Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban versus Vitamin K Antagonists: A French Nationwide Propensity-Matched Cohort Study

Running title: Maura et al.; Comparative effectiveness and safety of NOAC

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Abstract

Background—The safety and effectiveness of Non-VKA Oral AntiCoagulants (NOAC), dabigatran or rivaroxaban, were compared to vitamin K antagonists (VKA) in anticoagulant-naive nonvalvular atrial fibrillation (nv-AF) patients during the early phase of anticoagulant therapy.

Methods and Results—Using the French medico-administrative databases (SNIIRAM-PMSI), this nationwide cohort study included patients with nv-AF who initiated dabigatran or rivaroxaban in July-November 2012 or VKA in July-November 2011. Patients presenting a contraindication to OAC were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users using 1:2 matching on the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up or December 31 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated in an intent-to-treat analysis using Cox regression models. The population was composed of 19,713 VKA, 8,443 dabigatran and 4,651 rivaroxaban new users. All dabigatran- and rivaroxaban-treated patients were matched to 16,014 and 9,301 VKA-treated patients, respectively. Among dabigatran-, rivaroxaban- and their VKA matched-treated patients, 55 and 122 and 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-up, respectively. After matching, no statistically significant difference in bleeding (HR=0.88 [0.64-1.21]) or thromboembolic (HR=1.10 [0.72-1.69]) risk was observed between dabigatran and VKA new users. Bleeding (HR=0.98 [0.64-1.51]) and ischemic (HR=0.93 [0.47-1.85]) risks were comparable between rivaroxaban and VKA new users.

Conclusions—In this propensity-matched cohort study, our findings suggest that physicians should exercise caution when initiating either NOAC or VKA in nv-AF patients.

Key words: anticoagulant, pharmacoepidemiology, stroke prevention, hemorrhage, database, dabigatran, rivaroxaban, French medico-administrative databases, treatment effectiveness, safety
Introduction

Long-term prophylaxis with oral anticoagulants (OACs) is now widely recommended by international guidelines to prevent stroke in all atrial fibrillation (AF) patients without contraindications presenting an independent risk factor for stroke.1-3

However, there are several important considerations in the management of patients taking OACs, starting with initiation of therapy. The initial phase of anticoagulant therapy, especially in patients with newly diagnosed AF, is of concern: early bleeding and thromboembolic risks have been observed to be significantly higher during the first 90 days of therapy in AF patients initiating warfarin.4-6

Recently, Non-VKA Oral Anticoagulants (NOAC), such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, have been introduced as alternatives to vitamin K antagonists (VKA).7,8

Unlike VKA, NOAC have two fixed-dose regimens: dabigatran and rivaroxaban are usually given at 150mg twice daily and 20mg daily, respectively, except in patients with a high bleeding risk for whom the recommended doses are dabigatran 110mg twice daily in Europe and rivaroxaban 15mg daily (10 mg daily in Japan in elderly patients or patients with renal dysfunction).9-11 Large randomized trials have demonstrated the relative safety and efficacy of these agents versus warfarin, but in selected patients with nonvalvular AF (nv-AF),12-14 and subsequent observational data have provided conflicting results.15-19 Few of these studies specifically focused on the early phase of therapy15,20 and most of them were based on Medicare and Danish data. Large post-marketing studies using other databases are needed to better understand the short-term comparative effectiveness and safety of each specific agent and the dosage of NOAC versus VKA.
At the initiative of the French medicines agency, we therefore conducted an observational study using the French nationwide medico-administrative databases to assess the bleeding and arterial thrombotic risks of dabigatran and rivaroxaban, each compared with VKA, during the early phase of therapy.21 In this paper, we focused on newly treated patients with nv-AF.

Material and methods

Study design and data source

We performed a retrospective propensity-matched cohort study using two French nationwide datasets linked by a unique patient identifier:

(1) the French National Health Insurance information system (SNIIRAM), which collects all individualized and anonymous health care claims reimbursed by the French National Health Insurance covering the entire French population. This database also contains patient data such as age, gender, vital status and eligibility for 100% health insurance coverage for serious and costly long-term diseases (LTD) encoded in the International Classification of Diseases, 10th edition (ICD-10), as well as health care professional characteristics, but does not include outpatient medical indications;

(2) the French Hospital Discharge database (PMSI), which contains discharge diagnoses (ICD-10 codes) and medical procedures for all patients admitted to hospital in France.

This linkage has previously been used to conduct large-scale epidemiological or post-authorization studies.22,23

Study population

This study was based on the French National Health Insurance general scheme, covering almost 50 million people. To be eligible for inclusion, patients had to have evidence of continuous
general scheme enrolment for a five-year pre-index period.

The index date was the date of first reimbursement for an OAC. New users, defined as patients with no reimbursement for any OAC during the previous 24 months, were assigned to one of the three treatment groups according to their index OAC: dabigatran or rivaroxaban with both inclusion periods defined between July 20, 2012 (NOAC French market entry date) and November 30, 2012; or VKA with patients included during the same period of 2011. NOAC doses were classified as low (dabigatran 75mg and 110mg or rivaroxaban 10mg and 15mg) or high (dabigatran 150mg or rivaroxaban 20mg).

Patients under the age of 18, or who were reimbursed for both dabigatran and rivaroxaban or VKA and NOAC on the index date, or who died on the index date were excluded. Patients presenting a contraindication to treatment (history of valvular heart disease, ongoing cancer treatment, dialysis for end-stage renal disease, hematological disease or certain immune system disorders considered to be at higher risk of major bleeding (ie LTD or discharge diagnoses ICD-10 codes D50-D89), hepatic cirrhosis or fibrosis or liver failure, acute bleeding peptic ulcer) were also excluded. Finally, patients undergoing lower limb orthopedic procedures during the six-week pre-index period were excluded, as they were assumed to be treated for primary prevention of venous thromboembolic events (Supplementary table 1).

From the resulting cohort, we identified: (1) patients with nv-AF using LTD or discharge diagnoses with ICD-10 code I48 or specific procedures during the four-year pre-index period; (2) patients with deep-vein thrombosis/pulmonary embolism (DVT/PE) using discharge diagnoses (I26, I80 except I80.0, I81, I82) or specific procedures during the six-week pre-index period; (3) outpatients assumed to have nv-AF among the remaining patients with an algorithm using proxies discriminating AF from DVT/PE with a 95% specificity (age, gender, use of beta-
blockers, antiarrhythmics, antiplatelets, antihypertensives, Holter/echocardiography procedures, specialty of the first anticoagulant prescriber and D-dimer assessment; see supplementary data).24

**Outcomes**

The primary endpoints were (1) hospitalization for bleeding, including intracranial (hospital discharge ICD-10 codes I60, I61, I62, S06.3, S06.4, S06.5, S06.6), gastrointestinal (I85.0, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K29.2, K92.0, K92.1, K92.2) and other bleeding (D62, N02, R31, R58, H11.3, H35.6, H43.1, H45.0, H92.2, J94.2, K66.1, M25.0, N92.0, N92.1, N92.4, N93.8, N93.9, N95.0, R04.0, R04.1, R04.2, R04.8, R04.9) and (2) a composite outcome combining hospitalization for bleeding and all-cause mortality.

The secondary endpoints were (1) hospitalization for ischemic stroke (I63 except I63.6) or systemic embolism (I74) and (2) a composite outcome combining hospitalization for ischemic stroke or systemic embolism and all-cause mortality. Only principal discharge diagnoses were used to define endpoints.

**Follow-up**

Patients were followed for up to 90 days from the day after the index date until predefined outcome, loss to follow-up (more than two consecutive months with no reimbursement), death from any cause, end of the year of inclusion or end of the 90-day follow-up, whichever came first.

**Baseline covariates**

The following socio-demographic covariates were used: gender, age at initiation of treatment and the deprivation index of the patient's municipality of residence (divided into quintiles with a sixth group created for patients residing in overseas departments).25 Baseline covariates also
included the specialty of the first OAC prescriber and comorbidities or comediations deemed to be risk factors for bleeding and/or arterial thromboembolic events.

Comorbidities (heart failure, diabetes, coronary heart disease, dementia, history of stroke or systemic embolism, peripheral vascular disease, chronic kidney disease, history of transient ischemic attack, history of hospitalization for bleeding) were identified by hospital discharge/LTD diagnoses and specific procedures or drug reimbursements (Supplementary table 1). Comediations (antihypertensives, antiarrhythmics, non-steroidal anti-inflammatory drugs (NSAID), antiplatelets, lipid-lowering and antiulcer agents, cardiac glycosides, oral corticosteroids, benzodiazepine drugs) were defined as medications dispensed at least once during the four-month pre-index period.

As smoking status and alcohol abuse were not directly available from the databases, we used reimbursement of nicotine replacement therapy and hospital discharge diagnoses related to tobacco use (ICD-10 F17, Z71.6 and Z72.0) or alcohol abuse (F10, K70, T51 E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z50.2, Z71.4 and Z72.1). Clinical scores predicting the risk of stroke (CHA2DS2-VASc) or bleeding (HAS-BLED) in nv-AF patients adapted to medico-administrative data were calculated.

Statistical analyses

All analyses were performed separately according to type (dabigatran/rivaroxaban) and dose (low/high) of NOAC using an intent-to-treat approach. A propensity score (PS) matching analysis was carried out to create similar treatment groups with respect to observed characteristics. This PS was determined using a logistic regression model including the covariates listed above as potential confounders, with age as a categorical variable, except for smoking and alcohol abuse, as only a small proportion of tobacco and alcohol users was
identified. The CHA₂DS₂-VASc and HAS-BLED scores were not included in the PS as most of their clinical characteristics were already taken into account. One NOAC-treated patient was matched to two VKA-treated patients on the logit of the estimated PS without replacement.²⁶ We used nearest-neighbour matching within a caliper width equal to 0.2 of the standard deviation of the logit of the PS.²⁷

Before matching, categorical and continuous baseline covariates were compared between NOAC-exposed and VKA-exposed patients using the ² test and the Wilcoxon test, respectively, as well as absolute standardized differences. After matching, weighted standardized differences adapted to incomplete many-to-one matching were calculated to assess the balance between NOAC-exposed and their matched VKA-exposed patients.²⁸ Crude incidence rates were calculated and Cox models with robust sandwich estimates were used to account for the clustering within matched sets.²⁹ Hazard ratios and their 95% confidence intervals were reported.

Two sensitivity analyses were performed to assess the robustness of the findings based on the primary analyses: exclusion of traumatic bleeding events (S06.3, S06.4, S06.5, S06.6), and restriction of the study population to hospitalized or LTD nv-AF patients. Two subgroup analyses according to age (<75; ≥75) and level of the HAS-BLED score (<3; ≥3) were also carried out for the bleeding events in nv-AF patients.

All statistical analyses were performed using SAS Enterprise Guide 4.3 software (SAS Institute, Inc., Cary-NC).

Results

Characteristics of the cohort

Out of a total of 65,743 VKA new users, 15,400 (23.4%) were excluded because of
contraindications and 1,771 (2.7%) were excluded because of a lower limb orthopedic procedure. Among the NOAC new users, 3,185 (16.8%) of the 18,974 dabigatran patients and 3,050 (15.4%) of the 19,815 rivaroxaban patients were excluded because of contraindications and 4,149 (21.9%) and 7,548 (38.1%), respectively, were excluded because of a lower limb orthopedic procedure. The most frequent contraindication was the exclusion criterion “hematological disease or certain immune system disorders”, particularly nutritional anemia. Among the 71,589 eligible patients, 32,807 (45.8%) were identified as having nv-AF (26.9% by ICD-10 I48 or specific procedures and 18.9% using the algorithm). This population was composed of 19,713 VKA (fluindione: 83.7%, warfarin: 11.8%), 8,443 dabigatran (low doses: 69.8%) and 4,651 rivaroxaban (low doses: 38.5%) new users (Figure 1).

Baseline patient characteristics, before matching, are shown in Supplementary Tables 2 and 3. Dabigatran and rivaroxaban were more frequently initiated than VKA by private practice cardiologists. Dabigatran and rivaroxaban users had a lower mean CHA2DS2-VASc score and fewer comorbidities than VKA users. The mean HAS-BLED score was comparable between NOAC and VKA users. Patients treated with dabigatran 150mg or rivaroxaban 20mg were more frequently males, younger, with lower mean HAS-BLED and CHA2DS2-VASc scores and much fewer comorbidities than VKA users. Patients initiating low-dose dabigatran or rivaroxaban were more frequently females and older than VKA users. The proportion of antiplatelet users was higher among patients initiating low-dose dabigatran or rivaroxaban.

In the overall study population, the median duration from start of treatment (from the day after the index date) to end of follow-up was 87 days (IQR: 56–90 days) for the ‘dabigatran/matched VKA’ cohort and 80 days (IQR: 53–90 days) for the ‘rivaroxaban/matched VKA’ cohort.
Evaluation of propensity score matching

All 8,443 dabigatran- and 4,651 rivaroxaban-treated patients were matched with at least one VKA user, and 89.7% and 100.0% of these patients were matched with two VKA users, respectively. For each NOAC dose category, 100% of the patients were matched with two VKA users, except for the low-dose dabigatran category, in which 96.3% of patients were matched with two VKA users.

Before matching, across all variables included in the PS, the absolute standardized differences ranged from 0.000 to 0.861 for dabigatran and from 0.001 to 0.518 for rivaroxaban. After matching, all standardized differences were less than 0.030 and 0.050, respectively, indicating a good balance between treatment groups (Tables 1 and 2).

Association with primary endpoints

Table 3 presents the number of bleeding and arterial thromboembolic events, person-years at risk and crude event rates for each of the combinations of NOAC dose group and their matched VKA-treated patients.

No significant difference in bleeding risk was observed between VKA- and dabigatran- or rivaroxaban-treated patients (HR=0.88 [0.64-1.21] and HR=0.98 [0.64-1.51], respectively). The bleeding risk was not significantly different in patients exposed to either low or high doses of each NOAC compared to patients exposed to VKA (Figure 2).

The incidence of the composite outcome comprising hospitalization for bleeding and death was comparable between VKA and NOAC new users for all NOAC types and doses (Figure 2).

The results of sensitivity analyses confirmed those obtained with the primary analyses for both dabigatran and rivaroxaban. No significant difference between NOAC and VKA was
observed in the subgroup analyses (Figure 2).

Association with secondary endpoints

No significant difference was observed between VKA- and dabigatran- or rivaroxaban-treated patients (HR=1.10 [0.72-1.69] and HR=0.93 [0.47-1.85], respectively) in terms of arterial thromboembolic events. Analyses according to NOAC doses did not show any increased risk of stroke or systemic embolism. No significant difference in the incidence of the composite outcome comprising stroke, systemic embolism and death was observed according to the various NOAC types and doses (Table 3; Figure 3).

Discussion

In this large-scale, nationwide cohort study, no significant differences were observed between NOAC (dabigatran or rivaroxaban) and VKA in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of anticoagulant therapy among new users with nv-AF. To our knowledge, this is the first study to assess the short-term benefit/risk balance of both dabigatran and rivaroxaban versus VKA using French medico-administrative databases, as previous studies were conducted on Danish and US Medicare data.15-20 This study also provides insight into French prescribing patterns of dabigatran and rivaroxaban immediately following their approval for stroke prevention in nv-AF. Significant channeling of the new drugs i.e. NOAC over VKA towards a younger and healthier population was observed, as well as channeling of low doses of each NOAC (dabigatran 75/110mg or rivaroxaban 10/15mg) over high doses towards older patients with higher bleeding and stroke risks.

The results of this study are consistent with the overall findings of the randomized clinical trials and most of the subsequent observational studies that did not find any evidence for
increased stroke or bleeding risks with NOAC compared to warfarin in the short- to medium-term.\textsuperscript{7,8,15-17,20} Few observational studies on NOAC have been published to date and this study is one of the first large incident cohorts to assess rivaroxaban effectiveness and bleeding risks relative to VKA.\textsuperscript{17} The observed prescribing trends are in line with those described in the available observational studies.\textsuperscript{15-17} French prescribing practices appear to be strongly guided by bleeding risk, as suggested by the high proportion of patients who were prescribed low doses, especially dabigatran 75mg and rivaroxaban 10mg. These doses have not been approved in the European Union on the basis of clinical judgment, which raises the question of their effectiveness in patients at high risk of stroke.\textsuperscript{9,10} It should be noted that more than one third of dabigatran- or rivaroxaban-treated patients were aged 80 and over, a population that was underrepresented in pivotal clinical trials.\textsuperscript{7,8}

Nevertheless, as in the study by S\o{}rensen et al, our design focused on the early phase of oral anticoagulant therapy, bearing in mind that early events can have a major impact on the overall success of treatment, starting with treatment persistence.\textsuperscript{15} Although our overall results are reassuring in relation to initiation of NOAC in nv-AF patients in France with no marked excess thromboembolic or bleeding risk, they also suggest that particular caution is required when initiating NOAC. Indeed, initiation of VKA has been shown to be hazardous due to the increased risks of bleeding and stroke, which may partly explain the reported underuse of anticoagulant therapy in nv-AF.\textsuperscript{4-6,20} But on the basis of this study comparing NOAC to VKA, NOAC cannot be considered to be safer than VKA during the early phase of treatment. On the contrary, the clinical implications of our results are that physicians must be just as cautious when initiating NOAC as when initiating VKA, particularly in view of the absence of an antidote and objective monitoring of the extent of anticoagulation. However, one should keep in mind when
initiating OAC therapy that good anticoagulation control is difficult to achieve and maintain with VKA: the quality of anticoagulation in warfarin-treated patients with AF has been reported to be suboptimal by many authors in real-word setting, with the corresponding significantly increased risk of adverse clinical outcomes.

Due to the observational design and the two existing dosage regimens of NOAC, residual confounding by indication is a particular concern in this study. Various techniques were used to mitigate this bias. Firstly, we excluded patients with no nv-AF or with contraindications to avoid artificially biasing the treatment effect by ineligible populations or inappropriate treatment indications. Exclusion of these patients could partly explain the apparent discrepancy between our results and those of a recent study based on Medicare data, in which no exclusions were reported. Secondly, VKA-treated patients were selected in 2011, a period during which NOAC could not be prescribed in France for stroke prevention in nv-AF. Thirdly, analyses were restricted to low and high doses with consistent results. Finally, use of PS matching provides one of the best conditions for non-differential comparison between NOAC and VKA. Moreover, variables of the PS would be expected to be strong confounders. However, PS matching did not control for unobserved factors. As this study was based on administrative data, confounders such as lifestyle or alcohol consumption and differences between severity levels of certain diseases such as renal impairment were not taken into account. Residual confounding therefore cannot be excluded.

Identifying AF on the basis of administrative data is challenging and a source of selection bias. We therefore used a highly specific algorithm to more accurately identify treated AF outpatients. The results are consistent with those obtained on patients identified only by ICD-10 code or specific procedures.
Outcome misclassification, although non-differential, also constitutes a limitation, as the external validity of the ischemic stroke and bleeding diagnoses codes have not been previously assessed in the French PMSI database. However, only primary hospital discharge diagnoses were used to define outcomes. Furthermore, this database is used to calculate payments for acute inpatient care with internal and external quality control processes.

Intention-to-treat analysis was performed because of the short-term follow-up and the use of medico-administrative databases. The accuracy of this approach to estimate the treatment assignment effect could be open to criticism, as exposure to treatment was based on pharmacy claims, which do not indicate how the patient actually takes the medications.

With a maximum three-month follow-up period, our study only captured early events. The outcomes studied are rare events and the small number of events in this study may not have allowed identification of small-to-moderate differences between groups. As the study was conducted at the time of introduction of NOAC for nv-AF patients in France, time-varying characteristics of both patients and prescribers cannot be ruled out. Finally, a much longer follow-up would be necessary to assess the long-term benefit-risk balance of NOAC versus VKA, especially for arterial thromboembolic events.

In conclusion, in this study based on medico-administrative data, no statistically significant difference was observed between NOAC, dabigatran or rivaroxaban, and VKA in terms of the risk of bleeding or arterial thromboembolic events during the early phase of anticoagulant therapy in nv-AF patients. The same level of clinical caution is therefore required when initiating either NOAC or VKA. Similar analyses should be extended to other NOAC such as apixaban and observational studies should now focus on NOAC head-to-head comparison in a non-inferiority design.
**Acknowledgments:** The authors would like to thank the ANSM Epidemiology of Health Products Working group for providing us with their comments and suggestions concerning this study.

**Funding Sources:** The authors are employees of the French National Health Insurance (CNAMTS) or of the French National Agency for Medicines and Health Products Safety (ANSM) and received no funding.

**Conflict of Interest Disclosures:** None.

**References:**


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28. Austin PC. Assessing balance in measured baseline covariates when using many-to-one


### Table 1. Dabigatran- and VKA matched-treated patients: baseline characteristics according to treatment group after propensity score matching.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran all doses N=8,443</th>
<th>VKA D-all doses matched N=16,014</th>
<th>Dabigatran 75–110 mg N=5,895</th>
<th>VKA D75-110 matched N=11,571</th>
<th>Dabigatran 150 mg N=2,548</th>
<th>VKA D150 matched N=5,096</th>
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<tr>
<td></td>
<td>N (%)*</td>
<td>N (%)*</td>
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<td>3,903 (46)</td>
<td>7,430 (46)</td>
<td>3,048 (52)</td>
<td>5,912 (51)</td>
<td>855 (34)</td>
<td>1,711 (34)</td>
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<td>Age, mean (SD)</td>
<td>74.0 (11.3)</td>
<td>73.9 (11.2)</td>
<td>77.4 (10.1)</td>
<td>76.9 (10.0)</td>
<td>66.1 (10.0)</td>
<td>66.5 (10.3)</td>
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<td>18-49 years</td>
<td>271 (3)</td>
<td>508 (3)</td>
<td>97 (2)</td>
<td>191 (2)</td>
<td>174 (7)</td>
<td>353 (7)</td>
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<td>50-64 years</td>
<td>1,294 (15)</td>
<td>2,499 (16)</td>
<td>521 (9)</td>
<td>1,090 (9)</td>
<td>773 (30)</td>
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<td>65-74 years</td>
<td>2,305 (27)</td>
<td>4,322 (27)</td>
<td>1,214 (21)</td>
<td>2,417 (21)</td>
<td>1,091 (43)</td>
<td>2,229 (44)</td>
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<td>75-79 years</td>
<td>1,562 (19)</td>
<td>2,990 (19)</td>
<td>1,174 (20)</td>
<td>2,347 (20)</td>
<td>388 (15)</td>
<td>763 (15)</td>
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<td>≥80 years</td>
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<td>5,695 (36)</td>
<td>2,889 (49)</td>
<td>5,526 (48)</td>
<td>122 (5)</td>
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<td>Quintile 1</td>
<td>1,617 (19)</td>
<td>2,966 (19)</td>
<td>1,197 (20)</td>
<td>2,322 (20)</td>
<td>420 (16)</td>
<td>824 (16)</td>
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<td>Quintile 2</td>
<td>1,553 (18)</td>
<td>2,979 (19)</td>
<td>1,013 (17)</td>
<td>2,064 (18)</td>
<td>540 (21)</td>
<td>1,045 (21)</td>
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<td>Quintile 3</td>
<td>1,654 (20)</td>
<td>3,120 (19)</td>
<td>1,142 (19)</td>
<td>2,239 (19)</td>
<td>512 (20)</td>
<td>1,042 (20)</td>
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<td>Quintile 4</td>
<td>1,752 (21)</td>
<td>3,344 (21)</td>
<td>1,240 (21)</td>
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<td>512 (20)</td>
<td>1,049 (21)</td>
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<td>Quintile 5</td>
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<td>1,232 (21)</td>
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<td>Overseas dpts</td>
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<td>192 (1)</td>
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<td>Hospital practitioner</td>
<td>2,806 (33)</td>
<td>5,619 (35)</td>
<td>1,919 (33)</td>
<td>3,884 (34)</td>
<td>887 (35)</td>
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<td>3,786 (24)</td>
<td>1,410 (24)</td>
<td>2,743 (24)</td>
<td>455 (18)</td>
<td>942 (18)</td>
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<td>6,296 (39)</td>
<td>2,459 (42)</td>
<td>4,718 (41)</td>
<td>1,154 (45)</td>
<td>2,294 (45)</td>
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<td>Other specialties</td>
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<td>313 (2)</td>
<td>107 (2)</td>
<td>226 (2)</td>
<td>52 (2)</td>
<td>89 (2)</td>
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<td>HAS-BLED, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>2.3 (1.0)</td>
<td>2.4 (0.9)</td>
<td>2.4 (0.9)</td>
<td>2.0 (1.0)</td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc, mean (SD)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.6)</td>
<td>3.6 (1.5)</td>
<td>3.6 (1.5)</td>
<td>2.4 (1.5)</td>
<td>2.4 (1.5)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,901 (23)</td>
<td>3,681 (23)</td>
<td>1,407 (24)</td>
<td>2,739 (24)</td>
<td>494 (19)</td>
<td>941 (18)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,626 (19)</td>
<td>3,172 (20)</td>
<td>1,158 (20)</td>
<td>2,294 (20)</td>
<td>468 (18)</td>
<td>931 (18)</td>
</tr>
<tr>
<td>CKD</td>
<td>198 (2)</td>
<td>366 (2)</td>
<td>170 (3)</td>
<td>310 (3)</td>
<td>28 (1)</td>
<td>51 (1)</td>
</tr>
<tr>
<td>Dementia</td>
<td>326 (4)</td>
<td>592 (4)</td>
<td>303 (5)</td>
<td>584 (5)</td>
<td>23 (1)</td>
<td>54 (1)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>603 (7)</td>
<td>1,190 (7)</td>
<td>453 (8)</td>
<td>870 (8)</td>
<td>150 (6)</td>
<td>295 (6)</td>
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<tr>
<td>History of TIA</td>
<td>210 (2)</td>
<td>417 (3)</td>
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<td>305 (3)</td>
<td>59 (2)</td>
<td>100 (2)</td>
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<tr>
<td>CHD</td>
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<td>3,442 (21)</td>
<td>1,391 (24)</td>
<td>2,786 (24)</td>
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<td>771 (15)</td>
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<tr>
<td>Comedications</td>
<td>n</td>
<td>n</td>
<td>P</td>
<td>n</td>
<td>n</td>
<td>P</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>PVD</td>
<td>521 (6)</td>
<td>1,034 (6)</td>
<td>0.001</td>
<td>408 (7)</td>
<td>813 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>224 (3)</td>
<td>408 (3)</td>
<td>0.003</td>
<td>172 (3)</td>
<td>346 (3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Alcohol abuse‡</td>
<td>136 (2)</td>
<td>300 (2)</td>
<td>0.015</td>
<td>85 (1)</td>
<td>168 (1)</td>
<td>0.001</td>
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<tr>
<td>Smoking‡</td>
<td>301 (4)</td>
<td>570 (4)</td>
<td>0.006</td>
<td>173 (3)</td>
<td>312 (3)</td>
<td>0.016</td>
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<tr>
<td>Antihypertensives</td>
<td>6,758 (80)</td>
<td>12,905 (81)</td>
<td>0.001</td>
<td>4,883 (83)</td>
<td>9,590 (83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>994 (12)</td>
<td>2,000 (12)</td>
<td>0.004</td>
<td>739 (13)</td>
<td>1,429 (12)</td>
<td>0.012</td>
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<tr>
<td>Antiarrhythmics</td>
<td>5,905 (70)</td>
<td>11,141 (70)</td>
<td>0.007</td>
<td>4,025 (68)</td>
<td>7,915 (68)</td>
<td>0.005</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>3,959 (47)</td>
<td>7,570 (47)</td>
<td>0.001</td>
<td>2,850 (48)</td>
<td>5,524 (48)</td>
<td>0.013</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1,108 (13)</td>
<td>1,995 (12)</td>
<td>0.004</td>
<td>768 (13)</td>
<td>1,469 (13)</td>
<td>0.005</td>
</tr>
<tr>
<td>Antiulcer agents</td>
<td>3,458 (41)</td>
<td>6,513 (41)</td>
<td>0.005</td>
<td>2,557 (43)</td>
<td>5,012 (43)</td>
<td>0.003</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2,471 (29)</td>
<td>4,752 (30)</td>
<td>0.003</td>
<td>1,883 (32)</td>
<td>3,640 (31)</td>
<td>0.012</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>4,499 (53)</td>
<td>8,423 (53)</td>
<td>0.000</td>
<td>3,350 (57)</td>
<td>6,497 (56)</td>
<td>0.004</td>
</tr>
<tr>
<td>NSAID</td>
<td>1,636 (19)</td>
<td>2,976 (19)</td>
<td>0.001</td>
<td>1,072 (18)</td>
<td>2,053 (18)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
**Table 2. Rivaroxaban- and VKA matched-treated patients: baseline characteristics according to treatment group after propensity score matching.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rivaroxaban all doses N=4,651</th>
<th>VKA R-all doses matched N=9,301</th>
<th>Rivaroxaban 10-15 mg matched N=1,790</th>
<th>VKA R10-15 matched N=3,580</th>
<th>Rivaroxaban 20 mg matched N=2,861</th>
<th>VKA R20 matched N=5,722</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2,108 (45)</td>
<td>4,204 (45)</td>
<td>978 (55)</td>
<td>1,950 (54)</td>
<td>1,130 (39)</td>
<td>2,265 (40)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>73.6 (11.4)</td>
<td>73.4 (11.2)</td>
<td>79.1 (10.1)</td>
<td>78.5 (9.8)</td>
<td>70.2 (10.8)</td>
<td>70.5 (10.9)</td>
</tr>
<tr>
<td>18-49 years</td>
<td>160 (3)</td>
<td>334 (4)</td>
<td>32 (2)</td>
<td>71 (2)</td>
<td>128 (4)</td>
<td>262 (5)</td>
</tr>
<tr>
<td>50-64 years</td>
<td>747 (16)</td>
<td>1,511 (16)</td>
<td>125 (7)</td>
<td>233 (7)</td>
<td>622 (22)</td>
<td>1,209 (21)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>1,275 (27)</td>
<td>2,605 (28)</td>
<td>260 (15)</td>
<td>536 (15)</td>
<td>1,015 (35)</td>
<td>2,037 (36)</td>
</tr>
<tr>
<td>75-79 years</td>
<td>891 (19)</td>
<td>1,733 (19)</td>
<td>355 (20)</td>
<td>707 (20)</td>
<td>536 (19)</td>
<td>1,088 (19)</td>
</tr>
<tr>
<td>≥80 years</td>
<td>1,578 (34)</td>
<td>3,118 (34)</td>
<td>1,018 (57)</td>
<td>2,033 (57)</td>
<td>560 (20)</td>
<td>1,126 (20)</td>
</tr>
<tr>
<td>Deprivation index</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>934 (20)</td>
<td>1,835 (20)</td>
<td>378 (21)</td>
<td>773 (22)</td>
<td>556 (19)</td>
<td>1,130 (20)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>965 (21)</td>
<td>1,935 (21)</td>
<td>350 (20)</td>
<td>697 (19)</td>
<td>615 (21)</td>
<td>1,222 (21)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>956 (21)</td>
<td>1,905 (20)</td>
<td>364 (20)</td>
<td>712 (20)</td>
<td>592 (21)</td>
<td>1,174 (21)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>847 (18)</td>
<td>1,700 (18)</td>
<td>324 (18)</td>
<td>634 (18)</td>
<td>523 (18)</td>
<td>1,037 (18)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>908 (20)</td>
<td>1,851 (20)</td>
<td>358 (20)</td>
<td>708 (20)</td>
<td>550 (19)</td>
<td>1,111 (19)</td>
</tr>
<tr>
<td>Overseas dpts</td>
<td>41 (1)</td>
<td>75 (1)</td>
<td>16 (1)</td>
<td>36 (1)</td>
<td>25 (1)</td>
<td>48 (1)</td>
</tr>
<tr>
<td>First prescriber’s specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital practitioner</td>
<td>1,004 (22)</td>
<td>1,995 (21)</td>
<td>389 (22)</td>
<td>796 (22)</td>
<td>615 (21)</td>
<td>1,258 (22)</td>
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<tr>
<td>General practitioner</td>
<td>992 (21)</td>
<td>2,020 (22)</td>
<td>463 (26)</td>
<td>912 (25)</td>
<td>529 (18)</td>
<td>1,048 (18)</td>
</tr>
<tr>
<td>Private cardiologist</td>
<td>2,576 (55)</td>
<td>5,128 (55)</td>
<td>905 (51)</td>
<td>1,818 (51)</td>
<td>1,671 (58)</td>
<td>3,347 (58)</td>
</tr>
<tr>
<td>Other specialties</td>
<td>79 (2)</td>
<td>158 (2)</td>
<td>33 (2)</td>
<td>54 (2)</td>
<td>46 (2)</td>
<td>69 (1)</td>
</tr>
<tr>
<td>HAS-BLED, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>2.2 (1.0)</td>
<td>2.5 (0.9)</td>
<td>2.5 (0.9)</td>
<td>2.2 (1.0)</td>
<td>2.1 (1.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc, mean (SD)</td>
<td>3.1 (1.5)</td>
<td>3.1 (1.5)</td>
<td>3.7 (1.4)</td>
<td>3.6 (1.4)</td>
<td>2.8 (1.5)</td>
<td>2.7 (1.5)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>982 (21)</td>
<td>1,859 (20)</td>
<td>469 (26)</td>
<td>917 (26)</td>
<td>513 (18)</td>
<td>1,013 (18)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>875 (19)</td>
<td>1,665 (18)</td>
<td>319 (18)</td>
<td>593 (17)</td>
<td>556 (19)</td>
<td>1,055 (18)</td>
</tr>
<tr>
<td>CKD</td>
<td>117 (3)</td>
<td>237 (3)</td>
<td>75 (4)</td>
<td>163 (5)</td>
<td>42 (1)</td>
<td>72 (1)</td>
</tr>
<tr>
<td>Dementia</td>
<td>138 (3)</td>
<td>257 (3)</td>
<td>93 (5)</td>
<td>172 (5)</td>
<td>45 (2)</td>
<td>72 (1)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>219 (5)</td>
<td>408 (4)</td>
<td>97 (5)</td>
<td>182 (5)</td>
<td>122 (4)</td>
<td>234 (4)</td>
</tr>
<tr>
<td>History of TIA</td>
<td>100 (2)</td>
<td>189 (2)</td>
<td>49 (3)</td>
<td>73 (2)</td>
<td>51 (2)</td>
<td>90 (2)</td>
</tr>
<tr>
<td>CHD</td>
<td>963 (21)</td>
<td>1,908 (21)</td>
<td>430 (24)</td>
<td>840 (23)</td>
<td>533 (19)</td>
<td>1,011 (18)</td>
</tr>
<tr>
<td>Comedications</td>
<td>NOAC</td>
<td>VKA</td>
<td>Diff</td>
<td>NOAC</td>
<td>VKA</td>
<td>Diff</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>282 (6)</td>
<td>522 (6)</td>
<td>0.019</td>
<td>137 (8)</td>
<td>254 (7)</td>
<td>0.021</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>110 (2)</td>
<td>207 (2)</td>
<td>0.009</td>
<td>55 (3)</td>
<td>99 (3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Alcohol abuse†</td>
<td>50 (1)</td>
<td>132 (1)</td>
<td>0.031</td>
<td>19 (1)</td>
<td>33 (1)</td>
<td>0.014</td>
</tr>
<tr>
<td>Smoking‡</td>
<td>125 (3)</td>
<td>278 (3)</td>
<td>0.018</td>
<td>42 (2)</td>
<td>72 (2)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Comedications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>2,604 (56)</td>
<td>5,098 (55)</td>
<td>0.024</td>
<td>1,086 (61)</td>
<td>2,154 (60)</td>
<td>0.010</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>2,204 (47)</td>
<td>4,358 (47)</td>
<td>0.011</td>
<td>811 (45)</td>
<td>1,657 (46)</td>
<td>0.020</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>604 (13)</td>
<td>1,189 (13)</td>
<td>0.006</td>
<td>251 (14)</td>
<td>447 (12)</td>
<td>0.045</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>3,393 (73)</td>
<td>6,876 (74)</td>
<td>0.022</td>
<td>1,235 (69)</td>
<td>2,511 (70)</td>
<td>0.025</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1,343 (29)</td>
<td>2,574 (28)</td>
<td>0.027</td>
<td>597 (33)</td>
<td>1,199 (33)</td>
<td>0.003</td>
</tr>
<tr>
<td>Antiulcer agents</td>
<td>1,756 (38)</td>
<td>3,501 (38)</td>
<td>0.002</td>
<td>730 (41)</td>
<td>1,409 (39)</td>
<td>0.029</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>534 (11)</td>
<td>1,015 (11)</td>
<td>0.018</td>
<td>211 (12)</td>
<td>418 (12)</td>
<td>0.003</td>
</tr>
<tr>
<td>NSAID</td>
<td>867 (19)</td>
<td>1,636 (18)</td>
<td>0.027</td>
<td>297 (17)</td>
<td>583 (16)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Abbreviations: D, dabigatran; R, rivaroxaban; Stand Diff, absolute weighted standardized differences; Dpts, departments; CKD, Chronic kidney disease; TIA, Transient ischemic attack; CHD, Coronary heart disease; NSAID, non-steroidal anti-inflammatory drugs; PVD, Peripheral vascular disease.

* Dichotomous variables are expressed as N (%); continuous variables are expressed as mean (standard deviation).

† Absolute weighted standardized differences comparing baseline characteristics between NOAC- (all NOAC patients were matched) and VKA matched-treated patients.

‡ Smoking or alcoholism data: reimbursements for nicotine replacement therapy and hospital discharge diagnoses related to tobacco use or alcohol abuse.
Table 3. Events, person-years at risk and crude event rates among NOAC new users and matched VKA new users.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran all doses</th>
<th>VKA D-all doses matched</th>
<th>Dabigatran 75 - 110 matched</th>
<th>Dabigatran 150 matched</th>
<th>VKA D75-110 matched</th>
<th>Dabigatran 150 matched</th>
<th>Rivaroxaban all doses</th>
<th>VKA R-all doses matched</th>
<th>Rivaroxaban 10 - 15 matched</th>
<th>Rivaroxaban 20 matched</th>
<th>VKA R20 matched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding events</td>
<td>55/1,684/3.3</td>
<td>122/3,292/3.7</td>
<td>43/1,195/3.6</td>
<td>101/2,368/4.3</td>
<td>12/489/2.5</td>
<td>30/1,054/2.8</td>
<td>31/848/3.7</td>
<td>68/1,913/3.6</td>
<td>16/328/4.9</td>
<td>36/734/4.9</td>
<td>15/520/2.9</td>
</tr>
<tr>
<td>Bleeding events or death</td>
<td>158/1,684/9.4</td>
<td>341/3,292/10.4</td>
<td>137/1,195/11.5</td>
<td>295/2,368/12.5</td>
<td>21/489/4.3</td>
<td>56/1,054/5.3</td>
<td>75/848/8.8</td>
<td>161/1,913/8.4</td>
<td>43/328/13.1</td>
<td>89/734/12.1</td>
<td>32/520/6.2</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>33/1,687/2</td>
<td>58/3,300/1.8</td>
<td>28/1,198/2.3</td>
<td>37/2,376/1.6</td>
<td>5/490/1</td>
<td>14/1,056/1.3</td>
<td>12/851/1.4</td>
<td>28/1,918/1.5</td>
<td>6/329/1.8</td>
<td>13/736/1.8</td>
<td>6/521/1.2</td>
</tr>
<tr>
<td>Ischemic stroke or SE or death</td>
<td>136/1,687/8.1</td>
<td>280/3,300/8.5</td>
<td>121/1,198/10.1</td>
<td>243/2,376/10.2</td>
<td>15/490/3.1</td>
<td>43/1,056/4.1</td>
<td>60/851/7.1</td>
<td>125/1,918/6.5</td>
<td>37/329/11.2</td>
<td>66/736/9</td>
<td>23/521/4.4</td>
</tr>
</tbody>
</table>

Figures are events/person-years at risk/crude event rate/100 person-years.
Abbreviations: D, dabigatran; R, rivaroxaban; SE, systemic embolism.
Figure Legends:

**Figure 1.** Study population flow chart. All figures are numbers or percentages of patients.

**Figure 2.** Hazard ratios for bleeding events according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval.

**Figure 3.** Hazard ratios for stroke or systemic embolism according to type and dose of NOAC. All figures are hazard ratios and their 95% confidence interval.
<table>
<thead>
<tr>
<th></th>
<th>VKA new users</th>
<th>NOAC new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65,743</td>
<td>38,784</td>
</tr>
</tbody>
</table>

### Dabigatran
- N = 18,974
- 171 under 18 years of age
- 5 received several types of anticoagulant at initiation
- 7 deaths at index date
- Contraindications:
  - N = 15,400 (23.4%)
  - 5,892 valvular heart disease
  - 5,326 recent cancer
  - 432 dialysis
  - 6,550 haematological disease or immune system disorder
  - 995 hepatic cirrhosis / fibrosis or liver failure
  - 47 acute bleeding peptic ulcer
- Lower limb orthopedic procedures:
  - N = 1,771 (2.7%)
- DVT / PE and undetermined patients:
  - N = 29,037 (59.6%)

### Rivaroxaban
- N = 19,815
- 35 under 18 years of age
- 27 received several types of anticoagulant at initiation
- 0 deaths at index date
- Contraindications:
  - N = 3,050 (15.4%)
  - 680 valvular heart disease
  - 1,127 recent cancer
  - 2 dialysis
  - 1,547 haematological disease or immune system disorder
  - 112 hepatic cirrhosis / fibrosis or liver failure
  - 2 acute bleeding peptic ulcer
- Lower limb orthopedic procedures:
  - N = 7,548 (38.1%)
- DVT / PE and undetermined patients:
  - N = 5,785 (55.4%)

---

**Figure 1**
<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>Major bleeding</th>
<th>Major bleeding or death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main analyses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.88 [0.64 - 1.21]</td>
<td>0.90 [0.75 - 1.09]</td>
</tr>
<tr>
<td>Dabigatran 75 - 110</td>
<td>0.84 [0.59 - 1.20]</td>
<td>0.92 [0.75 - 1.13]</td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>0.85 [0.43 - 1.68]</td>
<td>0.80 [0.48 - 1.31]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.98 [0.64 - 1.51]</td>
<td>1.02 [0.77 - 1.35]</td>
</tr>
<tr>
<td>Rivaroxaban 10 - 15</td>
<td>0.97 [0.53 - 1.76]</td>
<td>1.07 [0.73 - 1.55]</td>
</tr>
<tr>
<td>Rivaroxaban 20</td>
<td>0.81 [0.44 - 1.49]</td>
<td>0.88 [0.59 - 1.33]</td>
</tr>
<tr>
<td><strong>Subgroup analyses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran &lt; 75 years</td>
<td>0.62 [0.35 - 1.10]</td>
<td>0.72 [0.48 - 1.08]</td>
</tr>
<tr>
<td>Dabigatran &gt;= 75 years</td>
<td>0.93 [0.63 - 1.36]</td>
<td>0.93 [0.75 - 1.15]</td>
</tr>
<tr>
<td>Rivaroxaban &lt; 75 years</td>
<td>0.60 [0.27 - 1.31]</td>
<td>0.67 [0.37 - 1.22]</td>
</tr>
<tr>
<td>Rivaroxaban &gt;= 75 years</td>
<td>0.95 [0.58 - 1.54]</td>
<td>1.07 [0.78 - 1.46]</td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized nr-AF patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.71 [0.47 - 1.08]</td>
<td>0.61 [0.64 - 1.02]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.03 [0.61 - 1.74]</td>
<td>1.03 [0.72 - 1.47]</td>
</tr>
<tr>
<td><strong>Non traumatic events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.85 [0.61 - 1.18]</td>
<td>0.89 [0.74 - 1.08]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.97 [0.62 - 1.51]</td>
<td>1.02 [0.77 - 1.34]</td>
</tr>
</tbody>
</table>

Figure 2
Figure 3
Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban versus Vitamin K Antagonists: A French Nationwide Propensity-Matched Cohort Study
Géric Maura, Pierre-Olivier Blotière, Kim Bouillon, Cécile Billionnet, Philippe Ricordeau, François Alla and Mahmoud Zureik

Circulation. published online July 21, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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**Supplementary Table 1.** ICD-10 codes/procedures used to identify comorbid conditions in the SNIIRAM-PMSI databases.

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Hospital discharge diagnoses*</th>
<th>LTD*</th>
<th>Specific procedures or drug reimbursements</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of valvular heart disease</td>
<td>I05-I09, I33-I39</td>
<td></td>
<td>Heart valve surgery</td>
</tr>
<tr>
<td>Cancer under treatment</td>
<td>C00-D09, D37-D48, Z510, Z511</td>
<td>C00-D09, D37-D48</td>
<td>Cancer radiotherapy</td>
</tr>
<tr>
<td>Hematological disease or certain immune system disorders</td>
<td>D50-D89</td>
<td>D50-D89</td>
<td></td>
</tr>
<tr>
<td>Hepatic cirrhosis or fibrosis or liver failure</td>
<td>R18, I85, K70, K71, K72, K74</td>
<td>R18, I85, K70, K71, K72, K74</td>
<td></td>
</tr>
<tr>
<td>Acute peptic ulcer bleeding</td>
<td>K25.0, K25.2, K26.0, K26.2, K27.0, K27.2</td>
<td></td>
<td>Specific diagnosis-related groups</td>
</tr>
<tr>
<td>Dialysis for end-stage renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb orthopedic procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>I48</td>
<td>I48</td>
<td>Radiofrequency ablation, cardioversion</td>
</tr>
<tr>
<td>Deep-vein thrombosis/pulmonary embolism</td>
<td>I26, I80 (except I80.0), I81, I82</td>
<td></td>
<td>Lower limb venous ultrasonography, pulmonary/lower limb angiography, ventilation/perfusion scan</td>
</tr>
<tr>
<td>Baseline covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>I50 or I11.0, I13.0, I13.2, I13.9, K76.1, J81 related to I50</td>
<td>I50</td>
<td>Specific beta-blockers approved for heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>E10-E14</td>
<td>E10-E14</td>
<td>Antidiabetic drugs</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>I20-I25</td>
<td>I20-I25</td>
<td>Nitrovasodilator</td>
</tr>
<tr>
<td>Dementia</td>
<td>F00-F03, G30</td>
<td>F00-F03, G30</td>
<td>Anticholinesterase inhibitors or NMDA receptor antagonist</td>
</tr>
<tr>
<td>History of stroke or systemic embolism</td>
<td>I63 (except I63.6) or G46 related to I63 or I69.3, I74</td>
<td>I63, I74</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>I70-I73</td>
<td>I70-I73</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>N18, I12, I13.1, I13.2</td>
<td>N18</td>
<td></td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>G45 (except G45.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hospitalization for bleeding</td>
<td>ICD-10 codes used to identify outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** LTD, long-term diseases; NOAC *ICD-10 codes
## Supplementary Table 2. Dabigatran- and VKA matched-treated patients: baseline characteristics according to treatment group before propensity score matching.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VKA N=19,713</th>
<th>Dabigatran all doses N=8,443</th>
<th>Dabigatran 75–110 mg N=5,895</th>
<th>Dabigatran 150 mg N=2,548</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>9,422 (48)</td>
<td>3,903 (46)</td>
<td>3,048 (52)</td>
<td>855 (34)</td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>74.1 (11.3)</td>
<td>74.0 (11.3)</td>
<td>77.4 (10.1)</td>
<td>66.1 (10.0)</td>
</tr>
<tr>
<td>18-49 years</td>
<td>621 (3)</td>
<td>271 (3)</td>
<td>97 (2)</td>
<td>174 (7)</td>
</tr>
<tr>
<td>50-64 years</td>
<td>3,215 (16)</td>
<td>1,294 (15)</td>
<td>521 (9)</td>
<td>773 (30)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>4,953 (25)</td>
<td>2,305 (27)</td>
<td>1,214 (21)</td>
<td>1,091 (43)</td>
</tr>
<tr>
<td>75-79 years</td>
<td>3,647 (19)</td>
<td>1,562 (19)</td>
<td>1,174 (20)</td>
<td>388 (15)</td>
</tr>
<tr>
<td>≥80 years</td>
<td>7,277 (37)</td>
<td>3,011 (36)</td>
<td>2,889 (49)</td>
<td>122 (5)</td>
</tr>
<tr>
<td><strong>Deprivation index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>3,419 (17)</td>
<td>1,617 (19)</td>
<td>1,197 (20)</td>
<td>420 (16)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>3,788 (19)</td>
<td>1,553 (18)</td>
<td>1,013 (17)</td>
<td>540 (21)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>3,822 (19)</td>
<td>1,654 (20)</td>
<td>1,142 (19)</td>
<td>512 (20)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>4,053 (21)</td>
<td>1,752 (21)</td>
<td>1,240 (21)</td>
<td>512 (20)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>4,359 (22)</td>
<td>1,767 (21)</td>
<td>1,232 (21)</td>
<td>535 (21)</td>
</tr>
<tr>
<td>Overseas dpts</td>
<td>272 (1)</td>
<td>100 (1)</td>
<td>71 (1)</td>
<td>29 (1)</td>
</tr>
<tr>
<td><strong>First prescriber’s specialty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital practitioner</td>
<td>7,470 (38)</td>
<td>2,806 (33)</td>
<td>1,919 (33)</td>
<td>887 (35)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>5,275 (27)</td>
<td>1,865 (22)</td>
<td>1,410 (24)</td>
<td>455 (18)</td>
</tr>
<tr>
<td>Private cardiologist</td>
<td>6,585 (33)</td>
<td>3,613 (43)</td>
<td>2,459 (42)</td>
<td>1,154 (45)</td>
</tr>
<tr>
<td>Other specialties</td>
<td>383 (2)</td>
<td>159 (2)</td>
<td>107 (2)</td>
<td>52 (2)</td>
</tr>
<tr>
<td>HAS-BLED, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>2.3 (1.0)</td>
<td>2.4 (0.9)</td>
<td>2.0 (1.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc, mean (SD)</td>
<td>3.4 (1.6)</td>
<td>3.2 (1.6)</td>
<td>3.6 (1.5)</td>
<td>2.4 (1.5)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>4,953 (25)</td>
<td>1,901 (23)</td>
<td>1,407 (24)</td>
<td>494 (19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4,253 (22)</td>
<td>1,626 (19)</td>
<td>1,158 (20)</td>
<td>468 (18)</td>
</tr>
<tr>
<td>CKD</td>
<td>903 (5)</td>
<td>198 (2)</td>
<td>170 (3)</td>
<td>28 (1)</td>
</tr>
<tr>
<td>Dementia</td>
<td>783 (4)</td>
<td>326 (4)</td>
<td>303 (5)</td>
<td>23 (1)</td>
</tr>
</tbody>
</table>

* p<0.05; † p<0.001; ‡ p<0.0001.
<table>
<thead>
<tr>
<th></th>
<th>Count 1</th>
<th>Count 2</th>
<th>p-value</th>
<th>OR 1</th>
<th>OR 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of stroke</strong></td>
<td>1,717 (9)</td>
<td>603 (7)</td>
<td>&lt;0.0001</td>
<td>0.058</td>
<td>453 (8)</td>
<td>0.0131</td>
</tr>
<tr>
<td><strong>History of TIA</strong></td>
<td>576 (3)</td>
<td>210 (2)</td>
<td>0.0425</td>
<td>0.027</td>
<td>151 (3)</td>
<td>0.1438</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>4,675 (24)</td>
<td>1,766 (21)</td>
<td>&lt;0.0001</td>
<td>0.067</td>
<td>1,391 (24)</td>
<td>0.8504</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>1,561 (8)</td>
<td>521 (6)</td>
<td>&lt;0.0001</td>
<td>0.068</td>
<td>408 (7)</td>
<td>0.0117</td>
</tr>
<tr>
<td><strong>History of bleeding</strong></td>
<td>491 (2)</td>
<td>224 (3)</td>
<td>0.4275</td>
<td>0.010</td>
<td>172 (3)</td>
<td>0.0701</td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td>412 (2)</td>
<td>136 (2)</td>
<td>0.0077</td>
<td>0.036</td>
<td>85 (1)</td>
<td>0.0016</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>750 (4)</td>
<td>301 (4)</td>
<td>0.3313</td>
<td>0.013</td>
<td>173 (3)</td>
<td>0.0017</td>
</tr>
<tr>
<td><strong>Comedications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td>16,159 (82)</td>
<td>6,758 (80)</td>
<td>0.0001</td>
<td>0.049</td>
<td>4,883 (83)</td>
<td>0.1294</td>
</tr>
<tr>
<td><strong>Cardiac glycosides</strong></td>
<td>2,915 (15)</td>
<td>994 (12)</td>
<td>&lt;0.0001</td>
<td>0.089</td>
<td>739 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td>13,258 (67)</td>
<td>5,905 (70)</td>
<td>&lt;0.0001</td>
<td>0.058</td>
<td>4,025 (68)</td>
<td>0.1412</td>
</tr>
<tr>
<td><strong>Lipid-lowering agents</strong></td>
<td>9,635 (49)</td>
<td>3,959 (47)</td>
<td>0.0023</td>
<td>0.040</td>
<td>2,850 (48)</td>
<td>0.4748</td>
</tr>
<tr>
<td><strong>Oral corticosteroids</strong></td>
<td>2,333 (12)</td>
<td>1,108 (13)</td>
<td>0.0025</td>
<td>0.039</td>
<td>768 (13)</td>
<td>0.0137</td>
</tr>
<tr>
<td><strong>Antiulcer agents</strong></td>
<td>8,198 (42)</td>
<td>3,458 (41)</td>
<td>0.3256</td>
<td>0.013</td>
<td>2,557 (43)</td>
<td>0.0146</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>6,191 (31)</td>
<td>2,471 (29)</td>
<td>0.0004</td>
<td>0.047</td>
<td>1,883 (32)</td>
<td>0.4365</td>
</tr>
<tr>
<td><strong>Antiplatelets</strong></td>
<td>10,336 (52)</td>
<td>4,499 (53)</td>
<td>0.1883</td>
<td>0.017</td>
<td>3,350 (57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td>3,425 (17)</td>
<td>1,636 (19)</td>
<td>&lt;0.0001</td>
<td>0.052</td>
<td>1,072 (18)</td>
<td>0.1513</td>
</tr>
</tbody>
</table>

**Comedications**
- **Antihypertensives**
- **Cardiac glycosides**
- **Antiarrhythmics**
- **Lipid-lowering agents**
- **Oral corticosteroids**
- **Antiulcer agents**
- **Benzodiazepines**
- **Antiplatelets**
- **NSAID**
### Supplementary Table 3. Rivaroxaban- and VKA matched-treated patients: baseline characteristics according to treatment group before propensity score matching.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VKA N=19,713</th>
<th>Rivaroxaban all doses N=4,651</th>
<th>Rivaroxaban 10-15 mg N=1,790</th>
<th>Rivaroxaban 20 mg N=2,861</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)*</td>
<td>N(%)*</td>
<td>p† Stand Diff‡</td>
<td>N(%)*</td>
</tr>
<tr>
<td>Female</td>
<td>9,422 (48)</td>
<td>2,108 (45)</td>
<td>0.0024 0.050</td>
<td>978 (55)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>7,470 (38)</td>
<td>1,275 (27)</td>
<td>0.0001 0.086</td>
<td>1,181 (65)</td>
</tr>
<tr>
<td>18-49 years</td>
<td>3,215 (16)</td>
<td>974 (21)</td>
<td>0.0013 0.052</td>
<td>350 (20)</td>
</tr>
<tr>
<td>50-64 years</td>
<td>4,953 (25)</td>
<td>1,075 (22)</td>
<td>0.0013 0.052</td>
<td>350 (20)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>3,647 (19)</td>
<td>891 (19)</td>
<td>0.0001 0.062</td>
<td>355 (20)</td>
</tr>
<tr>
<td>75-79 years</td>
<td>7,277 (37)</td>
<td>1,578 (34)</td>
<td>&lt;0.0001 0.408</td>
<td>1,018 (57)</td>
</tr>
<tr>
<td>Deprivation index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>3,419 (17)</td>
<td>934 (20)</td>
<td>&lt;0.0001 0.070</td>
<td>378 (21)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>3,788 (19)</td>
<td>965 (21)</td>
<td>0.0177 0.038</td>
<td>350 (20)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>3,822 (19)</td>
<td>956 (21)</td>
<td>0.0715 0.029</td>
<td>364 (20)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>4,053 (21)</td>
<td>847 (18)</td>
<td>0.0003 0.059</td>
<td>324 (18)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>4,359 (22)</td>
<td>908 (20)</td>
<td>0.0001 0.064</td>
<td>358 (20)</td>
</tr>
<tr>
<td>Overseas dpts</td>
<td>272 (1)</td>
<td>41 (1)</td>
<td>0.0066 0.047</td>
<td>16 (1)</td>
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<td>First prescriber’s specialty</td>
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<tr>
<td>Hospital practitioner</td>
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<td>1,004 (22)</td>
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<td>5,275 (27)</td>
<td>992 (21)</td>
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<tr>
<td>Private cardiologist</td>
<td>6,585 (33)</td>
<td>2,576 (55)</td>
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<td>905 (51)</td>
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<tr>
<td>Other specialties</td>
<td>383 (2)</td>
<td>79 (2)</td>
<td>0.2718 0.018</td>
<td>33 (2)</td>
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<tr>
<td>HAS-BLED, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>2.3 (1.0)</td>
<td>0.1270 0.030</td>
<td>2.5 (0.9)</td>
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<tr>
<td>CHA2DS2-VASc, mean (SD)</td>
<td>3.4 (1.6)</td>
<td>3.1 (1.5)</td>
<td>&lt;0.0001 0.149</td>
<td>3.7 (1.4)</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Heart failure</td>
<td>4,953 (25)</td>
<td>982 (21)</td>
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<tr>
<td>Diabetes</td>
<td>4,253 (22)</td>
<td>875 (19)</td>
<td>&lt;0.0001 0.069</td>
<td>319 (18)</td>
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<tr>
<td>CKD</td>
<td>903 (5)</td>
<td>117 (3)</td>
<td>&lt;0.0001 0.112</td>
<td>75 (4)</td>
</tr>
<tr>
<td>Condition</td>
<td>NOAC (N)</td>
<td>VKA (N)</td>
<td>p-value</td>
<td>NOAC (Mean ± SD)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>------------------</td>
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<tr>
<td>Dementia</td>
<td>783 (4)</td>
<td>138 (3)</td>
<td>0.0012</td>
<td>0.055</td>
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<tr>
<td>History of stroke</td>
<td>1,717 (9)</td>
<td>219 (5)</td>
<td>&lt;0.0001</td>
<td>0.160</td>
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<tr>
<td>History of TIA</td>
<td>576 (3)</td>
<td>100 (2)</td>
<td>0.0039</td>
<td>0.049</td>
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<tr>
<td>CHD</td>
<td>4,675 (24)</td>
<td>963 (21)</td>
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<tr>
<td>PVD</td>
<td>1,561 (8)</td>
<td>282 (6)</td>
<td>&lt;0.0001</td>
<td>0.073</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>491 (2)</td>
<td>110 (2)</td>
<td>0.6192</td>
<td>0.008</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>412 (2)</td>
<td>50 (1)</td>
<td>&lt;0.0001</td>
<td>0.081</td>
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<td>Smoking§</td>
<td>750 (4)</td>
<td>125 (3)</td>
<td>0.0002</td>
<td>0.063</td>
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Comedications

<table>
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<tr>
<th>Category</th>
<th>NOAC (N)</th>
<th>VKA (N)</th>
<th>p-value</th>
<th>NOAC (Mean ± SD)</th>
<th>VKA (Mean ± SD)</th>
<th>p-value</th>
<th>NOAC (N)</th>
<th>VKA (N)</th>
<th>p-value</th>
<th>NOAC (Mean ± SD)</th>
<th>VKA (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>16,159 (82)</td>
<td>3,624 (78)</td>
<td>&lt;0.0001</td>
<td>0.101</td>
<td>1,486 (83)</td>
<td>0.2697</td>
<td>0.028</td>
<td>2,138 (75)</td>
<td>&lt;0.0001</td>
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<td>Cardiac glycosides</td>
<td>2,915 (15)</td>
<td>604 (13)</td>
<td>0.0017</td>
<td>0.052</td>
<td>251 (14)</td>
<td>0.3819</td>
<td>0.022</td>
<td>353 (12)</td>
<td>0.0005</td>
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<td>Antiarrhythmics</td>
<td>13,258 (67)</td>
<td>3,393 (73)</td>
<td>&lt;0.0001</td>
<td>0.125</td>
<td>1,235 (69)</td>
<td>0.1328</td>
<td>0.037</td>
<td>2,158 (75)</td>
<td>&lt;0.0001</td>
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<td>Lipid-lowering agents</td>
<td>9,635 (49)</td>
<td>2,204 (47)</td>
<td>&lt;0.0001</td>
<td>0.030</td>
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<td>1,393 (49)</td>
<td>0.8516</td>
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<td>Oral corticosteroids</td>
<td>2,333 (12)</td>
<td>534 (11)</td>
<td>0.5010</td>
<td>0.011</td>
<td>211 (12)</td>
<td>0.9529</td>
<td>0.001</td>
<td>323 (11)</td>
<td>0.3978</td>
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<tr>
<td>Antiulcer agents</td>
<td>8,198 (42)</td>
<td>1,756 (38)</td>
<td>&lt;0.0001</td>
<td>0.078</td>
<td>730 (41)</td>
<td>0.5083</td>
<td>0.016</td>
<td>1,026 (36)</td>
<td>&lt;0.0001</td>
<td>0.118</td>
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<tr>
<td>Benzodiazepines</td>
<td>6,191 (31)</td>
<td>1,343 (29)</td>
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<td>0.055</td>
<td>597 (33)</td>
<td>0.0898</td>
<td>0.042</td>
<td>746 (26)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Antiplatelets</td>
<td>10,336 (52)</td>
<td>2,604 (56)</td>
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<td>1,086 (61)</td>
<td>&lt;0.0001</td>
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<td>1,518 (53)</td>
<td>0.5309</td>
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<td>NSAID</td>
<td>3,425 (17)</td>
<td>867 (19)</td>
<td>0.0414</td>
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<td>297 (17)</td>
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<td>0.021</td>
<td>570 (20)</td>
<td>0.0008</td>
<td>0.065</td>
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</table>

Abbreviations: D, dabigatran; R, rivaroxaban; Stand Diff, absolute weighted standardized differences; Dpts, departments; CKD, Chronic kidney disease; TIA, Transient ischemic attack; CHD, Coronary heart disease; NSAID, non-steroidal anti-inflammatory drugs; PVD, Peripheral vascular disease.

*Dichotomous variables are expressed as N (%); continuous variables are expressed as mean (standard deviation).

As all NOAC patients were matched, their baseline characteristics are the same as those presented in Tables 2 and 3 of the manuscript.

†p-value of the test comparing baseline characteristics between NOAC- and VKA-treated patients.

‡ Absolute weighted standardized differences comparing baseline characteristics between NOAC- and VKA-treated patients.