			
Apixaban	4 (0.1)		0.95 (0.35-2.66)
Dabigatran	4 (0.1)		0.89 (0.33-2.46)
Rivaroxaban	39 (1.1)		1.00 (0.68-1.48)

← Favors DOAC

0.1   1   10

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Figure S6. Association between all-cause mortality and dabigatran, rivaroxaban or vitamin K antagonist (VKA) compared to apixaban for stroke prevention with atrial fibrillation or acute venous thromboembolism (VTE)
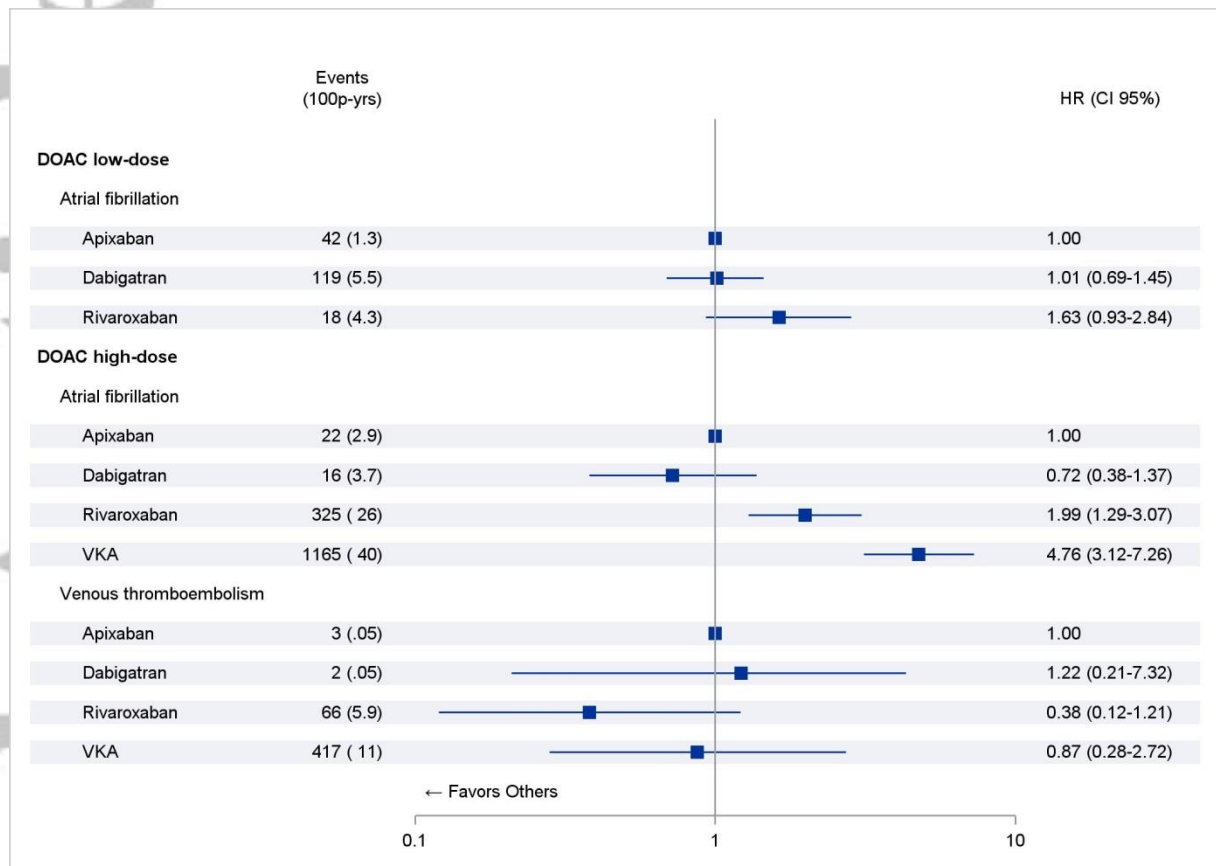

	Events (100p-yrs)		HR (CI 95%)
DOAC low-dose			
Atrial fibrillation			
Apixaban	42 (1.3)		1.00
Dabigatran	119 (5.5)		1.01 (0.69-1.45)
Rivaroxaban	18 (4.3)		1.63 (0.93-2.84)
DOAC high-dose			
Atrial fibrillation			
Apixaban	22 (2.9)		1.00
Dabigatran	16 (3.7)		0.72 (0.38-1.37)
Rivaroxaban	325 (26)		1.99 (1.29-3.07)
VKA	1165 (40)		4.76 (3.12-7.26)
Venous thromboembolism			
Apixaban	3 (.05)		1.00
Dabigatran	2 (.05)		1.22 (0.21-7.32)
Rivaroxaban	66 (5.9)		0.38 (0.12-1.21)
VKA	417 (11)		0.87 (0.28-2.72)

← Favors Others

0.1   1   10

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Figure S7. Number needed to harm compared with vitamin K antagonist (VKA) considering intracranial and other major non gastrointestinal bleeding
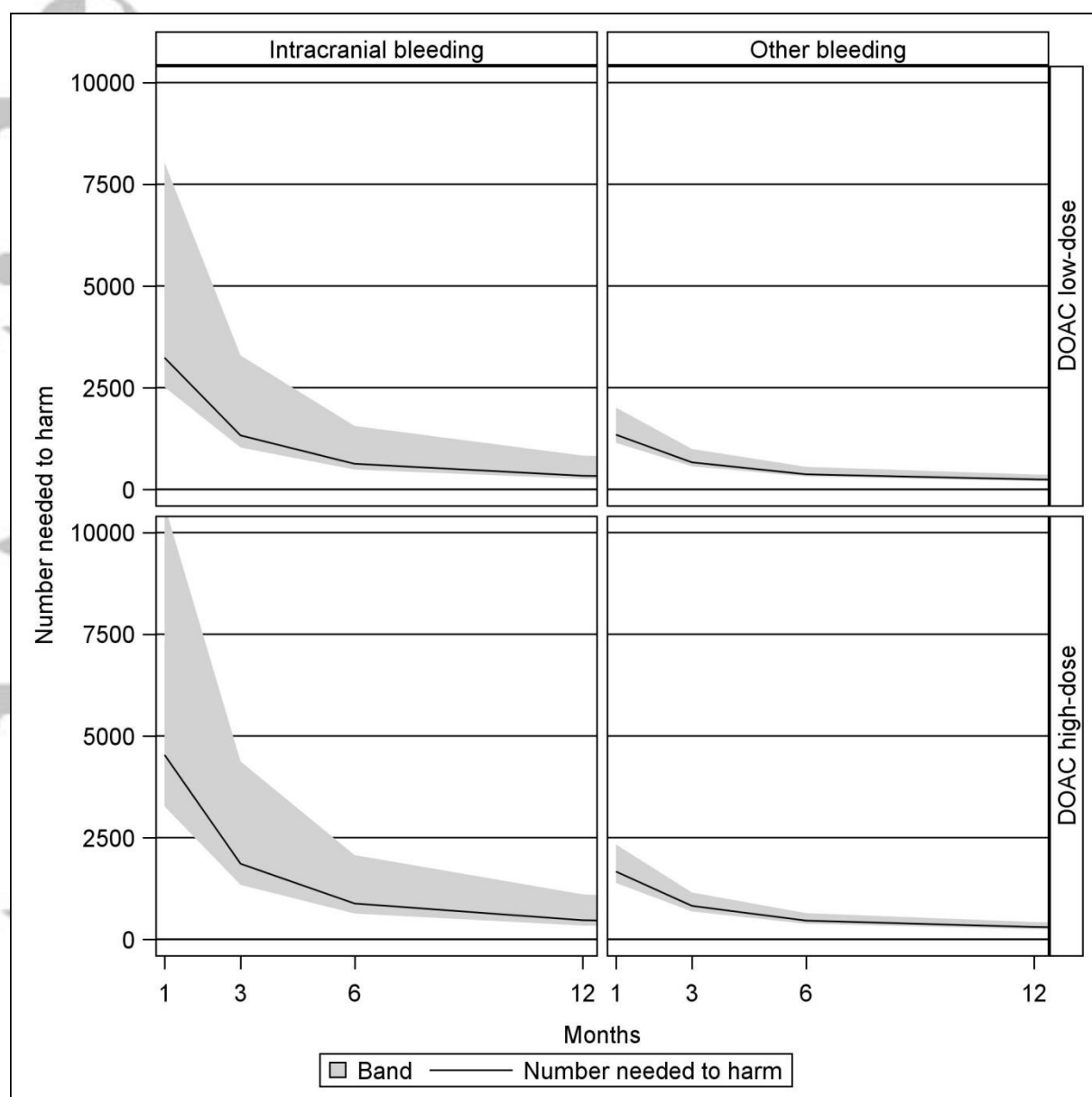
The calculations are based on the hazard ratios from adjusted Cox proportional hazard models with a given set of covariates (notably HASBLED score = 2, and modified Charlson score = "1-2").