BROTHER

Benefit-Risk Of arterial THrombotic prEvention with Rivaroxaban for atrial fibrillation in daily clinical practice.

A French cohort within the nationwide claims and hospital database

Study report

One-year of follow-up

Version 3.0, 20 November 2018

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PASS information

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Research question and objectives	**Research question:** To assess the one-year and two-year benefit-risk between rivaroxaban for stroke prevention in atrial fibrillation (SPAF) versus VKA and dabigatran among new users of anticoagulant. **Main objective:** To compare the one-year and two-year risk of following individual outcomes: stroke and systemic embolism, major bleeding, and death between new users of anticoagulant for SPAF during drug exposure, rivaroxaban versus VKA, and rivaroxaban versus dabigatran.
Country of study	France
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1. ABSTRACT

Title
Benefit-risk of arterial thrombotic prevention with rivaroxaban for atrial fibrillation in daily clinical practice. A French cohort within the nationwide claims and hospital database.

Keywords
Nonvalvular atrial fibrillation, VKA, direct oral anticoagulant, comparative effectiveness, comparative risk, stroke and systemic embolism, bleeding, death, acute coronary syndrome, claims and hospitalisation database, specific atrial fibrillation and total medical costs.

Rationale and background
The benefit-risk of the three direct oral anticoagulants (DOAC), rivaroxaban (Xarelto®), dabigatran (Pradaxa®), and apixaban (Eliquis®), for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) was considered better than that of vitamin K antagonists (VKA) in premarketing clinical trials. However, French health authorities have questioned the generalization of these results to current practice, where the physicians, the patients, drug prescription and use are not the same as those of the clinical trials. The BROTHER study was an analysis using the French nationwide health insurance database, starting six months after the beginning of DOAC launch in the NVAF indication.

Research question and objectives
The research question was to assess the one-year and two-year benefit-risk of rivaroxaban for stroke prevention in atrial fibrillation (SPAF) compared with VKA and dabigatran among new users of anticoagulant. The main objective was to compare the one-year and two-year risk of each of the following individual outcomes: stroke and systemic embolism (SSE), major bleeding and death between new users of anticoagulant for SPAF during drug exposure, rivaroxaban versus VKA, and rivaroxaban versus dabigatran.

Study design
Historical cohort study in the French nationwide healthcare claims and hospitalisation database (SNDS) including new users of rivaroxaban, dabigatran, or VKA for SPAF in 2013 or 2014 and followed until 31/12/2015.

Setting
New users of DOAC, dabigatran, rivaroxaban, or VKA for SPAF, identified and followed in a claims and hospitalisation database (apixaban was marketed in this indication during the inclusion period, starting in January 2014).

Subjects and study size, including dropouts
Among the 734 599 patients identified in the nationwide SNDS database with a first dispensing of rivaroxaban, dabigatran or VKA in 2013 or 2014, without history of prior DOAC or VKA dispensing in the 3 years, 220 011 patients were included in the specific NVAF population: 69 736 (32%) in the rivaroxaban group (19% with the 20 mg standard dose, 11% with the 15 mg reduced dose, and 1% with the 10 mg dose), 41 609 (19%) in the dabigatran group (8% with the 150 mg standard dose, 11% with the 110 mg reduced dose, and 1% with the 75 mg dose), and 108 666 (49%) in the VKA group. Patients of the specific population had an AF diagnosis from long-term disease (LTD) or hospitalisation or procedure for AF, without rheumatic valve disease or valve replacement. The sensitive NVAF population included the specific population, plus patients having a high probability to have an AF, based on an AF disease score. It concerned 302 031 patients: 101 009 (33%) in the rivaroxaban group (19.6% with the standard dose, 12.5% with the reduced dose, and 1.3% with the 10 mg dose), 56 523 (19%) in the dabigatran group (7.2% with the standard dose, 11.0% with the reduced dose, and 0.5% with the 75 mg dose), and 144 499 (48%) in the VKA group.
The number of new users was relatively stable for the VKA between 2013 and 2014 (+ 4%), while there was a small increase for rivaroxaban 20 mg (+ 8%), and a small decrease for rivaroxaban

15 mg (- 8%), associated with a fall of more than 50% of new users for dabigatran 150 mg (- 56%) and dabigatran 110 mg (- 65%).

For each comparison, patients were individually matched 1:1 on the date of the first drug (DOAC or VKA) dispensing (± 14 days), gender, age at index date (± 1 year), and logit of hdPS (± caliper): 31 171 patients per group for rivaroxaban 20 mg versus VKA in the specific population and 43 162 per group in the sensitive population (73% of rivaroxaban patients), 15 323 per group for rivaroxaban 20 mg versus dabigatran 150 mg in the specific population and 20 257 per group in the sensitive population (91% and 94% of dabigatran patients, respectively), 23 314 per group for rivaroxaban 15 mg versus VKA in the specific population and 35 585 per group in the sensitive population (95% of rivaroxaban patients), and 15 131 per group for rivaroxaban 15 mg versus dabigatran 110 mg in the specific population and 23 491 per group in the sensitive population (64% and 71% of dabigatran patients, respectively).

Variables and data sources

The index date was defined as the date of the first reimbursed dispensing of rivaroxaban, dabigatran or VKA in 2013 or 2014.

Clinical outcomes studied during the anticoagulant (rivaroxaban, dabigatran, VKA) exposure on the 1-year follow-up period were SSE, major bleeding, clinical relevant bleeding (CRB), death, a composite criterion (first event among SSE, major bleeding, and death), and acute coronary syndrome (ACS).

The specific AF healthcare resources use during the anticoagulant exposure was described using specific hospitalisations (hospitalisations for AF, CRB, SSE, ACS), stays in rehabilitation department (SSR) linked to specific hospitalisations non AF, AF drugs, specific lab tests, and specific medical consultations and visits. The total healthcare resources use was described using specific hospitalisations, SSR linked to specific hospitalisations non AF, other cardiovascular hospitalisations, other non-cardiovascular hospitalisations, medical consultations, visits and technical acts, public hospital external consultations and acts, cardiovascular and antidiabetic drugs, non-cardiovascular and non-antidiabetic drugs, lab tests, products and services, transports, nursing acts, physiotherapy acts, and allowances.
Healthcare resource costs were estimated during the anticoagulant exposure according to the collective perspective and the national health insurance perspective. The total medical specific cost per patient included costs of all specific AF healthcare expenditures, and the total medical cost included costs all healthcare expenditures, except allowances.

The SNDS database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry. It currently includes 99% of the French population of 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. It contains individual pseudonymised information on general characteristics (gender, date of birth, area of residence), date of death, long-term disease (LTD) with full insurance coverage, outpatient reimbursed healthcare expenditures (visits, medical procedures, nursing acts, …), and hospital discharge summaries for all private and public medical, obstetric and surgery hospitalisations.

Results

The description of patients at index date showed large differences between groups (standardised differences > 20% for a lot of variables). In particular, patients in the rivaroxaban 20 mg group were younger, with fewer comorbidities, hospitalisations before index date, stroke and bleeding risk factors compared to those in the VKA group, and more similar to those in the dabigatran 150 mg group with a mean of 3.4 years more and some risk factors linked to age more frequent for patients in the rivaroxaban group. For the reduced dose, patients in the rivaroxaban 15 mg group had similar age, but also fewer comorbidities, hospitalisations before index date, stroke and bleeding risk factors compared to those in the VKA group, and similar to those in the dabigatran 110 mg group with a mean of 1.2 years more and some risk factors linked to age slightly more frequent for patients in the rivaroxaban group. These differences were well demonstrated through hdPS distributions, with however a large overlap, allowing a 1:1 matching for a high rate of

patients of the smaller group. After matching, all standardised differences became weak or equal to zero, with a good overlapping of hdPS distributions.

The most common first prescriber of rivaroxaban 20 mg and 15 mg was a cardiologist for 39% of patients for both doses, followed by hospital physicians (30% and 25%, respectively), and GP (20% and 24%, respectively). It was similar for dabigatran 150 mg and 110 mg: cardiologists (38% and 32%, respectively), hospital physicians (34% and 32%, respectively), and GP (17% and 23%, respectively), while VKA were mainly prescribed by hospital physicians (40%), followed by GP (26%), and a few by cardiologists (17%).

In this real-life study, the reduced dose of DOAC was frequently used and concerned 35% of patients for the rivaroxaban group and 57% of those for the dabigatran group. The higher use of the reduced dabigatran dose is explained by the difference in indications/recommendations of use in special populations: dabigatran 110 mg is recommended for older patients (≥ 80 years), or 75-80 years old when thromboembolism risk is low and bleeding risk is high, patients with moderate renal impairment or high risk of bleeding, whereas rivaroxaban 15 mg is just recommended for patients with moderate renal impairment and can be used with caution in patients with severe renal impairment. It seems that physicians were particularly worried for the bleeding risk, especially for oldest patients.

For all patients of rivaroxaban 20 mg, dabigatran 150 mg and VKA groups respectively, the mean age was 68.6 (± 11.1), 65.2 (± 10.1) and 78.4 (± 11.0) years, with 64%, 69% and 52% of men, 66%, 58% and 91% of CHA_2DS_2-VASc ≥ 2, 4%, 3% and 17% of HAS-BLED > 3. For reduced DOAC doses, rivaroxaban 15 mg and dabigatran 110 mg, patients were more alike the VKA group, with a mean age of 79.8 (± 9.3) and 78.6 (± 9.4) years, 47% and 49% of men, 92% and 91% of CHA_2DS_2-VASc ≥ 2, 9% and 8% of HAS-BLED > 3, respectively.

After matching, the mean age was 71.2 (± 10.0) years with 62% of men, 76% of CHA_2DS_2-VASc ≥ 2, and 5% of HAS-BLED > 3 in both groups, for rivaroxaban 20 mg and VKA groups, 66.0 (± 9.3) years with 70% of men, 58% of CHA_2DS_2-VASc ≥ 2, and 3% of HAS-BLED > 3 in both groups, for rivaroxaban 20 mg and dabigatran 150 mg groups, 80.1 (± 8.7) years with 48% of men, 93% of CHA_2DS_2-VASc ≥ 2, 9% of HAS-BLED > 3 in both groups, for rivaroxaban 15 mg and VKA groups, 80.2 (± 7.8) years with 48% of men, 94% of CHA_2DS_2-VASc ≥ 2, 8% of HAS-BLED > 3 in both groups, respectively for rivaroxaban 15 mg and dabigatran 110 mg groups.

The main analysis was performed for the specific population with a grace period of 60 days for drug discontinuation definition. The 1-year cumulative incidence of discontinuation or switch was 43.1% (95%CI [42.6% to 43.5%]) with rivaroxaban 20 mg (about 2/3 of discontinuations and 1/3 of switches), 49.7% [48.9% to 50.4%] with dabigatran 150 mg (58% discontinuations and 42% switches), and 40.4% [40.1% to 40.7%] with VKA (3/4 of discontinuations and 1/4 of switches). It was 44.6% [44.0% to 45.3%] with rivaroxaban 15 mg (57% discontinuations and 43% switches) and 49.4% [48.8% to 50.1%] with dabigatran 110 mg (50% discontinuations and 50% switches).

The number of person-years (PY) during the first drug exposure was 29 391, 11 101, and 77 480 PY, respectively for all rivaroxaban 20 mg, dabigatran 150 mg, and VKA patients, and 16 124 and 15 079 PY, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients. For matched patients, there were 21 921 and 22 786 PY, respectively for rivaroxaban 20 mg and VKA groups, 10 613 and 10 160 PY, respectively for rivaroxaban 20 mg and dabigatran 150 mg groups, 15 383 and 17 254 PY, respectively for rivaroxaban 15 mg and VKA groups, and 10 045 and 9 596 PY, respectively for rivaroxaban 15 mg and dabigatran 110 mg groups. For all treatment groups, the Medication Possession Ratio was greater than 80% for more than 90% for all and matched patients.

For all patients of rivaroxaban 20 mg, dabigatran 150 mg and VKA groups, respectively, the incidence rate of first event per 100 PY was 1.5 [1.4 to 1.6], 1.4 [1.2 to 1.6] and 3.1 [3.0 to 3.2] for SSE, 1.4 [1.3 to 1.5], 0.6 [0.5 to 0.7], and 3.8 [3.7 to 3.9] for major bleedings, 3.4 [3.2 to 3.6], 1.9 [1.6 to 2.2] and 15.6 [15.3 to 15.9] for death, 5.8 [5.5 to 6.1], 3.7 [3.3 to 4.1] and 20.6 [20.3 to 20.9] for the composite criterion (first event from SSE, major bleeding, and death). For reduced DOAC doses, rivaroxaban 15 mg and dabigatran 110 mg, respectively, it was 2.6 [2.4 to 2.8] and 2.1 [1.9 to 2.3] for SSE, 2.8 [2.5 to 3.1] and 2.0 [1.8 to 2.2] for major bleeding, 10.1 [9.6 to 10.6] and 8.5 [8.1 to 8.9] for death, 14.3 [13.8 to 14.8] and 11.7 [11.2 to 12.2] for the composite.

The risk of all main outcomes, SSE, major bleeding (ISTH definition, Schulman 2005) and death, as well as the composite of these three events was significantly lower with rivaroxaban 20 mg compared to VKA for matched patients: 21% [10% to 31%], 33% [23% to 41%], 33% [27% to 39%], and 30% [26% to 35%], respectively. The risk was also significantly lower with rivaroxaban 20 mg for individual SSE outcomes, 20% [5% to 33%] for ischemic or undefined stroke, and 24% [5% to 39%] for other systemic embolism or surgical procedure for systemic embolism. That was also the case for most important bleeding subgroups: CRB, haemorrhagic stroke, other critical organ or site bleeding, and other bleeding (17% [9% to 24%], 33% [14% to 48%], 50% [33% to 62%], 32% [19% to 43%], respectively), without significant increase of GI bleeding (HR: 1.11 [0.95 to 1.31]). For ACS, the risk was significantly lower with the rivaroxaban, including STEMI and NSTEMI (20% [7% to 31%], 38% [15% to 55%] and 43% [15% to 62%], respectively). Results were similar when all patients were considered with adjusted analysis on gender, age, and hdPS in deciles.

Stratified analyses were performed for main and secondary outcomes, according to index date, gender, age classes, CHA_2DS_2-VASc score and its individual risk factors (congestive heart failure, hypertension, diabetes mellitus, stroke or TIA history, vascular disease history, age 65-74 years, age ≥ 75 years), HAS-BLED score and hdPS quintiles. The lower risk with rivaroxaban 20 mg compared to VKA was confirmed for most subgroups, with substantial HR point estimate variations from: 0.60 (last quintile) to 1.04 (CHA_2DS_2-VASc scores 0-1) for SSE, 0.40 (last quintile) to 1.04 (vascular disease history) for major bleeding, 0.54 (75-79 years old) to 0.82 (stroke or TIA history) for death, 0.56 (75-79 years old) to 0.85 (vascular disease history) for the composite criterion, with a HAS-BLED HR gradient from 0-1 to > 3 scores for all main outcomes, SSE (0.76 to 0.92), major bleeding (0.66 to 0.72), death (0.61 to 0.74), composite criterion (0.66 to 0.76), and a quintile HR gradient from the last to the first quintile of logit hdPS for major bleeding (0.40 to 0.83), CRB (0.64 to 0.99), and composite criterion (0.59 to 0.78), and no clear systematic variation for the other factors and outcomes.

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, the risk of SSE was lower, but not significantly with rivaroxaban for matched patients (HR: 0.90 [0.71 to 1.13]), while the risk of major bleeding, death, and the composite of the three main outcomes (SSE, major bleeding and death) was significantly lower with dabigatran: 43% [22% to 58%], 22% [6% to 35%] and 17% [5% to 28%], respectively. The risk was also significantly lower with dabigatran for CRB, haemorrhagic stroke, and GI bleeding (44% [32% to 54%], 57% [24% to 76%], 30% [4% to 48%], respectively), but not for other critical organ or site bleeding (HR: 0.96 [0.53 to 1.74]). For ACS, the risk was significantly lower with dabigatran (26% [5% to 43%]). Results were similar when all patients were considered with adjusted analysis on gender, age, and hdPS in deciles. Stratified analyses for main outcomes showed non-systematic substantial variations according to sub-groups, mostly in favour of rivaroxaban for SSE, from a HR of 0.54 (vascular disease history) to 1.22 (HAS-BLED scores > 3), in favour of dabigatran for major bleeding, from 1.11 (2014 index date) to 4.12 (second quintile of logit hdPS), mainly in favour of dabigatran for death, from 0.83 (HAS-BLED scores > 3) to 2.02 (second quartile), and for the composite criterion, from 0.88 (vascular disease history) to 1.52 (third quintile).

For the reduced dose comparison, there was no statistical difference between risk with rivaroxaban 15 mg and VKA for matched patients for SSE (HR: 1.05 [0.92 to 1.21]) and a significant lower risk for the two other outcomes of the main objective, major bleeding and death, as well as for the composite of these three events: 16% [4% to 26%], 15% [10% to 21%], and 11% [6% to 16%], respectively. The lack of SSE risk difference persisted for individual outcomes, ischemic or undefined stroke, and other systemic embolism or surgical procedure for systemic embolism. The risk was also significantly lower for haemorrhagic stroke and CRB (26% [5% to 42%] and 11% [2% to 19%], respectively) and at the significant threshold for ACS and other critical organ or site bleeding (HR: 0.85 [0.73 to 1.00], and 0.76 [0.58 to 1.00], respectively), without significant increase for GI bleeding (HR: 1.13 [0.96 to 1.33]). The risk of ACS was at the significant threshold (HR: 0.85 [0.73 to 1.00]). Results were similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles. Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.74 (last quintile) to 1.32 (CHA_2DS_2-VASc scores 0-1) with a gradient from the first to the last quintile (0.74 to 1.16), and not one significant HR. For the three other outcomes, the risk was in favour of rivaroxaban for almost all

subgroups, with a HR from 0.54 (HAS-BLED scores > 3) to 1.16 (CHA_2DS_2-VASc scores 0-1) for major bleeding, with a HAS-BLED gradient, from 0.54 to 1.11 for scores > 3 to 0-1, 0.76 (last quintile) to 1.23 (CHA_2DS_2-VASc scores 0-1) for death, with a CHA_2DS_2-VASc gradient from 0.83 to 1.23 for scores ≥ 4 to 0-1, and 0.78 (last quintile) to 1.26 (CHA_2DS_2-VASc scores 0-1) for the composite criterion, without clear systematic variation for the other factors and outcomes.

For the rivaroxaban 15 mg and dabigatran 110 mg comparison, the risk of SSE, major bleeding and the composite of the three main outcomes (SSE, major bleeding and death) was significantly lower with dabigatran 110 mg compared to rivaroxaban 15 mg: 21% [6% to 35%], 22% [7% to 35%], and 8% [1% to 15%], respectively, with no difference for death risk (HR: 1.04 [0.95 to 1.14]). For individual SSE outcomes, there was also a significant lower risk with dabigatran for other systemic embolism or surgical procedure for systemic embolism (39% [16% to 56%]), but not for ischemic or undefined stroke (HR: 1.12 [0.90 to 1.39]). The risk was significantly lower with dabigatran for CRB (28% [17% to 36%]), haemorrhagic stroke (54% [33% to 69%]), urogenital bleeding (34% [5% to 54%]), and other bleeding (40% [21 to 54]), but not for other critical organ or site bleeding (1.40 [0.95 to 2.08]), and GI bleeding (1.02 [0.83 to 1.29]). The ACS risk, as well as individual ACS outcomes, STEMI, NSTEMI and unstable angina were not different (HR: 0.97 [0.79 to 1.19], 0.90 [0.62 to 1.30], 0.68 [0.39 to 1.19], 1.12 [0.87 to 1.44], respectively). Results were mostly similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles. Stratified analyses for main and secondary outcomes showed non-systematic substantial variations across sub-groups, mainly in favour of dabigatran, from a HR of 0.75 (< 65 years old) to 1.90 (vascular disease history) for SSE, 1.07 (CHA_2DS_2-VASc score 2 and fourth quintile) to 2.14 (second quintile) for major bleeding, 0.69 (CHA_2DS_2-VASc scores 0-1) to 1.62 (65-69 years old) for death, 0.93 (< 65 years old) to 1.61 (65-69 years old) for the composite criterion.

For the 4 comparisons, rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, rivaroxaban 15 mg versus dabigatran 110 mg, hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses for the specific population with a 30-day grace period for drug discontinuation definition, and for the sensitive population with a 60-day grace period for drug discontinuation definition.

The total medical specific cost per patient according to the national health perspective was €130 higher with rivaroxaban 20 mg compared to VKA for matched patients, due to the high cost of DOAC drugs, and similar between rivaroxaban 20 mg and dabigatran 150 mg. However, the total medical cost was about €1,400 lower with rivaroxaban 20 mg compared to VKA, due to a slightly higher frequency of other cardiovascular and other non-cardiovascular hospitalisations, and €340 higher with rivaroxaban 20 mg compared to dabigatran 150 mg.

For the reduced dose comparison, the total medical specific cost was almost the same for rivaroxaban 15 mg and VKA, and €71 higher with rivaroxaban 15 mg compared to dabigatran 110 mg. The total medical cost remained €1,600 lower with rivaroxaban 15 mg compared to VKA, and €400 higher with rivaroxaban 15 mg compared to dabigatran 110 mg.

Discussion

The SNDS is the nationwide healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It is therefore fully representative of the French population. It provided a unique opportunity to identify new users of DOAC or VKA for NVAF in 2013 and 2014, with exhaustive information about reimbursed outpatient healthcare resources including reimbursed drugs, as well as all public and private hospitalisations with high specificity of diagnosis for NVAF and outcomes, excluding selection and information biases. The main limit was that the database was built for administrative and reimbursement purposes with a lack of clinical information that could impact the patient prognosis. However, an hdPS was built to matched patients 1:1 for each comparison, to obtain well-balanced groups for a large set of variables. They could act as a proxy for potential unmeasured confounders, limiting the risk of residual confounding. The analysis comparing similar hdPS matched patients was strengthened by the hdPS adjusted analysis, which confirms the results for the whole 2013-2014 NVAF population.

Results of this study can be generalisable to the French population because patients were identified from a whole population database, without any sampling. Patients were therefore fully representative of patients with NVAF diagnosis from LTD or hospitalisation or procedure for AF, as well as those with probable AF based on an AF disease score. These results were set within a specific healthcare system in which the most used VKA was fluindione, and might or not apply to other countries. Furthermore, the study showed non-systematic substantial variations across subgroups stratified analysis that could impact the global result according the distribution of theses subgroup in the population analyses, as for example between 2013 and 2014 index date, in relation with the fall of dabigatran first prescription and use in 2014.

From the conditions of use in 2013 and 2014 in France, rivaroxaban and VKA were prescribed preferentially to rather different patients, while differences between the two DOAC were less marked. When effects were compared within similar patients in hdPS matched groups, as well as for all patients from adjusted analyses and most subgroups from stratified analyses, this nationwide cohort study showed a significantly overall better benefit-risk of rivaroxaban versus VKA, for both doses, including for SSE, death, major bleeding and haemorrhagic stroke, without increased risk of gastrointestinal bleeding with the 20 mg, and with the 15 mg, for death, major bleeding, including haemorrhagic stroke, but not for SSE, and also without increase of GI bleeding. Moreover, rivaroxaban was cost-saving for both doses (20 mg and 15 mg) compared to VKA with a 18% lower total medical cost for the national health perspective.

For the two DOAC comparisons, the study showed a better benefit and lower risk with dabigatran for either dose (20 mg and 15 mg vs 150 mg and 110 mg, respectively). The risk was not different between rivaroxaban 20 mg and dabigatran 150 mg for SSE, but higher with rivaroxaban for death, major bleeding, including haemorrhagic stroke and GI bleeding. For reduced dose, the risk was higher with rivaroxaban 15 mg than dabigatran 110 mg for SSE and major bleeding, including haemorrhagic stroke, but not for death or GI bleeding; with however, substantial variations across stratification subgroups analysed. Moreover, the medical cost result was also in favour of dabigatran for either dose (150 mg and 110 mg) with a 6-7% lower total medical cost.

Marketing Authorisation Holder(s)
Bayer AG

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2. LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ANSM	*Agence Nationale de Sécurité du Médicament et des produits de santé* (French Medicines Agency)
ASA	AcetylSalicylic Acid
CHA_2DS_2-VASc	Risk score of stroke in patients with atrial fibrillation
CI	Confidence Interval
CNAMTS	*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés* (French national health insurance fund for salaried workers)
CNIL	*Commission Nationale de l'Informatique et des Libertés* (French data protection commission)
CRB	Clinically Relevant Bleeding
DDD	Defined Daily Dose
DOAC	Direct Oral AntiCoagulants
DRG	Diagnosis-Related Groups (or GHM for *Groupes Homogènes de Malades*)
DVT	Deep Vein Thrombosis
EGB	*Echantillon Généraliste de Bénéficiaires* (1/97 random sample of the national health insurance database)
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
GI	Gastro-Intestinal
HAS	*Haute Autorité de Santé* (French health authority)
HAS-BLED	Risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation
hdPS	high-dimensional Propensity Score
HR	Hazard Ratio
ICD-10	International Classification of Disease, 10^{th} revision
IDS	*Institut des Données de Santé* (Institute of Health Data)
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
MI	Myocardial Infarction
MPR	Medication Possession Ratio
NSTEMI	Non ST Elevation Myocardial Infarction
NVAF	Non-Valvular Atrial Fibrillation
PMSI	*Programme de Médicalisation des Systèmes d'Information* (National hospital discharge summary database)
PS	Propensity Score
PY	Person-Years
SAP	Statistical Analysis Plan
SE	Systemic Embolism
SNDS	*Système National des Données de Santé* (French national healthcare insurance system database)
SPAF	Stroke Prevention in Atrial Fibrillation

SRG	Stay-Related Groups (or GHS for *Groupes Homogènes de Séjour*)
SSE	Stroke and Systemic Embolism
SSR	*Soins de Suite et de Réadaptation* (Stays in rehabilitation department)
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolic Events

3. INVESTIGATORS

Not applicable.

4. OTHER RESPONSIBLE PARTIES

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5. MILESTONES

	Planned date	Actual date	Comments
Data reception	– Q3-Q4 2016	– November 2016	
Data management and statistical analysis	– Q4 2016-Q1 2017	– November 2016-July 2017 (one-year clinical outcomes) – April 2017-October 2017 (one-year healthcare resources use and costs) – April 2018-October 2018 (one-year sensitivity analyses)	
Final report of study results	– Q2 2017	– September 2017 (one-year clinical outcomes) – February 2018 (one-year clinical outcomes and one-year healthcare resources use and costs) – November 2018 (one-year clinical outcomes, one-year healthcare resources use and costs, and one-year sensitivity analyses)	

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by irregular beating. AF is associated with a five-fold increased risk of ischemic stroke, and accounts for up to 15% of strokes in persons of all ages and 30% in those over 80 years (Wolf 1987, Camm 2010). Ischemic stroke in AF is often severe and results in long-term disability or death (Camm 2010). Vitamin K antagonists (VKA) were the reference treatment for stroke prevention in atrial fibrillation (SPAF) and recommended for persons at increased risk of stroke (Camm 2010, Steinberg 2014).

Xarelto® (rivaroxaban) is a direct oral anticoagulant (DOAC) with a different mode of action from VKA. Xarelto®, 15 mg or 20 mg once daily, received a European market authorization for the prevention of stroke and systemic embolism in adult patients with non-valvular AF (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (EMA/CHMP/753436/2011, 22 September 2011). Two other DOAC received a European market authorization for the same indication: Pradaxa® (dabigatran) 110 mg or 150 mg twice daily (EMA/CHMP/ 304146/2011, 14 April 2011) and Eliquis® (apixaban) 2.5 mg or 5 mg twice daily (EMA/CHMP/ 608476/2012, 20 September 2012).

The market authorization of rivaroxaban is based on the ROCKET-AF trial which randomized 14,264 subjects with NVAF at increased risk of stroke, to receive either rivaroxaban (at a daily dose of 20 mg) or adjusted-dose warfarin (Patel 2011). In the primary analysis, the incidence of stroke or systemic embolism was 1.71% per year in the rivaroxaban group and 2.16% per year in the warfarin group (hazard ratio (HR), 0.79; 95%CI, 0.66 to 0.96; $p < 0.001$ for non-inferiority). Major and non-major clinically relevant bleeding incidence was 14.9% per year in the rivaroxaban group and 14.5% per year in the warfarin group (HR, 1.03; 95%CI, 0.96 to 1.11), with significant reductions in intracranial haemorrhage (0.5% vs 0.7%, $p = 0.02$) and fatal bleeding (0.2% vs 0.5%, $p = 0.003$) in the rivaroxaban group.

In France, Xarelto® and Pradaxa® were launched in this indication in August 2012, and Eliquis® in January 2014. The Transparency Committee of the *Haute Autorité de Santé* (HAS) gave a positive opinion for the reimbursement in this indication with a substantial medical benefit (SMR important) but no improvement in existing benefit (ASMR V), no expected public health impact, and a target population of 500 000 patients. As part of this procedure, the Transparency Committee requested Bayer to provide additional data documenting the therapeutic benefit of Xarelto® under actual conditions of use compared with the normal treatment of at-risk patients with NVAF:

- The characteristics of the treated patients, in particular age, gender, history and cardiovascular risk factors,
- The conditions of use of Xarelto®: reasons for starting treatment (particularly, first-line or second-line prescription, and risk factors associated with AF), any previous anticoagulant treatment and level of control thus obtained, concomitant treatments (in particular, antiplatelet agents and medicines with a risk of interaction), prescribed dose (dose, amount administered daily and duration of prescription), frequency and reasons for any discontinuation of treatment and treatments started as a back-up,
- The impact on morbidity and mortality (events avoided and adverse effects, particularly bleeding), treatment compliance and quality of life in the medium and long term.

ANSM, the French medicines agency, commissioned two studies using the French national claims and hospital database:

- The NACORA-BR study, performed by the CNAMTS, was a cohort study with a main objective to compare the short-term risk of major bleeding for new DOAC users naive of VKA during the second half of 2012 to new users of VKA during the second half of 2011. Secondary objectives were to compare the risk of arterial events (stroke, systemic embolism), the risk of myocardial infarction (MI) over the same period in patients starting treatment within the AF indication, and the 30-day survival for patients hospitalised for major bleeding. This study concluded to no significant statistical difference between DOAC, dabigatran or rivaroxaban, and VKA for the short-term risk of bleeding or arterial thromboembolic short-term risk during the early phase of anticoagulant therapy in NVAF patients (CNAMTS 2014, Maura 2015).
- The NACORA-Switch study, led by the ANSM, was a cohort study with the same main and secondary objectives for patients who switched from VKA to DOAC compared to matched

patients who remained on VKA. The authors concluded that the short-term risk of severe bleeding, stroke and systemic embolism, MI was not increased for patients switching from VKA to DOAC compared to those remaining on VKA (ANSM 2014).

The two studies underline that they were conducted at the early phase of dabigatran and rivaroxaban marketing for SPAF with a short-term follow-up (3 months). The early period of marketing of a new drug is generally considered as a learning period during which disease severity and history, drug prescription and utilisation do not necessary reflect the use of the drug in daily practice some months later.

In order to provide additional information to answer the HAS requests, especially the impact on morbidity and mortality, with a longer follow-up than for the NACORA studies, a rivaroxaban versus VKA comparison, as well as a face to face comparison between the two DOAC (rivaroxaban versus dabigatran), Bayer committed to a cohort study to be initiated about six months after the launch of the two first DOAC for SPAF with two years of follow-up, using the French national claims and hospital database.

This document is written according to the guidance for the format and content of the final study report for non-interventional post-authorisation safety study provided by the European Medicines Agency (EMA) (http://www.ema.europa.eu) in accordance with procedures of the Bordeaux PharmacoEpi platform. It contains all elements listed in the methodological guidance of the HAS which are included in Appendix 1-1. This appendix presents the correspondence between the model recommended by the HAS and the EMA template.

7. RESEARCH QUESTION AND OBJECTIVES

The research question was to assess the one-year and two-year benefit-risk of rivaroxaban for SPAF compared with VKA and dabigatran among new users of anticoagulant.

The main objective was to compare the one-year and two-year risk of each of the following individual outcomes: stroke and systemic embolism (SSE), major bleeding and death between new users of anticoagulant for SPAF during drug exposure, rivaroxaban versus VKA, and rivaroxaban versus dabigatran.

The secondary objectives defined in the protocol were:

- To describe the drug exposure to rivaroxaban, dabigatran, and VKA for SPAF in new users, as well as pattern of use;
- To compare the one-year and two-year risk of the following individual outcomes: a composite of SSE, major bleeding and death, clinically relevant bleeding (CRB) and acute coronary syndrome (ACS) between new users of anticoagulant for SPAF during drug exposure, rivaroxaban versus VKA, and rivaroxaban versus dabigatran;
- To estimate the cumulative incidence and the incidence rate of each individual main and secondary outcome (SSE, major bleeding, CRB, death, composite criteria, and ACS), as well as according individual diagnosis of each of these outcomes, during drug exposure for rivaroxaban, dabigatran, and VKA;
- To estimate the cumulative incidence of each individual main and secondary outcome (SSE, major bleeding, CRB, death, composite criteria, and ACS), as well as according individual diagnosis of each of these outcomes during post-anticoagulant exposure for rivaroxaban, dabigatran, and VKA (i.e. after anticoagulant discontinuation);
- To assess outcome risk factors, including (but not limited to) gender, age, stroke and bleeding risk scores (CHA_2DS_2-VASc and HAS-BLED), low or high dosage at index date for DOAC, drug predisposing to bleeding during drug exposure and significant baseline characteristics;
- To describe and compare healthcare resources use related to SPAF during rivaroxaban, dabigatran, and VKA exposure, including outcomes, and their related costs from the societal perspective and from the French healthcare insurance perspective.

8. AMENDMENTS AND UPDATES TO THE STUDY PROTOCOL

None.

9. RESEARCH METHODS

9.1. Study design

The study was a historical cohort study performed in the French national healthcare claims and hospitalisation database (SNDS, *Système National des Données de Santé*) including new users of rivaroxaban, dabigatran, or VKA for SPAF in 2013 or 2014 and followed until 31/12/2015 (at least one year of follow-up except for death) (**Figure 1**).

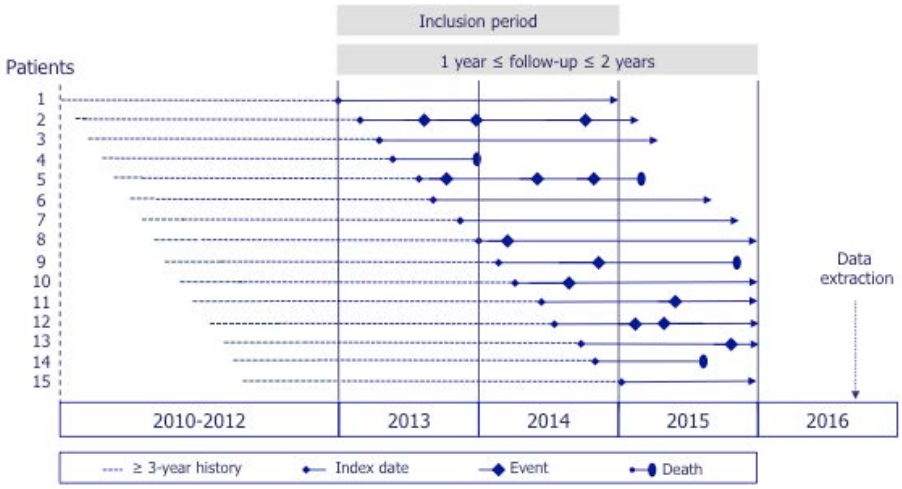


Figure 1. Study design

9.2. Setting

It was a database study in a real world setting of patients identified by a first dispensing of an anticoagulant (DOAC or VKA) for SPAF, and followed in the French national healthcare claims and hospitalisation database.

9.3. Subjects

9.3.1. Extracted population

All patients with a first reimbursed dispensing of rivaroxaban, dabigatran or VKA in 2013 or 2014[1] and without previous reimbursed dispensing of DOAC (dabigatran, rivaroxaban, or apixaban) or VKA during the previous three years were extracted from the database. Data were extracted from 01/01/2010 to 31/12/2015.

9.3.2. Study population

Two populations were studied according to the specificity of the NVAF information in the database:

- **Specific NVAF population** (for the main analysis) including definite NVAF patients (see section 9.4.2);
- **Sensitive NVAF population** (as secondary analysis) including definite NVAF and probable NVAF patients (see section 9.4.2).

[1] *Apixaban was marketed in the NVAF indication during the inclusion period (January 2014)*

Definite NVAF patients were defined with all the following inclusion criteria:

- A first reimbursed dispensing of rivaroxaban, dabigatran, or VKA in 2013 or 2014,
- No previous DOAC (rivaroxaban, dabigatran, apixaban) or VKA dispensing during the previous three years,
- Definite AF information in the database (see section 9.4.2),
- No other indication for the use of anticoagulant (treatment of venous thromboembolic events (VTE), prevention of VTE after orthopaedic surgery),
- No history of rheumatic valve disease or valve replacement (NVAF definition from the 2012 European Society of cardiology guidelines, Camm 2012).

Probable NVAF patients were defined with all the following inclusion criteria:

- A first reimbursed dispensation of rivaroxaban, dabigatran, or VKA in 2013 or 2014,
- No previous DOAC (rivaroxaban, dabigatran, apixaban) or VKA dispensation during the previous three years,
- Probable AF information in the database (using the development of an AF disease score, see section 9.4.2),
- No other indication for the use of anticoagulant (treatment of VTE, prevention of VTE after orthopaedic surgery),
- No history of rheumatic valve disease or valve replacement (NVAF definition from the 2012 European Society of cardiology guidelines, Camm 2012).

For comparison analysis (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg), patients were matched 1:1 on the date of the first drug (DOAC or VKA) dispensing (± 14 days), gender, age at index date (± 1 year), and logit of high dimensional Propensity Score (hdPS, ± caliper).

9.4. Variables

9.4.1. Index date

The index date was defined as the date of the first reimbursed dispensing of rivaroxaban, dabigatran, or VKA in 2013 or 2014.

9.4.2. Diseases

Diseases were defined using following variables:

- **Definite AF**, defined as a Long-Term Disease (LTD) registration for AF or a hospitalisation with an AF diagnosis (primary, linked or associated, I48 ICD-10 code) or a procedure for AF (cardioversion, catheter ablation) before index date (3-year history) or within six months after;
- **Probable AF**, defined as no definite AF, and having a high probability to have an AF, based on an AF disease score, using the following parameters:
  - Gender and age at index date,
  - Cardiologist or hospital physician (undetermined specialty) prescriber of the first DOAC or VKA dispensing,
  - Investigation within 2 months before index date (CCAM and NBAM codes listed in Appendix 1-3, SAP, Appendix 2): holter ECG monitoring, echocardiography, T3-T4 thyroid hormone test, D-dimer test, venous echo-doppler, pulmonary scintigraphy, chest CT angiography,
  - ≥ 1 drug dispensing within 2 months before index date for each of following drugs or drug classes: acetylsalicylic acid (ASA), ASA in association, clopidogrel, fondaparinux, heparin or low-molecular-weight heparin,
  - ≥ 1 drug dispensing within 2 months before or 2 months after index date for each of following drugs or drug classes: sotalol, other beta-blockers excluding associations, other

beta-blockers in association, verapamil or diltiazem, digoxin or digitoxin, amiodarone or drodenarone, other antiarrhythmic drug, other calcium channel blocker, agents acting on the renin-angiotensin, diuretic,

- Other parameters identified within 3 years before index date: congestive heart failure, hypertension, diabetes mellitus, stroke or transient ischemic attack (TIA) history, vascular disease history;

– **Disease definitions for exclusion criteria:**
  - **Rheumatic valve disease**, defined as a LTD registration for a rheumatic valve disease or a hospitalisation with rheumatic valve disease diagnosis (primary, linked or associated I01-I09 ICD-10 codes) before index date (3-year history);
  - **Valve replacement**, defined as a hospitalisation with diagnosis-related groups (DRG) of valve replacement or a medical procedure for valve replacement (LPP, CCAM and ICD-10 codes listed in Appendix 1-3, SAP, Appendix 1) before index date (3-year history);
  - **Other probable indications of anticoagulant dispensing:**
    - ✓ **Treatment of venous thromboembolic events (VTE)**, defined as the first DOAC or VKA dispensing within 2 months after hospital discharge for a pulmonary embolism (I26 ICD-10 code) or deep vein thrombosis (DVT) (I80, I81, I82 ICD-10 codes);
    - ✓ **Prevention of VTE after orthopaedic surgery**, defined as the first DOAC or VKA dispensing within 2 months after hospital discharge for an orthopaedic surgery (DRG codes listed in Appendix 1-3, SAP, Appendix 3) or as the first DOAC or VKA dispensing during or within 7 days after the patient stay in rehabilitation department which occurring within 2 days after hospital discharge for an orthopaedic surgery.

9.4.3. Exposure

Exposure definitions were defined using following variables:

– **VKA**, defined as the dispensing of B01AA ATC code;

– **DOAC**, defined as the dispensing of B01AF01 ATC code for rivaroxaban, and B01AE07 ATC code for dabigatran;

– **DOAC high dosage (standard dose** in the rest of this report**)**, defined as CIP codes for rivaroxaban 20 mg, and CIP codes for dabigatran 150 mg;

– **DOAC low dosage (reduced dose** in the rest of this report**)**, defined as CIP codes for rivaroxaban 15 mg, and CIP codes for dabigatran 110 mg;

– **DOAC very low dosage** (rivaroxaban 10 mg and dabigatran 75 mg in the rest of this report), defined as CIP codes for rivaroxaban 10 mg, and CIP codes for dabigatran 75 mg;

– **Treatment group**, defined by the first anticoagulant dispensing in 2013 or 2014 (rivaroxaban standard or reduced dose, dabigatran standard or reduced dose or VKA);

– **Duration of a drug dispensing**, defined as the number of packs of drug dispensed, the number of units per pack, and the defined daily dose (DDD, Appendix 1-3, SAP, Appendix 6) for the drug;

– **Discontinuation of initial treatment (DOAC or VKA)**, defined as a grace period of 60 days for the main analysis and 30 days for a sensitivity analysis: i.e. no dispensing of the drug after the duration of the last dispensing plus the grace period;

– **Switch of initial treatment (DOAC or VKA)**, defined as a dispensing of another anticoagulant, including heparin and low-molecular-weight heparin dispensing, for patients with a discontinuation of initial treatment;

– **Date of drug (DOAC or VKA) withdrawal**, defined as the date of the last dispensing of the drug plus the duration of this dispensing or the date of drug switch if it was occurred before for patients with a discontinuation of initial treatment;

– **Drug (DOAC or VKA) exposure**, defined as the period starting at the index date and ending at the end of follow-up for patients without drug withdrawal, else at the date of drug withdrawal;

– **Post-drug (DOAC or VKA) exposure**, defined as the period starting at date of the end of drug exposure and ending at the date of a new prescription of an anticoagulant or at the end of follow-up, whichever was the earliest;

- **Drug (DOAC or VKA) compliance**, defined as the drug Medication Possession Ratio (MPR) during drug exposure defined by the number of DDD dispensed, divided by the number of days of drug exposure.

9.4.4. Healthcare resources use

The healthcare resources use was described during the anticoagulant (rivaroxaban, dabigatran, VKA) exposure period from reimbursed claims and hospitalisation information.

For the specific AF healthcare resources use, different following areas of expenditure were defined:

- Specific hospitalisations, defined as hospitalisations with primary diagnosis of AF, CRB, SSE (or surgical procedure for systemic arterial embolism), and ACS,
- Stays in rehabilitation department (or SSR for *Soins de Suite et de Réadaptation*) linked to specific hospitalisations non AF defined as a stay in rehabilitation department with specific nosological group within the week after a specific hospitalisation non AF discharge (specific nosological groups listed in Appendix 1-3, SAP, Appendix 10),
- AF drugs, defined as reimbursements of DOAC, VKA, amiodarone, dronedarone, beta-blockers alone if no amiodarone/dronedarone reimbursements, and other antiarrhythmics (flecaine, cibenzoline, propafenone),
- Specific lab tests, defined as INR, hemostasis, coagulation, creatinine, urea, ALAT, ASAT tests,
- Specific medical consultations and visits, defined as medical consultations and visits linked to the prescription of AF drugs or specific lab tests.

For the total healthcare resources use, different following areas of expenditure were defined:

- Specific hospitalisations, defined as hospitalisations with primary diagnosis of AF, CRB, SSE (or surgical procedure for systemic arterial embolism), and ACS,
- Stays in rehabilitation department (or SSR for *Soins de Suite et de Réadaptation*) linked to specific hospitalisations non AF defined as a stay in rehabilitation department occurred in the week after a specific hospitalisation non AF discharge,
- Other cardiovascular hospitalisations, defined as non-specific hospitalisations and hospitalisations with cardiovascular primary diagnosis or DRG of cardiovascular disease (Appendix 1-3, SAP, Appendix 9),
- Other non-cardiovascular hospitalisations, defined as all other hospitalisations than those defined above,
- Medical consultations, visits and technical acts,
- Public hospital external consultations and acts,
- Cardiovascular and antidiabetic drugs,
- Non-cardiovascular and non-antidiabetic drugs,
- Lab tests,
- Products and services,
- Transports,
- Nursing acts,
- Physiotherapy acts,
- Sick leave and daily allowances,
- Assistance, pensions and disability allowances,
- Other medical healthcare resources.

9.4.5. Healthcare resource costs

Healthcare resource costs were described during the anticoagulant (rivaroxaban, dabigatran, VKA) exposure period.

For the cost of specific hospitalisations, stays in SSR after an outcome specific hospitalisation, specific medical consultations/visits, and specific lab tests, the cost of the related transport was included. For the cost of specific lab tests, the cost of related nursing acts and travel allowances were also taken into account.

The three following total costs were defined:

- **Total medical specific cost per patient**, including costs of specific hospitalisations, stays in SSR after an outcome specific hospitalisation, AF drugs, specific lab tests, and specific medical consultations and visits;
- **Total medical cost per patient**, including costs of all healthcare expenditures, except areas of expenditure "Sick leave and daily allowances" and "Assistance, pensions and disability allowances";
- **Total allowances cost per patient**, including costs of areas of expenditure "Sick leave and daily allowances" and "Assistance, pensions and disability allowances".

Costs were estimated in Euros (€) according to two perspectives:

- the collective perspective,
- the national health insurance perspective.

Outpatient healthcare resource costs:

- For the collective perspective, outpatient healthcare resource costs included amounts of healthcare resources paid by patients;
- For the national health insurance perspective, outpatient healthcare resource costs included amounts of healthcare resources reimbursed by the national health insurance.

Hospitalisation costs for *Médecine, Chirurgie et Obstétrique* (MCO) stays:

- For the collective perspective, hospitalisation costs (linked to a couple of DRG/SRG codes attributed to each stay) were estimated from mean costs (complete costs plus structural costs) calculated for every SRG from the data of the *Etude Nationale de Coûts* (ENC, source ATIH) relating annual hospital activity in public and private health establishments;
- For the national health insurance perspective, hospitalisation costs were valued in taking into account amounts of hospitalisation reimbursed by the national health insurance.

9.4.6. Outcomes

Outcomes were analysed during the anticoagulant (DOAC or VKA) exposure period (on treatment) using survival methods, with censure at the end of follow-up, or drug exposure or event (outcome), whichever was earliest. Outcomes studied were the followings:

- **Stroke and systemic embolism (SSE)**, defined as a hospitalisation with one of the two following primary diagnoses:
  - Ischemic or undefined stroke (I63, I64 ICD-10 codes) (Giroud 2015),
  - Other systemic arterial embolism (I74, N28, D73.5, K76.3 ICD-10 codes) or surgical procedure for systemic arterial embolism (CCAM codes listed in Appendix 1-3, SAP, Appendix 7);
- **Major bleeding**, defined as a hospitalisation with primary diagnosis (ICD-10 and CCAM codes listed in Appendix 1-3, SAP, Appendix 4) of:
  - Haemorrhagic stroke (primary, linked, or associated diagnosis); linked and associated diagnoses were secondary added at the request of the scientific committee considering that it should be an event for or during the hospitalisation, and not a history,
  - Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),

- Other bleeding (gastro-intestinal (GI), urogenital and other bleeding) with a transfusion during hospital stay, or resulting in death.

Clinical relevant bleeding (CRB), defined as a hospitalisation with primary diagnosis (ICD-10 codes listed in Appendix 1-3, SAP, Appendix 4) of:

- Haemorrhagic stroke (primary, linked, or associated diagnosis); linked and associated diagnoses were secondary added at the request of the scientific committee considering that it should be an event for or during the hospitalisation, and not a history,
- Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular),
- GI bleeding,
- Urogenital bleeding,
- Other bleeding;

- **Death,** defined as all-cause death (cause of death not available in the database);
- **Composite criterion**, defined as a composite of the first event among SSE, major bleeding, and death;
- **Acute Coronary Syndrome (ACS)**, defined as a hospitalisation with primary diagnosis of myocardial infarction (MI, I21 and I23 ICD-10 codes) or unstable angina (I20.0 ICD-10 code). MI was also analysed according to subtypes: ST elevation MI (STEMI, I21.0, I21.1, I21.2, I21.3, I21.9 and I23 ICD-10 codes), and non-ST elevation MI (NSTEMI, I21.4 ICD-10 code) (Bezin 2015).

9.4.7. Confounding

The choice of anticoagulant could be in relation with patient, history or AF characteristics. These characteristics have been compared at index date between treatment groups (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg), and taken into account in comparisons (using both adjustment and matching).

The potential confounders considered were:

- **Gender and age** at index date;
- **CHA_2DS_2-VASc score** (Lip 2010) at index date, modified to take into account the availability of information in the database, and defined as the sum of points from following stroke risk factors (defined in Appendix 1-3, SAP, sections 2.2.4.4 and 3.2): congestive heart failure (+1), hypertension (+1), diabetes mellitus (+1), stroke or transient ischemic attack (TIA) history (+2), vascular disease history (+1), age ≥ 75 years (+2), age 65-74 years (+1), female gender (+1), within 3-year database history;
- **$CHADS_2$ score** (for descriptive analysis, Waterman 2001) at index date, modified to take into account the availability of information in the database, and defined as the sum of points from following stroke risk factors: congestive heart failure (+1), hypertension (+1), age ≥ 75 years (+1), diabetes mellitus (+1), stroke or TIA history (+2), within 3-year database history;
- **HAS-BLED score** (Pister 2010, Lip 2011) at index date, modified to take into account the availability of information in the database, and defined as the sum of points from bleeding risk factors (defined in Appendix 1-3, SAP, sections 2.2.4.4 and 3.2): hypertension (+1), abnormal renal function (+1), abnormal liver function (+1), stroke history (+1), bleeding history (+1), age > 65 years (+1), drug predisposing to bleeding (+1), within 3-year database history;
- **hdPS**, defined as the probability to be treated by one of the anticoagulant studied (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) and estimated taking into account all information of the database, with multiple data dimensions from patients and healthcare reimbursements during the 3-year period before index date (see section 9.9.2).

9.5. Data sources and measurement

The SNDS (*Système National des Données de Santé*) database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The SNDS contains individual pseudonymised information on (Tuppin 2010, Moulis 2015, Bezin 2017):

- General characteristics: gender, year of birth, affiliation scheme, area of residence; deprivation status (CMU-c);
- Date of death for those concerned and very soon cause of death;
- LTD and associated ICD-10 codes with starting and ending date. LTD mainly concerned costly chronic diseases. LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical imageries, lab tests, drugs, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensation), and codes (but not the medical indication nor result);
- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnosis) for all private and public medical, obstetric and surgery hospitalisations, with the date and duration of hospitalisation, medical procedures, and cost coding system, as well as most of very costly drugs. The hospital discharge summary includes the medical unit summaries when the patient is hospitalised successively in several medical units. Data from PMSI psychiatry, and rehabilitation centres are available in the SNDS but not yet in the EGB (a permanent 1/97 representative sample of the SNDS). Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalised successively in several medical units, the primary diagnosis of the hospitalisation, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure. As primary diagnosis, it is taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

Non-hospital data are updated every month and hospital-discharge summaries yearly at end of Q3 for the previous year. Access to the SNDS is regulated and needs approval from the National Institute of Health Data (*Institut National des Données de Santé* - INDS) and the French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL). The BROTHER study received the IDS (the INDS today) approval on the 1st February 2016 and the CNIL authorization (Decision DE-2016-053) on the 8th April 2016. All data for the 2010-2015 period were received on the 4th November 2016.

9.6. Bias

Biases are discussed below in section 11.2.

9.7. Study size

The Bordeaux PharmacoEpi has performed a previous VKA study in the EGB database using similar definitions used in this protocol (Blin 2016). From 2007 to 2011, the numbers of patients who initiated a VKA for AF were 2 197 for the specific AF population and 3 345 for the sensitive AF population, which represent about 50 000 and 75 000 subjects respectively in the SNDS per year, and 100 000 and 150 000 for two years, respectively.

The number of new users of rivaroxaban, dabigatran and VKA for NVAF, as well as the number of patients matched for each comparison (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) are a result of the BROTHER study. More than 7 000 patients were expected in rivaroxaban (all doses) and VKA groups (size of the ROCKET-AF trial, Patel 2011).

9.8. Data transformation

Database extraction criteria were described in a data extraction plan approved prior to initiating extraction. The data extraction was provided by CNAMTS, in charge of SNDS organisation and management.

Data transformation, including decision rules, definition of diseases, of drug exposure and of outcomes studied, and calculated variables are detailed in the statistical analysis plan (SAP, Appendix 1-3, SAP, sections 3.2 and 3.3).

9.9. Statistical methods

As planned in the protocol, the main analysis was performed in the specific NVAF population and with a grace period of 60 days for drug (rivaroxaban, dabigatran, VKA) discontinuation.

In the protocol, healthcare resources use and costs should be described for all and matched patients according to the treatment group during the one-year of follow-up period, and compared only for matched patients. In the end, all these descriptive and comparison analyses were performed in the specific NVAF matched populations during the drug exposure (rivaroxaban, dabigatran or VKA) in the one-year of follow-up period, and with a grace period of 60 days for drug discontinuation.

9.9.1. Main summary measures

A flow chart depicting the number of new anticoagulant (rivaroxaban, dabigatran, VKA) users in 2013-2014, the number of patients according to the treatment group and the initial dose of treatment, and the number of matched patients for each comparison (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) was presented (Appendices 1-4 to 1-7, Figure 1).

Following analyses were performed for each comparison (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) according to the treatment group and the initial dose for all and matched patients:

- Description of new users of anticoagulant: demographic characteristics at index date, history of clinical characteristics,
- Description of the usage patterns of anticoagulant treatment during the 1-year follow-up and during drug exposure: dispensing frequency, DDD, MPR, discontinuation, switch,
- Description of healthcare resources use during the drug exposure on the 1-year follow-up: hospitalisations, drugs, medical visits, lab tests,

- Estimation and distribution of the probability to be treated by rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg, for NVAF using hdPS,
- Estimation of the 1-year incidence of outcomes (clinical events) during the drug exposure,
- Comparison of the 1-year risk of each outcome between treatment groups regarding the initial dose (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg).

Following analyses were also performed for each comparison (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) according to the treatment group and the initial dose for matched patients:

- Description of healthcare resources use during the drug exposure,
- Estimation of their related costs from collective and national health insurance perspectives.

9.9.2. Main statistical methods

Statistical analysis was conducted by the Bordeaux PharmacoEpi using SAS® software (SAS Institute, Version 9.4, North Carolina, USA).

Descriptive statistics used classic presentation, number and proportion of each modality for qualitative and ordinal variables, denominator, number of patients with missing data, arithmetic mean, standard deviation, median, first and third quartiles, and extreme values for quantitative variables.

Probable NVAF population

The probable NVAF population was estimated using a multiple logistic regression model to predict the specific NVAF population (patients with LTD or hospitalisation or a procedure for AF, without valvular disease history nor another probable indication), comparatively to no NVAF diagnosis, with independent variables defined above, a specificity of 70% and a sensitivity of 80% for the NVAF population. This model with this threshold was secondarily applied to patients without definite NVAF, to identify the probable NVAF population.

High-dimensional propensity score (hdPS)

The hdPS reflects the probability to be treated by one of the studied anticoagulant (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) (Rassen 2012, Schneeweiss 2009). A hdPS was estimated for each comparison (one for rivaroxaban 20 mg *versus* VKA, one for rivaroxaban 20 mg *versus* dabigatran 150 mg, one for rivaroxaban 15 mg *versus* VKA, and one for rivaroxaban 15 mg *versus* dabigatran 110 mg.), using a logistic regression model with large data set including:

- **Fixed variables**: age at index date, gender, specialty prescriber of the first DOAC/VKA dispensing, stroke risk factors, bleeding risk factors, hospitalisation other than cardioversion or catheter-based ablation in the month before index date, chronic obstructive pulmonary disease before index date, diabetes before and until one year after index date, coronary diseases before index date, and hospital and non-hospital costs during the year and the month before index date; hospital and non-hospital costs during the year and the month before index date were secondary added at the request of the scientific committee in order to well balance groups for cost comparison during the follow-up, as well as global proxies of health condition.
- And **500 covariables** (Garbe 2012) selected from **4 dimensions**:
  - LTD (ICD-10 code 3 digits) during the 3 years before index date,
  - Hospitalisations (ICD-10 code 3 digits) during the 3 years before index date,
  - Medical and paramedical visits and lab tests (NABM code) during the year before index date**,**
  - All drug dispensing (ATC code 7 digits) during the year before index date.

Patient characteristics

Patient characteristics at index date and during the 3 years history period were described according to the treatment groups (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg *versus* VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) for:

- all patients with crude and adjusted (regression model with hdPS) standardized differences between treatment groups (Appendix 1-3, SAP, section 4.5.2),
- 1:1 matched patients on the date of the first drug (DOAC or VKA) dispensing (± 14 days), gender, age at index date (± 1 year), and logit of the hdPS (± caliper which was equal to 0.2 of the standard deviation of the logit of the hdPS).

Outcomes analysis

Outcomes were analysed during the anticoagulant (DOAC or VKA) exposure period (on treatment) using survival methods, with censure at the end of follow-up, or drug exposure or event (outcome) whichever was earliest:

- Incidence rate in person-years (PY);
- Kaplan-Meier estimate for cumulative incidence of death, and of composite criterion;
- Cumulative incidence function (CIF) estimate for single outcomes (except death and composite criterion), in order to take into account of death as a competing risk;
- Cox proportional hazard risk model (for death and composite criterion, Cox 1972), and Fine and Gray model (for other single outcomes, Fine 1999) to compare the 1-year risk of each outcome between treatment groups (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg) with hazard ratio (HR) and 95%CI for:
  - a crude analysis,
  - an adjusted analysis on gender, age at index date, and hdPS (in deciles),
  - a matched analysis (1:1) on the date of the first drug (DOAC or VKA) dispensing, gender, age at index date, and logit of the hdPS with standardized differences between treatment groups.
- Stratified analyses of matched patients for the main criteria, requested by the scientific committee for: year of inclusion (2013, 2014), gender, age classes (< 65, 65-69, 70-74, 75-79, ≥ 80; and < 70, 70-74, 75-79, 80-84, ≥ 85), CHA_2DS_2-VASc score and its individual risk factors, HAS-BLED score, and quintiles of the hdPS.

Analyses of healthcare resources use and costs

Healthcare resources use and costs were analysed during the anticoagulant (DOAC or VKA) exposure period (on treatment) on the 1-year follow-up according to the different defined areas of expenditure for matched populations and each comparison (rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg).

9.9.3. Missing values

The number of missing data is indicated for each variable in Appendices 1-4 to 1-7, and 1-9 to 1-17. The SNDS database records all reimbursed claims and hospitalisations without missing values.

9.9.4. Sensitivity analyses

Two sensitivity analyses of outcomes were conducted using:

- The specific NVAF population with a grace period of 30 days for drug discontinuation;
- The sensitive NVAF population and a grace period of 60 days for drug discontinuation.

Another sensitivity analysis was performed considering undefined strokes as haemorrhagic strokes.

For analyses of healthcare resources use and costs, three other following definitions were used for estimating the cost of stays in SSR:

- Stays in SSR with a specific nosological group within two weeks after an outcome specific hospitalisation,
- All stays in SSR within the week after an outcome specific hospitalisation,
- All stays in SSR within two weeks after an outcome specific hospitalisation.

9.9.5. Amendments to the statistical analysis plan

Not applicable.

9.10. Quality control

The Bordeaux PharmacoEpi, INSERM CIC1401, has implemented a quality management system for all its activities. The CNAMTS data extraction was validated using the expected population size from EGB. An independent double programming was performed for main criteria analyses, and the results compared for validation. All statistical logs were kept and can be provided. In the case of interim analyses, the database for the interim analysis was frozen and kept for ulterior validation if needed. All results (Appendices 1-4 to 1-17) are included in this study report.

10. RESULTS

All results in this report are presented for the specific population (patients with AF diagnosis information in the database, i.e. LTD or hospital diagnosis or procedure for AF, without other indication for the use of anticoagulant and no history of rheumatic valve disease or valve replacement) with a grace period of 60 days (main analysis). Furthermore, results are discussed for sensitivity analyses: i) the specific population with a grace period of 30 days, ii) the sensitive population (specific population plus patients having a high probability to have a NVAF) with a grace period of 60 days.

Results for sensitivity analyses by classifying undefined strokes (primary diagnosis) as haemorrhagic strokes, and then all diagnosis (primary, linked or associated) for haemorrhagic strokes are presented for the main analysis in Appendices 1-4 to 1-7.

Results for stratified analyses for year of inclusion, gender, age classes, CHA_2DS_2-VASc score and its individual risk factors, HAS-BLED score, and quintiles of the hdPS are presented for the main analysis in the Appendix 1-8.

Results for sensitivity analyses, specific NVAF population with a grace period of 30 days for drug discontinuation and sensitive NVAF population with a grace period of 60 days for drug discontinuation, are presented in Appendices 1-9 to 1-16.

Results for healthcare resources use and costs during the drug exposure on the 1-year follow-up period are presented for the main analysis in the Appendix 1-17.

10.1. Populations

Over two years (2013-2014), 734 599 patients have been identified in the nationwide SNDS database with a first dispensing of DOAC (dabigatran or rivaroxaban) or VKA, without history of prior DOAC (dabigatran, rivaroxaban or apixaban) or VKA dispensing in the 3 years (**Figure 2**). Among them, 220 011 patients were included in the specific study population: 69 736 (31.7%) in the rivaroxaban group (19.3% with the 20 mg standard dose, 11.2% with the 15 mg reduced dose, and 1.2% with the 10 mg dose), 41 609 (18.9%) in the dabigatran group (7.7% with the 150 mg standard dose, 10.8% with the 110 mg reduced dose, and 0.5% with the 75 mg dose), and 108 666 (49.4%) in the VKA group (**Figure 2**; Appendices 1-4 to 1-7, Figure 1, Table 1*)*. The specific population represented 72.8% of the sensitive population with few variations between treatment groups: 69.0% for rivaroxaban, 73.6% for dabigatran, and 75.2% for VKA, respectively.

For the specific population, the number of new users was relatively stable for VKA between 2013 and 2014 (+ 4%), while there was a small increase for rivaroxaban 20 mg (+ 8%), and a small decrease for rivaroxaban 15 mg (- 8%), associated with a fall of more than 50% of new users for dabigatran 150 mg (- 56%) and dabigatran 110 mg (- 65%) (**Table 1**).

Table 1. VKA and DOAC dose new users according to index date

	VKA	Rivaroxaban			Dabigatran		
		20 mg	15 mg	10 mg	150 mg	110 mg	75 mg
2013	53252	20465	12800	1538	11685	17557	751
2014	55414	22066	11785	1082	5187	6152	277

	All populations N	
Selection criteria - First reimbursed dispensing of dabigatran, rivaroxaban or VKA - Between 1st January 2013 and 31 December 2014 - Without a 3-year history of DOAC or VKA dispensing	**734 599**	
Exclusion criteria	**514 588**	
- Missing or incorrect data (age, death date)	1 507	
- Less than 18 years at index date	1 840	
- At least two treatment groups at index date	252	
- Death at index date	85	
- Less than 3 years history in the SNDS before index date	28 060	
- Alive at index date and without complete follow-up (1-year after index date)	5 270	
- Other probable indications	167 474	
- SSR after orthopaedic surgery	1 167	
- Rheumatic valve disease history before index date	10 368	
- Valve replacement before index date	14 013	
- Uncertain identification (several twins or beneficiaries)	8 200	
- No atrial fibrillation (neither diagnostic nor probabilistic)	194 332	
- Patient without atrial fibrillation diagnosis but probabilistic information (for the sensitive population definition)	82 020	
	Specific population n	**Sensitive population n**
Study Population	**220 011**	**302 031**
- With NVAF diagnosis information without other probable indication criteria	X	
- With NVAF diagnosis or probabilistic information without other probable indication criteria		X
- rivaroxaban	69 736	101 009
• *rivaroxaban 20 mg*	*42 531*	*59 268*
• *rivaroxaban 15 mg*	*24 585*	*37 697*
• *rivaroxaban 10 mg*	*2 620*	*4 044*
- dabigatran	41 609	56 523
• *dabigatran 150 mg*	*16 872*	*21 670*
• *dabigatran 110 mg*	*23 709*	*33 329*
• *dabigatran 75 mg*	*1 028*	*1 524*
- VKA	108 666	144 499
All patients after hdPS trimming* for group comparisons		
- rivaroxaban 20 mg versus VKA	42 480 vs 108 656	59 219 vs 144 488
- rivaroxaban 20 mg versus dabigatran 150 mg	42 514 vs 16 834	59 259 vs 21 637
- rivaroxaban 15 mg versus VKA	24 529 vs 108 639	37 564 vs 144 425
- rivaroxaban 15 mg versus dabigatran 110 mg	24 548 vs 23 665	37 644 vs 33 250
1:1 matched populations		
- rivaroxaban 20 mg versus VKA	31 171 vs 31 171	43 162 vs 43 162
- rivaroxaban 20 mg versus dabigatran 150 mg	15 323 vs 15 323	20 257 vs 20 257
- rivaroxaban 15 mg versus VKA	23 314 vs 23 314	35 585 vs 35 585
- rivaroxaban 15 mg versus dabigatran 110 mg	15 131 vs 15 131	23 491 vs 23 491

* Exclusion of outliers (patients with extreme values of hdPS)

Figure 2. Identification and selection of patients for the specific and sensitive populations

The number of matched patients 1:1 on the date of the first drug (DOAC or VKA) dispensing (± 14 days), gender, age at index date (± 1 year), and logit of hdPS (± caliper) was:

- 31 171 patients per group for the comparison rivaroxaban 20 mg versus VKA (73.3% and 28.7% of rivaroxaban 20 mg and VKA patients, respectively) in the specific population, and 43 162 patients per group in the sensitive population (72.8% and 29.9% of rivaroxaban 20 mg and VKA patients, respectively);
- 15 323 patients per group for the comparison rivaroxaban 20 mg versus dabigatran 150 mg (36.0% and 90.8% of rivaroxaban 20 mg and dabigatran 150 mg patients, respectively) in the specific population, and 20 257 patients per group in the sensitive population (34.2% and 93.5% of rivaroxaban 20 mg and dabigatran 150 mg patients, respectively);
- 23 314 patients per group for the comparison rivaroxaban 15 mg versus VKA (94.8% and 21.5% of rivaroxaban 15 mg and VKA patients, respectively) in the specific population, and 35 585 patients per group in the sensitive population (94.4% and 24.6% of rivaroxaban 15 mg and VKA patients, respectively);
- 15 131 patients per group for the comparison rivaroxaban 15 mg versus dabigatran 110 mg (61.5% and 63.8% of rivaroxaban 15 mg and dabigatran 110 mg patients, respectively) in the specific population, and 23 491 patients per group in the sensitive population (62.3% and 70.5% of rivaroxaban 15 mg and dabigatran 110 mg patients, respectively).

For each comparison, the hdPS was trimmed when no patient of the comparative group have corresponding extreme hdPS values on the left or right side of the hdPS distribution, and then few patients were excluded for analyses, with:

- a minimum of 10 patients for the VKA group (0.01%) and rivaroxaban standard dose comparison, and a maximum of 56 patients for the rivaroxaban 15 mg group (0.23%) and VKA comparison in the specific population;
- a minimum of 9 patients for the rivaroxaban standard dose group (0.02%) and dabigatran standard dose comparison, and a maximum of 133 patients for the rivaroxaban 15 mg group (0.35%) and VKA comparison in the sensitive population (**Figure 2**).

10.2. Descriptive data

10.2.1. First DOAC and VKA prescription

First DOAC dose

In the specific population, the rivaroxaban standard dose (20 mg) was the most used, 61% for all patients with rivaroxaban, whereas for dabigatran, the most used was the reduced dose (110 mg), 57% for all patients with dabigatran (**Table 2**; Appendices 1-4 to 1-7, Figure 1). In addition, a few patients received rivaroxaban 10 mg or dabigatran 75 mg, which do not have the indication for NVAF. The description for patients with rivaroxaban 10 mg or dabigatran 75 mg is presented in the Appendix 1-7, section 2.2.

Table 2. All patients distribution according to initial dose of rivaroxaban and dabigatran

	Rivaroxaban exposure (%)		Dabigatran exposure (%)	
	Dose (mg)	**All patients n = 69 736**	**Dose (mg)**	**All patients n = 41 609**
Standard dose	20	61.0	150	40.5
Reduced dose	15	35.3	110	57.0
Rivaroxaban 10 mg or dabigatran 75 mg	10	3.8	75	2.5

Prescriber speciality

Table 3. Prescriber speciality of the first DOAC or VKA dispensing for the specific population

	All patients				Matched patients			
	Rivaroxaban 20 mg n = 42480		VKA n = 108656		Rivaroxaban 20 mg n = 31171		VKA n = 31171	
Cardiologist	16710	(39.3)	18574	(17.1)	9878	(31.7)	9153	(29.4)
Hospital physician (undetermined specialty)	12872	(30.3)	43590	(40.1)	10219	(32.8)	10445	(33.5)
General practitioner	8283	(19.5)	28603	(26.3)	7324	(23.5)	7794	(25.0)
Other medical specialty	4615	(10.9)	17889	(16.5)	3750	(12.0)	3779	(12.1)
	Rivaroxaban 20 mg n = 42514		Dabigatran 150 mg n = 16834		Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323	
Cardiologist	16754	(39.4)	6467	(38.4)	6277	(41.0)	6066	(39.6)
Hospital physician (undetermined specialty)	12863	(30.3)	5645	(33.5)	4759	(31.1)	4927	(32.2)
General practitioner	8282	(19.5)	2837	(16.9)	2687	(17.5)	2659	(17.4)
Other medical specialty	4615	(10.9)	1885	(11.2)	1600	(10.4)	1671	(10.9)
	Rivaroxaban 15 mg n = 24529		VKA n = 108639		Rivaroxaban 15 mg n = 23314		VKA n = 23314	
Cardiologist	9621	(39.2)	18557	(17.1)	8568	(36.8)	8458	(36.3)
Hospital physician (undetermined specialty)	6255	(25.5)	43590	(40.1)	6192	(26.6)	6143	(26.3)
General practitioner	5964	(24.3)	28603	(26.3)	5893	(25.3)	6047	(25.9)
Other medical specialty	2689	(11.0)	17889	(16.5)	2661	(11.4)	2666	(11.4)
	Rivaroxaban 15 mg n = 24548		Dabigatran 110 mg n = 23665		Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131	
Cardiologist	9657	(39.3)	7631	(32.2)	5579	(36.9)	5463	(36.1)
Hospital physician (undetermined specialty)	6245	(25.4)	7477	(31.6)	4059	(26.8)	4131	(27.3)
General practitioner	5959	(24.3)	5354	(22.6)	3713	(24.5)	3693	(24.4)
Other medical specialty	2687	(10.9)	3203	(13.5)	1780	(11.8)	1844	(12.2)

The main prescribers of rivaroxaban 20 mg at index date for the specific population were cardiologists (39%), followed by hospital physicians (30%), and general practitioners (20%). Similar results were found for rivaroxaban 15 mg: cardiologists (39%), hospital physicians (25%), and general practitioners (24%) (**Table 3**; Appendices 1-4 to 1-7, Table 25).

For dabigatran 150 mg, the main prescribers were cardiologists (38%), followed by hospital physicians (34%), and general practitioners (17%), while the main prescribers of dabigatran 110 mg were cardiologists and hospital physicians (32%), followed by general practitioners (23%) (**Table 3**; Appendices 1-6 and 1-7, Table 25).

While VKA were more prescribed at index date by hospital physicians (40%), followed by general practitioners (26%). Cardiologists represented only 17% of the prescribers, more than two times less than in rivaroxaban groups (**Table 3**; Appendices 1-4 and 1-5, Table 25).

10.2.2. High-dimensional propensity score (hdPS)

A hdPS was defined for each comparison, rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg, including age at index date, gender, specialty of DOAC/VKA prescriber, stroke risk factors, bleeding risk factors, hospitalisation other than cardioversion or catheter-based ablation in the month before index date, chronic obstructive pulmonary disease, diabetes, coronary diseases, and hospital and non-hospital costs on year and one month before index date, as well as 500 selected from 4 dimensions: i) LTD, ii) 3-year hospitalisation diagnosis history, iii) 1-year medical and paramedical visits and lab tests history and iv) 1-year drugs (ATC code 7 digits) dispensing history.

Figure 3 shows that the hdPS distribution (after trimming) was not the same for each DOAC and VKA, but sharing an overlap (Appendices 1-4 to 1-7, Figures 3a and 3b for the specific population, and Appendices 1-9 to 1-12, Figures 3a and 3b for the sensitive population). This overlap allows a 1:1 matching for most of the DOAC patients (the smaller groups) to VKA patients with a very good hdPS overlap for matched cohorts (**Figure 4**, Appendices 1-4 to 1-7, Figures 4a and 4b for the specific population, and Appendices 1-9 to 1-12, Figures 4a and 4b for the sensitive population).

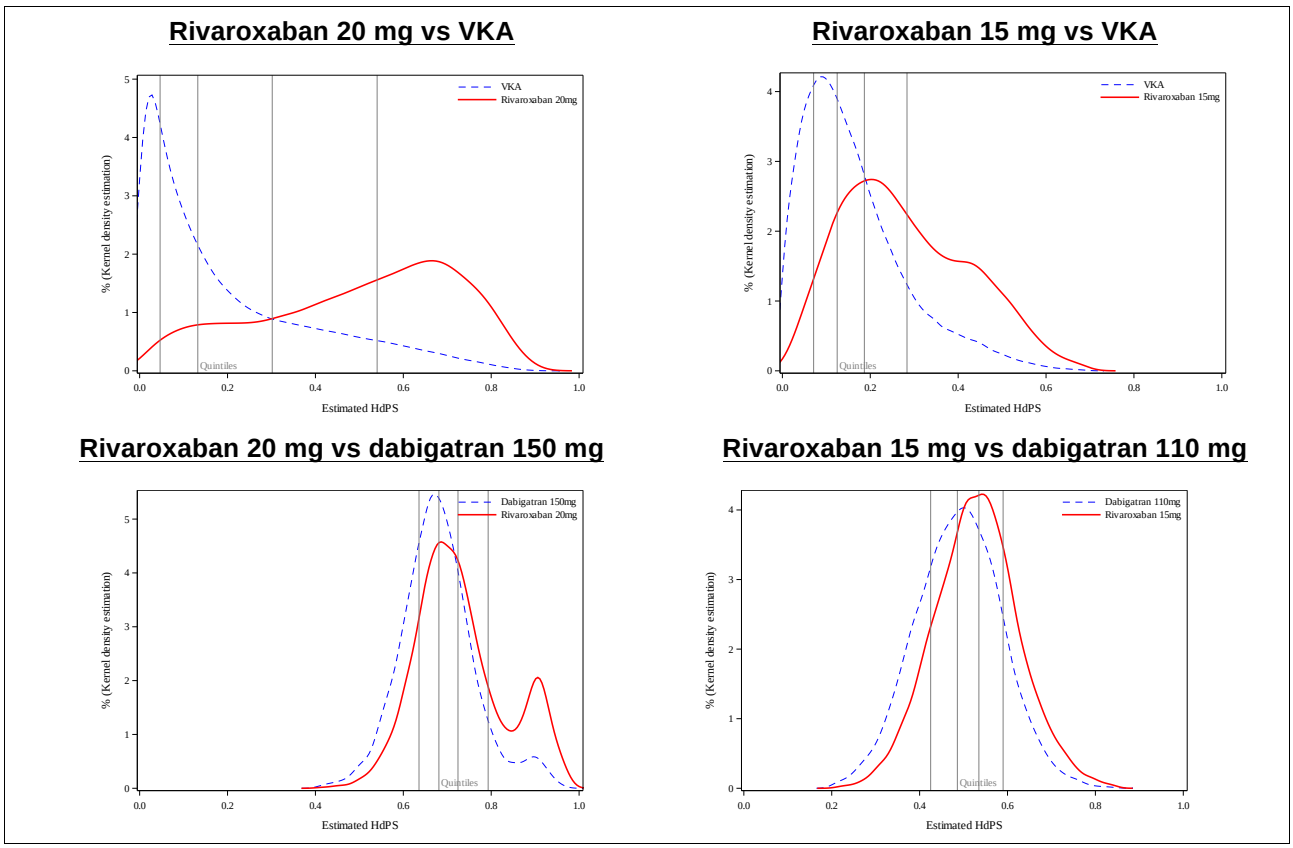


Figure 3. HdPS distribution for all patients of the specific population according to treatment groups after trimming

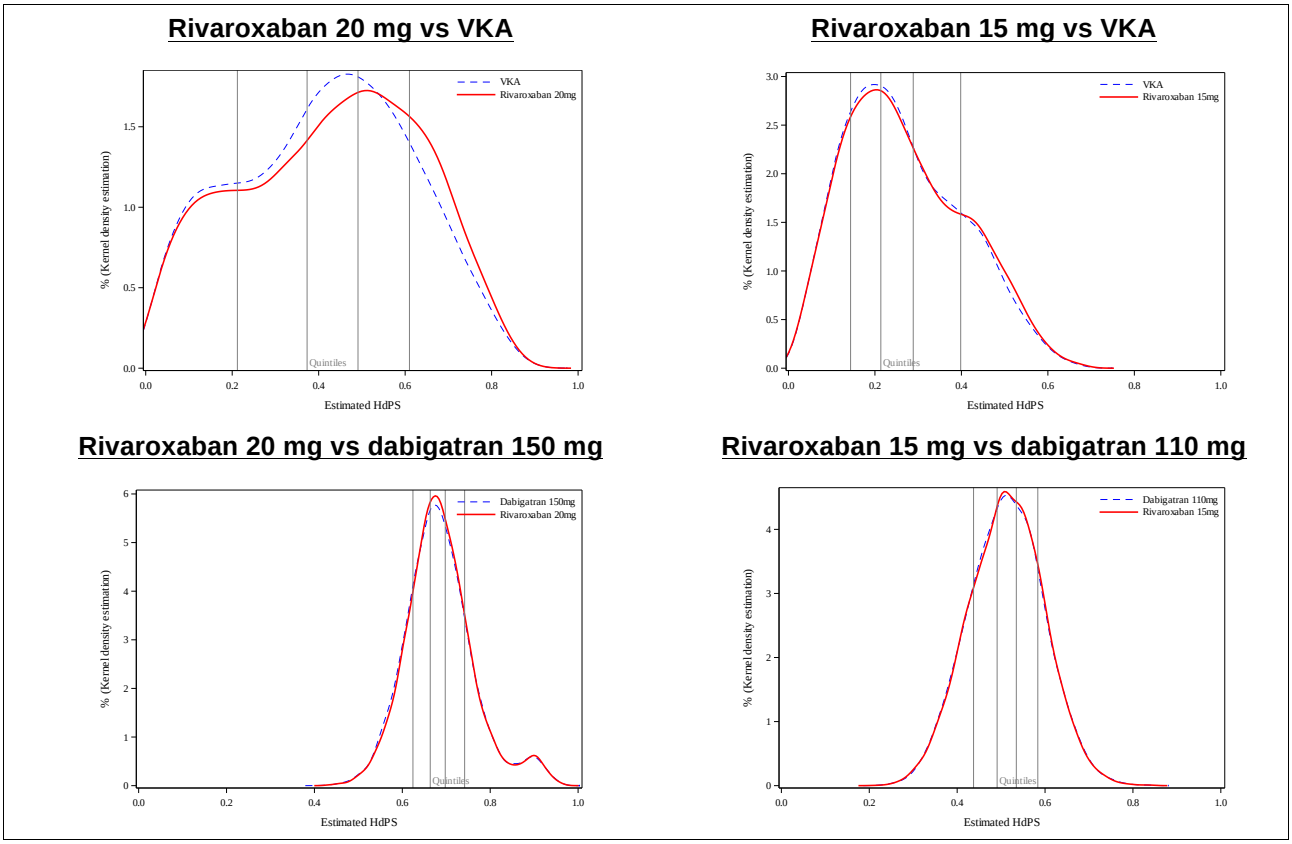


Figure 4. HdPS distribution for matched patients of the specific population according to treatment groups

10.2.3. Baseline demographic characteristics

Patients of the rivaroxaban 20 mg group for the specific population had a mean age of 68.6 (± 11.1) years, with 16% aged 80 years or more, and 64% of men, those of dabigatran 150 mg were younger (65.2 ± 10.1 years), with few aged 80 years or more (< 5%), and about 70% of men, while VKA patients were older (78.4 ± 11.0 years) with more than half of patients aged 80 years or more, and about 52% of men (**Tables 4 and 5**; Appendices 1-4 and 1-5, Table 5). Similar results were found for the sensitive population (Appendices 1-9 and 1-10, Table 4).

For rivaroxaban 20 mg versus VKA, and rivaroxaban 20 mg versus dabigatran 150 mg comparisons in the specific population, crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching, with a mean age of 71.2 (± 10.0) years and 62% of men in both matched groups for the comparison with VKA, and 66.0 (± 9.3) years and 70% of men in both groups for the comparison with dabigatran. Similar results were found for the sensitive population.

Table 4. Demographic characteristics of patients at the index date for rivaroxaban 20 mg and VKA groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 20 mg vs VKA		
	Rivaroxaban 20 mg n = 42480	VKA n = 108656	Rivaroxaban 20 mg n = 31171	VKA n = 31171	Crude	Adjusted	Matched
Gender, n (%)					-25.6	0.5	0.0
Male	27352 (64.4)	56349 (51.9)	19329 (62.0)	19329 (62.0)			
Female	15128 (35.6)	52307 (48.1)	11842 (38.0)	11842 (38.0)			
Age at index date (in years)					-88.2	-4.6	-0.2
Size (missing data)	42480 (0)	108656 (0)	31171 (0)	31171 (0)			
Mean (± SD)	68.6 (11.1)	78.4 (11.0)	71.2 (10.0)	71.2 (10.0)			
Median	69.0	81.0	72.0	72.0			
[p25% - p75%]	[62.0;77.0]	[72.0;86.0]	[65.0;78.0]	[65.0;78.0]			
[Min - Max]	[18.0;104.0]	[18.0;108.0]	[22.0;101.0]	[22.0;101.0]			
Age at index date (in categories), n (%)							
< 65 years	13331 (31.4)	12892 (11.9)	7305 (23.4)	7278 (23.3)			
[65-80[	22544 (53.1)	36631 (33.7)	17326 (55.6)	17550 (56.3)			
≥ 80	6605 (15.5)	59133 (54.4)	6540 (21.0)	6343 (20.3)			

Table 5. Demographic characteristics of patients at the index date for rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 20 mg vs dabigatran 150 mg		
	Rivaroxaban 20 mg n = 42514	Dabigatran 150 mg n = 16834	Rivaroxaban 20 mg n = 15323	Dabigatran 150 mg n = 15323	Crude	Adjusted	Matched
Gender, n (%)					10.6	-0.1	0.0
Male	27385 (64.4)	11680 (69.4)	10724 (70.0)	10724 (70.0)			
Female	15129 (35.6)	5154 (30.6)	4599 (30.0)	4599 (30.0)			
Age at index date (in years)					31.8	2.6	0.2
Size (missing data)	42514 (0)	16834 (0)	15323 (0)	15323 (0)			
Mean (± SD)	68.6 (11.1)	65.2 (10.1)	66.0 (9.3)	66.0 (9.3)			
Median	69.0	66.0	67.0	67.0			
[p25% - p75%]	[62.0;77.0]	[60.0;72.0]	[61.0;73.0]	[61.0;73.0]			
[Min - Max]	[18.0;104.0]	[19.0;95.0]	[21.0;93.0]	[22.0;94.0]			
Age at index date (in categories), n (%)							
< 65 years	13361 (31.4)	7039 (41.8)	5970 (39.0)	6005 (39.2)			
[65-80[	22548 (53.0)	9098 (54.0)	8700 (56.8)	8656 (56.5)			
≥ 80	6605 (15.5)	697 (4.1)	653 (4.3)	662 (4.3)			

Patients of rivaroxaban 15 mg and dabigatran 110 mg groups for the specific population, clearly different from rivaroxaban 20 mg and dabigatran 150 mg groups, were more alike to those in the VKA group (79.8 ± 9.4 years and 78.6 ± 9.4 years, 60% and 55% aged 80 years or more, 47% and 49% of men, respectively) (**Tables 6 and 7**; Appendices 1-6 and 1-7, Table 5). Similar results were found for the sensitive population (Appendices 1-11 and 1-12, Table 4).

For rivaroxaban 15 mg versus VKA, and rivaroxaban 15 mg versus dabigatran 110 mg comparisons in the specific population, crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching, with a mean age of 80.1 ± 8.7 years and 47% of men in both matched groups for the comparison with VKA, and 80.2 ± 7.8 years and 48% of men in both groups for the comparison with dabigatran. Similar results were found for the sensitive population.

Table 6. Demographic characteristics of patients at the index date for rivaroxaban 15 mg and VKA groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 15 mg vs.VKA		
	Rivaroxaban 15 mg n = 24529	VKA n = 108639	Rivaroxaban 15 mg n = 23314	VKA n = 23314	Crude	Adjusted	Matched
Gender, n (%)					9.4	-0.7	0.0
Male	11574 (47.2)	56350 (51.9)	11070 (47.5)	11070 (47.5)			
Female	12955 (52.8)	52289 (48.1)	12244 (52.5)	12244 (52.5)			
Age at index date (in years)					14.2	-0.5	0.0
Size (missing data)	24529 (0)	108639 (0)	23314 (0)	23314 (0)			
Mean (± SD)	79.8 (9.4)	78.4 (11.0)	80.1 (8.7)	80.1 (8.7)			
Median	81.0	81.0	81.0	81.0			
[p25% - p75%]	[76.0;86.0]	[72.0;86.0]	[76.0;86.0]	[76.0;86.0]			
[Min - Max]	[19.0;105.0]	[18.0;108.0]	[24.0;103.0]	[23.0;103.0]			
Age at index date (in categories), n (%)							
< 65 years	1648 (6.7)	12899 (11.9)	1369 (5.9)	1380 (5.9)			
[65-80[	8145 (33.2)	36624 (33.7)	7851 (33.7)	7768 (33.3)			
≥ 80	14736 (60.1)	59116 (54.4)	14094 (60.5)	14166 (60.8)			

Table 7. Demographic characteristics of patients at the index date for rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 15 mg vs dabigatran 110 mg		
	Rivaroxaban 15 mg n = 24548	Dabigatran 110 mg n = 23665	Rivaroxaban 15 mg n = 15131	Dabigatran 110 mg n = 15131	Crude	Adjusted	Matched
Gender, n (%)					4.6	0.1	0.0
Male	11565 (47.1)	11695 (49.4)	7229 (47.8)	7229 (47.8)			
Female	12983 (52.9)	11970 (50.6)	7902 (52.2)	7902 (52.2)			
Age at index date (in years)					13.6	3.2	0.1
Size (missing data)	24548 (0)	23665 (0)	15131 (0)	15131 (0)			
Mean (± SD)	79.8 (9.3)	78.6 (9.4)	80.2 (7.8)	80.2 (7.8)			
Median	81.0	80.0	81.0	81.0			
[p25% - p75%]	[76.0;86.0]	[74.0;85.0]	[76.0;86.0]	[76.0;86.0]			
[Min - Max]	[19.0;105.0]	[20.0;105.0]	[28.0;101.0]	[28.0;100.0]			
Age at index date (in categories), n (%)							
< 65 years	1646 (6.7)	2006 (8.5)	686 (4.5)	692 (4.6)			
[65-80[	8150 (33.2)	8711 (36.8)	5274 (34.9)	5169 (34.2)			
≥ 80	14752 (60.1)	12948 (54.7)	9171 (60.6)	9270 (61.3)			

10.2.4. History of clinical characteristics

History of long-term diseases and hospitalisations

During the 3 years before index date, 63% of patients in the rivaroxaban 20 mg group and 78% of patients in the VKA group for the specific population had at least one LTD. The five most frequent (≥ 10% of patients) were: LTD 5 (severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy), LTD 8 (type 1 diabetes, type 2 diabetes), LTD 30 (malignant tumours, malignant lymphatic or hematopoietic tissue), LTD 13 (coronary heart disease) and LTD 12 (severe arterial hypertension) (**Table 8**; Appendix 1-4, Table 6). More than 3/4 of patients in the rivaroxaban 20 mg group (75%) and in the VKA group (89%) had at least one hospitalisation within the 3-year history, and the most frequent primary diagnosis was diseases of the circulatory system (47% and 63%, respectively). Within the month before index date, 45% of patients in the rivaroxaban 20 mg group and 58% in the VKA group had at least one hospitalisation (**Table 8**; Appendix 1-4, Tables 7 and 9). Crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching.

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, results for LTD and hospitalisations were very similar: 60% of LTD in the dabigatran 150 mg group, 75% of hospitalisations within the 3-year history, and 49% within the month before index date (**Table 9**; Appendix 1-5, Tables 7 and 9).

Table 8. History of long-term diseases and hospitalisations before index date for rivaroxaban 20 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs VKA		
	Rivaroxaban 20 mg n = 42480		VKA n = 108656		Rivaroxaban 20 mg n = 31171		VKA n = 31171		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**26744**	**(63.0)**	**85218**	**(78.4)**	**21126**	**(67.8)**	**22453**	**(72.0)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	12531	(29.5)	33285	(30.6)	9670	(31.0)	10037	(32.2)	-2.5	3.7	-2.5
LTD 8: Type 1 diabetes , type 2 diabetes	5675	(13.4)	19612	(18.0)	4588	(14.7)	4783	(15.3)	-12.9	3.1	-1.8
LTD 30: Malignant tumours, malignant lymphatic or hematopoietic tissue	4846	(11.4)	16616	(15.3)	3969	(12.7)	4305	(13.8)	-11.4	3.1	-3.2
LTD 13: Coronary heart disease	3936	(9.3)	17559	(16.2)	3429	(11.0)	3691	(11.8)	-20.8	4.1	-2.6
LTD 12: Severe arterial hypertension	3759	(8.8)	15217	(14.0)	3142	(10.1)	3193	(10.2)	-16.3	2.3	-0.5
At least one hospitalisation within 3 years before, n (%)	**31888**	**(75.1)**	**96759**	**(89.1)**	**24227**	**(77.7)**	**24337**	**(78.1)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	20106	(47.3)	67942	(62.5)	15482	(49.7)	15195	(48.7)	-30.9	1.4	1.8
Factors influencing health status and contact with health services	5559	(13.1)	22366	(20.6)	4390	(14.1)	4833	(15.5)	-20.1	3.1	-4.0
Diseases of the digestive system	5682	(13.4)	15743	(14.5)	4160	(13.3)	4142	(13.3)	-3.2	0.6	0.2
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	4501	(10.6)	19720	(18.1)	3643	(11.7)	3612	(11.6)	-21.7	2.7	0.3
Neoplasms	4100	(9.7)	11956	(11.0)	3181	(10.2)	3333	(10.7)	-4.4	2.4	-1.6
Diseases of the eye and adnexa	3614	(8.5)	13135	(12.1)	3066	(9.8)	3054	(9.8)	-11.8	3.1	0.1
Injury, poisoning and certain other consequences of external causes	2216	(5.2)	11262	(10.4)	1813	(5.8)	1837	(5.9)	-19.3	0.1	-0.3
Diseases of the respiratory system	2334	(5.5)	14590	(13.4)	2053	(6.6)	2200	(7.1)	-27.4	2.1	-1.9
At least one hospitalisation within 3 months before, n (%)	**21722**	**(51.1)**	**79027**	**(72.7)**	**16826**	**(54.0)**	**17592**	**(56.4)**			
At least one hospitalisation within 1 month before, n (%)	**19131**	**(45.0)**	**62794**	**(57.8)**	**14661**	**(47.0)**	**14814**	**(47.5)**			

Table 9. History of long-term diseases and hospitalisations before index date for rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs dabigatran 150 mg		
	Rivaroxaban 20 mg n = 42514		Dabigatran 150 mg n = 16834		Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**26749**	**(62.9)**	**10121**	**(60.1)**	**9241**	**(60.3)**	**9193**	**(60.0)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	12533	(29.5)	4999	(29.7)	4527	(29.5)	4533	(29.6)	-0.5	1.0	-0.1
LTD 8: Type 1 diabetes , type 2 diabetes	5673	(13.3)	2226	(13.2)	2079	(13.6)	2039	(13.3)	0.4	0.6	0.8
LTD 30: Malignant tumours, malignant lymphatic or hematopoietic tissue	4844	(11.4)	1576	(9.4)	1461	(9.5)	1443	(9.4)	6.7	-0.9	0.4
At least one hospitalisation within 3 years before, n (%)	**31915**	**(75.1)**	**12534**	**(74.5)**	**11238**	**(73.3)**	**11222**	**(73.2)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	20125	(47.3)	8535	(50.7)	7276	(47.5)	7482	(48.8)	-6.7	2.1	-2.7
Factors influencing health status and contact with health services	5563	(13.1)	1985	(11.8)	1731	(11.3)	1744	(11.4)	3.9	-1.2	-0.3
Diseases of the digestive system	5690	(13.4)	1931	(11.5)	1946	(12.7)	1783	(11.6)	5.8	2.1	3.3
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	4504	(10.6)	1446	(8.6)	1385	(9.0)	1292	(8.4)	6.8	1.1	2.1
At least one hospitalisation within 3 months before, n (%)	**21741**	**(51.1)**	**9069**	**(53.9)**	**7830**	**(51.1)**	**7965**	**(52.0)**			
At least one hospitalisation within 1 month before, n (%)	**19148**	**(45.0)**	**8303**	**(49.3)**	**7071**	**(46.1)**	**7275**	**(47.5)**			

For the reduced dose comparison, history of long-term diseases and hospitalisations during the 3 years before index date were also less frequent for the rivaroxaban 15 mg group than the VKA group (72% vs 78%, and 80% vs 89%, respectively). The difference was more important for the occurrence of hospitalisations within 3-month and 1-month before index date (53% vs 73%, and 44% vs 58%, respectively) (**Table 10**; Appendix 1-6, Tables 7 and 9). The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching.

For the rivaroxaban 15 mg and dabigatran 110 mg comparison, results for LTD and hospitalisations during the 3 years before index date were similar, while the occurrence of hospitalisations within 3-month and 1-month before index date were slightly less frequent for the rivaroxaban 15 mg group than the dabigatran 110 mg group (53% vs 59%, and 44% vs 50%, respectively) (**Table 11**; Appendix 1-7, Tables 7 and 9) with really weak standardized differences after adjustment and matching.

Table 10. History of long-term diseases and hospitalisations before index date for rivaroxaban 15 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs VKA		
	Rivaroxaban 15 mg n = 24529		VKA n = 108639		Rivaroxaban 15 mg n = 23314		VKA n = 23314		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**17575**	**(71.6)**	**85203**	**(78.4)**	**16862**	**(72.3)**	**17351**	**(74.4)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	7494	(30.6)	33277	(30.6)	7157	(30.7)	7354	(31.5)	-0.2	-1.5	-1.8
LTD 8: Type 1 diabetes , type 2 diabetes	3403	(13.9)	19611	(18.1)	3283	(14.1)	3312	(14.2)	-11.4	-0.3	-0.4
LTD 30: Malignant tumours, malignant lymphatic or hematopoietic tissue	3693	(15.1)	16609	(15.3)	3550	(15.2)	3581	(15.4)	-0.6	-0.3	-0.4
LTD 13: Coronary heart disease	3381	(13.8)	17556	(16.2)	3276	(14.1)	3294	(14.1)	-6.7	1.6	-0.2
LTD 12: Severe arterial hypertension	3151	(12.8)	15214	(14.0)	3048	(13.1)	3068	(13.2)	-3.4	0.5	-0.3
At least one hospitalisation within 3 years before, n (%)	**19708**	**(80.3)**	**96743**	**(89.0)**	**18807**	**(80.7)**	**18794**	**(80.6)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	12065	(49.2)	67931	(62.5)	11586	(49.7)	11424	(49.0)	-27.1	2.4	1.4
Factors influencing health status and contact with health services	3625	(14.8)	22362	(20.6)	3457	(14.8)	3589	(15.4)	-15.3	0.0	-1.6
Diseases of the digestive system	3351	(13.7)	15737	(14.5)	3179	(13.6)	3114	(13.4)	-2.4	0.7	0.8
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	3738	(15.2)	19716	(18.1)	3553	(15.2)	3396	(14.6)	-7.8	3.8	1.9
Neoplasms	2496	(10.2)	11952	(11.0)	2366	(10.1)	2391	(10.3)	-2.7	1	-0.4
Diseases of the eye and adnexa	3482	(14.2)	13124	(12.1)	3302	(14.2)	3274	(14.0)	6.3	-0.3	0.3
At least one hospitalisation within 3 months before, n (%)	**13085**	**(53.3)**	**79023**	**(72.7)**	**12586**	**(54.0)**	**13216**	**(56.7)**			
At least one hospitalisation within 1 month before, n (%)	**10756**	**(43.9)**	**62791**	**(57.8)**	**10353**	**(44.4)**	**10361**	**(44.4)**			

Table 11. History of long-term diseases and hospitalisations before index date for rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs dabigatran 110 mg		
	Rivaroxaban 15 mg n = 24548		Dabigatran 110 mg n = 23665		Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**17578**	**(71.6)**	**16645**	**(70.3)**	**10783**	**(71.3)**	**10587**	**(70.0)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	7496	(30.5)	7133	(30.1)	4684	(31.0)	4600	(30.4)	0.9	0.0	1.2
LTD 8: Type 1 diabetes , type 2 diabetes	3401	(13.9)	3255	(13.8)	2062	(13.6)	1999	(13.2)	0.3	1.3	1.2
LTD 30: Malignant tumours, malignant lymphatic or hematopoietic tissue	3696	(15.1)	3401	(14.4)	2223	(14.7)	2230	(14.7)	1.9	-0.6	-0.1
LTD 13: Coronary heart disease	3379	(13.8)	2943	(12.4)	1980	(13.1)	1920	(12.7)	3.9	0.5	1.2
LTD 12: Severe arterial hypertension	3145	(12.8)	2937	(12.4)	1973	(13.0)	1866	(12.3)	1.2	0.1	2.1
At least one hospitalisation within 3 years before, n (%)	**19725**	**(80.4)**	**19564**	**(82.7)**	**12160**	**(80.4)**	**12228**	**(80.8)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	12059	(49.1)	12807	(54.1)	7503	(49.6)	7640	(50.5)	-10.0	-3.1	-1.8
Factors influencing health status and contact with health services	3629	(14.8)	3178	(13.4)	2053	(13.6)	2007	(13.3)	3.9	0.3	0.9
Diseases of the digestive system	3358	(13.7)	3122	(13.2)	2028	(13.4)	1972	(13.0)	1.4	-0.1	1.1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	3735	(15.2)	3452	(14.6)	2181	(14.4)	2177	(14.4)	1.8	-0.3	0.1
Neoplasms	2499	(10.2)	2339	(9.9)	1499	(9.9)	1459	(9.6)	1	-0.4	0.9
Diseases of the eye and adnexa	3494	(14.2)	3184	(13.5)	2206	(14.6)	2152	(14.2)	2.3	0.6	1.0
At least one hospitalisation within 3 months before, n (%)	**13086**	**(53.3)**	**14041**	**(59.3)**	**8233**	**(54.4)**	**8347**	**(55.2)**			
At least one hospitalisation within 1 month before, n (%)	**10752**	**(43.8)**	**11891**	**(50.2)**	**6874**	**(45.4)**	**6943**	**(45.9)**			

Stroke and bleeding risk factors

All stroke and bleeding risk factors were less frequent in the rivaroxaban 20 mg group than in the VKA group for the specific population, with a CHA_2DS_2-VASc score ≥ 2 for 66% and 91% of patients, respectively, and HAS-BLED score ≥ 3 for 20% and 48% of patients, respectively (**Table 12**; Appendix 1-4, Tables 10 and 12). The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching. Similar results were found for the sensitive population (Appendices 1-9, Table 5).

For the rivaroxaban 20 mg and dabigatran 150 mg comparison of the specific population, stroke and bleeding risk factors were similar, except for age ≥ 75 years (32% vs 18%, respectively) and age > 65 years (65% vs 54%, respectively): 66% with a CHA_2DS_2-VASc score ≥ 2 in the rivaroxaban 20 mg group and 58% in the dabigatran 150 mg group; 20% with HAS-BLED score ≥ 3 in the rivaroxaban 20 mg group and 16% in the dabigatran 150 mg group (**Table 13**; Appendix 1-5, Tables 10 and 12). The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching. Similar results were found for the sensitive population (Appendices 1-10, Table 5).

For the reduced dose comparison of the specific population, all stroke and bleeding risk factors were less frequent in the rivaroxaban 15 mg group than in the VKA group, except for age ≥ 75 years (78% vs 69%, respectively), women gender (53% vs 48%, respectively), and age > 65 years (92% vs 87%, respectively), with a CHA_2DS_2-VASc score ≥ 2 for 92% and 91% of patients, respectively, and HAS-BLED score ≥ 3 for 36% and 48% of patients, respectively (**Table 14**; Appendix 1-6, Tables 10 and 12). The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching. Similar results were found for the sensitive population (Appendices 1-11, Table 5).

For the rivaroxaban 15 mg and dabigatran 110 mg comparison of the specific population, stroke and bleeding risk factors were almost the same in two groups, with really weak standardized differences after adjustment and matching (**Table 15**; Appendix 1-7, Tables 10 and 12). Similar results were found for the sensitive population (Appendices 1-12, Table 5).

Table 12. Stroke and bleeding risk factors before index date for rivaroxaban 20 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs VKA		
	Rivaroxaban 20 mg n = 42480		VKA n = 108656		Rivaroxaban 20 mg n = 31171		VKA n = 31171		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	5282	(12.4)	38534	(35.5)	4853	(15.6)	4949	(15.9)	-56.0	-0.1	-0.8
Hypertension	14284	(33.6)	60473	(55.7)	11908	(38.2)	12354	(39.6)	-45.4	2.9	-2.9
Age ≥ 75 years	13678	(32.2)	75405	(69.4)	12824	(41.1)	12930	(41.5)	-80.2	-3.0	-0.7
Diabetes mellitus	8713	(20.5)	29335	(27.0)	7016	(22.5)	7285	(23.4)	-15.3	4.3	-2.1
Stroke or transient ischemic attack (TIA) history	3735	(8.8)	16225	(14.9)	3329	(10.7)	3521	(11.3)	-19.1	7.2	-2.0
Vascular disease history	4645	(10.9)	24993	(23.0)	4098	(13.1)	4315	(13.8)	-32.6	3.7	-2.0
Age 65-74 years	15471	(36.4)	20359	(18.7)	11042	(35.4)	10963	(35.2)	40.4	13.1	0.5
Women	15128	(35.6)	52307	(48.1)	11842	(38.0)	11842	(38.0)	-25.6	0.5	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	5565	(13.1)	3101	(2.9)	2546	(8.2)	2522	(8.1)			
1	8805	(20.7)	6957	(6.4)	5072	(16.3)	4901	(15.7)			
≥ 2	28110	(66.2)	98598	(90.7)	23553	(75.6)	23748	(76.2)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	14284	(33.6)	60473	(55.7)	11908	(38.2)	12354	(39.6)	-45.4	2.9	-2.9
Abnormal renal function	891	(2.1)	19538	(18.0)	852	(2.7)	1043	(3.3)	-54.8	-4.7	-3.6
Abnormal liver function	579	(1.4)	3531	(3.2)	526	(1.7)	558	(1.8)	-12.6	3.8	-0.8
Stroke history	3107	(7.3)	14124	(13.0)	2825	(9.1)	3014	(9.7)	-18.9	7.4	-2.1
Bleeding history	647	(1.5)	3658	(3.4)	554	(1.8)	627	(2.0)	-12.0	2.1	-1.7
Age > 65 years	27590	(64.9)	93976	(86.5)	22846	(73.3)	22890	(73.4)	-51.9	2.7	-0.3
Medication use predisposing to bleeding	22611	(53.2)	72275	(66.5)	18476	(59.3)	18899	(60.6)	-27.4	13.5	-2.8
HAS-BLED score (in categories), n (%)											
0	6106	(14.4)	2825	(2.6)	2610	(8.4)	2266	(7.3)			
1	13470	(31.7)	17231	(15.9)	8843	(28.4)	8555	(27.4)			
2	14266	(33.6)	36637	(33.7)	11742	(37.7)	11985	(38.4)			
3	6998	(16.5)	33943	(31.2)	6395	(20.5)	6746	(21.6)			
> 3	1640	(3.9)	18020	(16.6)	1581	(5.1)	1619	(5.2)			

[1] *Based on general characteristics of patients, long-term disease with full insurance coverage (LTD), as well as 3-year history of hospital-discharge summary diagnosis, and drugs reimbursed*

Table 13. Stroke and bleeding risk factors before index date for rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs dabigatran 150 mg		
	Rivaroxaban 20 mg n = 42514		Dabigatran 150 mg n = 16834		Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	5279	(12.4)	2188	(13.0)	1837	(12.0)	1854	(12.1)	-1.7	4.3	-0.3
Hypertension	14283	(33.6)	5348	(31.8)	4792	(31.3)	4788	(31.2)	3.9	1.8	0.1
Age ≥ 75 years	13676	(32.2)	2954	(17.5)	2840	(18.5)	2824	(18.4)	34.3	6.2	0.3
Diabetes mellitus	8713	(20.5)	3471	(20.6)	3207	(20.9)	3190	(20.8)	-0.3	0.0	0.3
Stroke or transient ischemic attack (TIA) history	3726	(8.8)	1466	(8.7)	1191	(7.8)	1260	(8.2)	0.2	2.3	-1.7
Vascular disease history	4643	(10.9)	1537	(9.1)	1455	(9.5)	1411	(9.2)	6.0	-0.3	1.0
Age 65-74 years	15477	(36.4)	6841	(40.6)	6513	(42.5)	6494	(42.4)	-8.7	-6.2	0.3
Women	15129	(35.6)	5154	(30.6)	4599	(30.0)	4599	(30.0)	10.6	-0.1	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	5592	(13.2)	2960	(17.6)	2584	(16.9)	2627	(17.1)			
1	8818	(20.7)	4189	(24.9)	3812	(24.9)	3790	(24.7)			
≥ 2	28104	(66.1)	9685	(57.5)	8927	(58.3)	8906	(58.1)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	14283	(33.6)	5348	(31.8)	4792	(31.3)	4788	(31.2)	3.9	1.8	0.1
Abnormal renal function	890	(2.1)	232	(1.4)	194	(1.3)	206	(1.3)	5.5	0.4	-0.7
Abnormal liver function	579	(1.4)	220	(1.3)	197	(1.3)	189	(1.2)	0.5	0.1	0.5
Stroke history	3099	(7.3)	1252	(7.4)	1008	(6.6)	1059	(6.9)	-0.6	2.9	-1.3
Bleeding history	646	(1.5)	204	(1.2)	190	(1.2)	181	(1.2)	2.7	-0.1	0.5
Age > 65 years	27591	(64.9)	9071	(53.9)	8671	(56.6)	8645	(56.4)	22.6	1.9	0.3
Medication use predisposing to bleeding	22609	(53.2)	8186	(48.6)	7693	(50.2)	7579	(49.5)	9.1	-1.8	1.5
HAS-BLED score (in categories), n (%)											
0	6138	(14.4)	3327	(19.8)	2760	(18.0)	2857	(18.6)			
1	13480	(31.7)	5733	(34.1)	5308	(34.6)	5232	(34.1)			
2	14262	(33.5)	5065	(30.1)	4782	(31.2)	4748	(31.0)			
3	6996	(16.5)	2218	(13.2)	2044	(13.3)	2055	(13.4)			
> 3	1638	(3.9)	491	(2.9)	429	(2.8)	431	(2.8)			

[1] *Based on general characteristics of patients, long-term disease with full insurance coverage (LTD), as well as 3-year history of hospital-discharge summary diagnosis, and drugs reimbursed*

Table 14. Stroke and bleeding risk factors before index date for rivaroxaban 15 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs VKA		
	Rivaroxaban 15 mg n = 24529		VKA n = 108639		Rivaroxaban 15 mg n = 23314		VKA n = 23314		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	5580	(22.7)	38533	(35.5)	5467	(23.4)	5393	(23.1)	-28.3	0.2	0.8
Hypertension	11084	(45.2)	60462	(55.7)	10694	(45.9)	10710	(45.9)	-21.0	0.4	-0.1
Age ≥ 75 years	19172	(78.2)	75383	(69.4)	18344	(78.7)	18325	(78.6)	20.0	2.5	0.2
Diabetes mellitus	5186	(21.1)	29333	(27.0)	4997	(21.4)	5088	(21.8)	-13.7	0.1	-0.9
Stroke or transient ischemic attack (TIA) history	2683	(10.9)	16224	(14.9)	2619	(11.2)	2654	(11.4)	-11.9	3.3	-0.5
Vascular disease history	4051	(16.5)	24989	(23.0)	3922	(16.8)	3989	(17.1)	-16.3	1.0	-0.8
Age 65-74 years	3709	(15.1)	20357	(18.7)	3601	(15.4)	3609	(15.5)	-9.7	-1.7	-0.1
Women	12955	(52.8)	52289	(48.1)	12244	(52.5)	12244	(52.5)	9.4	-0.7	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	539	(2.2)	3107	(2.9)	455	(2.0)	470	(2.0)			
1	1342	(5.5)	6958	(6.4)	1202	(5.2)	1195	(5.1)			
≥ 2	22648	(92.3)	98574	(90.7)	21657	(92.9)	21649	(92.9)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	11084	(45.2)	60462	(55.7)	10694	(45.9)	10710	(45.9)	-21.0	0.4	-0.1
Abnormal renal function	1660	(6.8)	19538	(18.0)	1625	(7.0)	1651	(7.1)	-34.6	-0.4	-0.4
Abnormal liver function	397	(1.6)	3531	(3.3)	382	(1.6)	377	(1.6)	-10.6	-0.9	0.2
Stroke history	2240	(9.1)	14123	(13.0)	2191	(9.4)	2214	(9.5)	-12.4	3.0	-0.3
Bleeding history	588	(2.4)	3657	(3.4)	565	(2.4)	586	(2.5)	-5.8	1.4	-0.6
Age > 65 years	22625	(92.2)	93952	(86.5)	21694	(93.1)	21717	(93.2)	18.8	1.1	-0.4
Medication use predisposing to bleeding	15249	(62.2)	72267	(66.5)	14641	(62.8)	14727	(63.2)	-9.1	2.8	-0.8
HAS-BLED score (in categories), n (%)											
0	630	(2.6)	2830	(2.6)	489	(2.1)	446	(1.9)			
1	5309	(21.6)	17225	(15.9)	4912	(21.1)	4628	(19.9)			
2	9710	(39.6)	36627	(33.7)	9280	(39.8)	9663	(41.4)			
3	6722	(27.4)	33938	(31.2)	6519	(28.0)	6536	(28.0)			
> 3	2158	(8.8)	18019	(16.6)	2114	(9.1)	2041	(8.8)			

[1] *Based on general characteristics of patients, long-term disease with full insurance coverage (LTD), as well as 3-year history of hospital-discharge summary diagnosis, and drugs reimbursed*

Table 15. Stroke and bleeding risk factors before index date for rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs dabigatran 110 mg		
	Rivaroxaban 15 mg n = 24548		Dabigatran 110 mg n = 23665		Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	5573	(22.7)	5173	(21.9)	3391	(22.4)	3267	(21.6)	2.0	-0.2	2.0
Hypertension	11080	(45.1)	10895	(46.0)	6876	(45.4)	6808	(45.0)	-1.8	-0.1	0.9
Age ≥ 75 years	19191	(78.2)	17557	(74.2)	12169	(80.4)	12179	(80.5)	9.4	0.4	-0.2
Diabetes mellitus	5185	(21.1)	5111	(21.6)	3204	(21.2)	3147	(20.8)	-1.2	0.1	0.9
Stroke or transient ischemic attack (TIA) history	2675	(10.9)	3131	(13.2)	1679	(11.1)	1746	(11.5)	-7.2	1.0	-1.4
Vascular disease history	4051	(16.5)	3531	(14.9)	2355	(15.6)	2252	(14.9)	4.3	-0.1	1.9
Age 65-74 years	3711	(15.1)	4102	(17.3)	2276	(15.0)	2260	(14.9)	-6.0	-0.3	0.3
Women	12983	(52.9)	11970	(50.6)	7902	(52.2)	7902	(52.2)	4.6	0.1	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	539	(2.2)	625	(2.6)	242	(1.6)	245	(1.6)			
1	1343	(5.5)	1463	(6.2)	719	(4.8)	719	(4.8)			
≥ 2	22666	(92.3)	21577	(91.2)	14170	(93.6)	14167	(93.6)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	11080	(45.1)	10895	(46.0)	6876	(45.4)	6808	(45.0)	-1.8	-0.1	0.9
Abnormal renal function	1646	(6.7)	1129	(4.8)	814	(5.4)	723	(4.8)	8.3	0.2	2.7
Abnormal liver function	395	(1.6)	389	(1.6)	242	(1.6)	206	(1.4)	-0.3	-0.1	2.0
Stroke history	2232	(9.1)	2672	(11.3)	1404	(9.3)	1458	(9.6)	-7.3	1.2	-1.2
Bleeding history	588	(2.4)	530	(2.2)	343	(2.3)	328	(2.2)	1.0	0.0	0.7
Age > 65 years	22647	(92.3)	21342	(90.2)	14296	(94.5)	14287	(94.4)	7.3	0.6	0.3
Medication use predisposing to bleeding	15244	(62.1)	14001	(59.2)	9302	(61.5)	9108	(60.2)	6.0	0.1	2.6
HAS-BLED score (in categories), n (%)											
0	630	(2.6)	761	(3.2)	263	(1.7)	282	(1.9)			
1	5330	(21.7)	5336	(22.5)	3308	(21.9)	3351	(22.1)			
2	9721	(39.6)	9262	(39.1)	6117	(40.4)	6233	(41.2)			
3	6720	(27.4)	6346	(26.8)	4218	(27.9)	4090	(27.0)			
> 3	2147	(8.7)	1960	(8.3)	1225	(8.1)	1175	(7.8)			

[1] *Based on general characteristics of patients, long-term disease with full insurance coverage (LTD), as well as 3-year history of hospital-discharge summary diagnosis, and drugs reimbursed*

History of drug dispensing

Almost all patients of the specific population (99%) had one or more drugs dispensed within the 3-year before index date whatever the treatment group. The five most frequent drug classes dispensed (first level of the ATC classification) were those of: nervous system, alimentary tract and metabolism, anti-infectives for systemic use, musculo-skeletal system, and cardiovascular system, with similar frequency in rivaroxaban 20 mg and VKA groups, except for cardiovascular drugs (83% and 91%, respectively) (**Table 16**; Appendix 1-4, Table 14). Within the 3-year before index date, the most frequent antiarrhythmic drugs prescribed were flecainide and amiodarone in two groups, and the most frequent antithrombotic agents were acetylsalicylic acid, clopidogrel and enoxaparin (Appendix 1-4, Table 13). The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching.

History of drug dispensing was almost the same for rivaroxaban 20 mg and dabigatran 150 mg groups (**Table 17**; Appendix 1-5, Tables 13 and 14) with really weak standardized differences after adjustment and matching, as well as for reduced dose comparisons, rivaroxaban 15 mg versus VKA, rivaroxaban 15 mg versus dabigatran 110 mg (**Tables 18 and 19**; Appendices 1-6 and 1-7, Tables 13 and 14).

Table 16. Drug dispensing within the 3 years before index date for rivaroxaban 20 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs VKA		
	Rivaroxaban 20 mg n = 42480		VKA n = 108656		Rivaroxaban 20 mg n = 31171		VKA n = 31171		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**42118**	**(99.1)**	**107534**	**(99.0)**	**30915**	**(99.2)**	**30730**	**(98.6)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	39335	(92.6)	102095	(94.0)	28960	(92.9)	28667	(92.0)	-5.5	3.0	3.6
Alimentary tract and metabolism (A)	37518	(88.3)	100027	(92.1)	27784	(89.1)	27854	(89.4)	-12.6	0.6	-0.7
General antiinfectives for systemic use (J)	37093	(87.3)	97428	(89.7)	27413	(87.9)	27202	(87.3)	-7.4	2.1	2.1
Musculo-skeletal system (M)	34051	(80.2)	84557	(77.8)	24844	(79.7)	24421	(78.3)	5.7	2.6	3.3
Cardiovascular system (C)	35455	(83.5)	98814	(90.9)	26864	(86.2)	26906	(86.3)	-22.5	2.5	-0.4
C09 - Agents acting on the renin-angiotensin system	*22127*	*(52.1)*	*69565*	*(64.0)*	*17482*	*(56.1)*	*17628*	*(56.6)*	*-24.4*	*4.5*	*-0.9*
C10 - Lipid modifying agents	*19229*	*(45.3)*	*56476*	*(52.0)*	*15263*	*(49.0)*	*15378*	*(49.3)*	*-13.5*	*9.0*	*-0.7*
C07 - Beta blocking agents	*18085*	*(42.6)*	*53650*	*(49.4)*	*13762*	*(44.2)*	*14243*	*(45.7)*	*-13.7*	*1.3*	*-3.1*
C03 - Diuretics	*9765*	*(23.0)*	*50044*	*(46.1)*	*8398*	*(26.9)*	*8797*	*(28.2)*	*-50.0*	*0.3*	*-2.9*
C01 - Cardiac therapy	*13675*	*(32.2)*	*42971*	*(39.5)*	*10388*	*(33.3)*	*10284*	*(33.0)*	*-15.4*	*1.4*	*0.7*
C08 - Calcium channel blockers	*10668*	*(25.1)*	*39783*	*(36.6)*	*8660*	*(27.8)*	*8815*	*(28.3)*	*-25.1*	*3.0*	*-1.1*
C02 - Antihypertensives	*2785*	*(6.6)*	*12944*	*(11.9)*	*2355*	*(7.6)*	*2386*	*(7.7)*	*-18.6*	*1.9*	*-0.4*
C04 - Peripheral vasodilators	*1404*	*(3.3)*	*6720*	*(6.2)*	*1216*	*(3.9)*	*1240*	*(4.0)*	*-13.6*	*0.4*	*-0.4*
C05 - Vasoprotectives	*1552*	*(3.7)*	*4000*	*(3.7)*	*1194*	*(3.8)*	*1129*	*(3.6)*	*-0.1*	*1.2*	*1.1*
Dermatologicals (D)	30425	(71.6)	82306	(75.7)	22606	(72.5)	22530	(72.3)	-9.4	2.2	0.5
Respiratory system (R)	31102	(73.2)	78798	(72.5)	22798	(73.1)	22562	(72.4)	1.6	3.7	1.7
Blood and blood forming organs (B)	25007	(58.9)	78180	(72.0)	19561	(62.8)	19495	(62.5)	-27.8	6.3	0.4
B01 - Antithrombotic agents	*22560*	*(53.1)*	*69935*	*(64.4)*	*17795*	*(57.1)*	*17544*	*(56.3)*	*-23.0*	*9.4*	*1.6*
B03 - Antianemic preparations	*3821*	*(9.0)*	*22201*	*(20.4)*	*3180*	*(10.2)*	*3495*	*(11.2)*	*-32.7*	*-1.4*	*-3.3*
B05 - Plasma substitutes and perfusion solutions	*4195*	*(9.9)*	*16335*	*(15.0)*	*3293*	*(10.6)*	*3375*	*(10.8)*	*-15.7*	*2.0*	*-0.9*
B02 - Antihemorrhagics	*474*	*(1.1)*	*1578*	*(1.5)*	*334*	*(1.1)*	*398*	*(1.3)*	*-3.0*	*-0.5*	*-1.9*
Systemic hormonal prep, excluding sex hormones (H)	22073	(52.0)	55801	(51.4)	16092	(51.6)	15789	(50.7)	1.2	2.3	1.9
Sensory organs (S)	20764	(48.9)	58878	(54.2)	15711	(50.4)	15485	(49.7)	-10.6	1.6	1.5
Genito urinary system and sex hormones (G)	11582	(27.3)	30538	(28.1)	8690	(27.9)	8352	(26.8)	-1.9	4.3	2.4
Various (V)	11789	(27.8)	31032	(28.6)	8832	(28.3)	8971	(28.8)	-1.8	5.4	-1.0
Antiparasitic products (P)	3194	(7.5)	7249	(6.7)	2266	(7.3)	2197	(7.0)	3.3	1.1	0.9
Antineoplastic and immunomodulating agents (L)	1944	(4.6)	8053	(7.4)	1592	(5.1)	1868	(6.0)	-12.0	0.5	-3.9

Table 17. Drug dispensing within the 3 years before index date for rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 20 mg vs. dabigatran 150 mg		
	Rivaroxaban 20 mg n = 42514		Dabigatran 150 mg n = 16834		Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**42153**	**(99.2)**	**16635**	**(98.8)**	**15164**	**(99.0)**	**15158**	**(98.9)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	39370	(92.6)	15446	(91.8)	14032	(91.6)	14052	(91.7)	3.2	0.3	-0.5
Alimentary tract and metabolism (A)	37554	(88.3)	14528	(86.3)	13212	(86.2)	13247	(86.5)	6.1	-0.3	-0.7
General antiinfectives for systemic use (J)	37127	(87.3)	14436	(85.8)	13179	(86.0)	13141	(85.8)	4.6	-0.2	0.7
Musculo-skeletal system (M)	34087	(80.2)	13501	(80.2)	12200	(79.6)	12262	(80.0)	-0.1	-1.1	-1.0
Cardiovascular system (C)	35481	(83.5)	13409	(79.7)	12393	(80.9)	12345	(80.6)	9.8	-1.1	0.8
C09 - Agents acting on the renin-angiotensin system	*22132*	*(52.1)*	*8210*	*(48.8)*	*7626*	*(49.8)*	*7610*	*(49.7)*	*6.6*	*-0.6*	*0.2*
C10 - Lipid modifying agents	*19230*	*(45.2)*	*7096*	*(42.2)*	*6622*	*(43.2)*	*6637*	*(43.3)*	*6.2*	*-1.3*	*-0.2*
C07 - Beta blocking agents	*18094*	*(42.6)*	*6845*	*(40.7)*	*6338*	*(41.4)*	*6298*	*(41.1)*	*3.9*	*-2.8*	*0.5*
C03 - Diuretics	*9763*	*(23.0)*	*3269*	*(19.4)*	*3007*	*(19.6)*	*3009*	*(19.6)*	*8.7*	*0.1*	*0.0*
C01 - Cardiac therapy	*13701*	*(32.2)*	*4572*	*(27.2)*	*4485*	*(29.3)*	*4260*	*(27.8)*	*11.1*	*-1.4*	*3.3*
C08 - Calcium channel blockers	*10665*	*(25.1)*	*3663*	*(21.8)*	*3433*	*(22.4)*	*3384*	*(22.1)*	*7.9*	*-0.1*	*0.8*
C02 - Antihypertensives	*2784*	*(6.5)*	*1018*	*(6.0)*	*921*	*(6.0)*	*934*	*(6.1)*	*2.1*	*-1.2*	*-0.4*
C04 - Peripheral vasodilators	*1405*	*(3.3)*	*457*	*(2.7)*	*431*	*(2.8)*	*421*	*(2.7)*	*3.5*	*-0.6*	*0.4*
C05 - Vasoprotectives	*1557*	*(3.7)*	*729*	*(4.3)*	*641*	*(4.2)*	*651*	*(4.2)*	*-3.4*	*-5.0*	*-0.3*
Dermatologicals (D)	30452	(71.6)	11548	(68.6)	10623	(69.3)	10536	(68.8)	6.6	0.0	1.2
Respiratory system (R)	31132	(73.2)	12417	(73.8)	11090	(72.4)	11249	(73.4)	-1.2	-2.1	-2.3
Blood and blood forming organs (B)	25025	(58.9)	8948	(53.2)	8395	(54.8)	8220	(53.6)	11.5	-1.0	2.3
B01 - Antithrombotic agents	*22574*	*(53.1)*	*7954*	*(47.2)*	*7564*	*(49.4)*	*7354*	*(48.0)*	*11.7*	*-1.0*	*2.7*
B03 - Antianemic preparations	*3823*	*(9.0)*	*1200*	*(7.1)*	*1066*	*(7.0)*	*1048*	*(6.8)*	*6.9*	*0.3*	*0.5*
B05 - Plasma substitutes and perfusion solutions	*4197*	*(9.9)*	*1460*	*(8.7)*	*1369*	*(8.9)*	*1299*	*(8.5)*	*4.1*	*0.2*	*1.6*
B02 - Antihemorrhagics	*473*	*(1.1)*	*193*	*(1.1)*	*146*	*(1.0)*	*160*	*(1.0)*	*-0.3*	*-1.1*	*-0.9*
Systemic hormonal prep, excluding sex hormones (H)	22100	(52.0)	8531	(50.7)	7721	(50.4)	7755	(50.6)	2.6	-0.7	-0.4
Sensory organs (S)	20784	(48.9)	7501	(44.6)	6841	(44.6)	6871	(44.8)	8.7	0.7	-0.4
Genito urinary system and sex hormones (G)	11595	(27.3)	4124	(24.5)	3712	(24.2)	3756	(24.5)	6.3	0.0	-0.7
Various (V)	11810	(27.8)	4124	(24.5)	3918	(25.6)	3777	(24.6)	7.5	1.1	2.1
Antiparasitic products (P)	3196	(7.5)	1202	(7.1)	1097	(7.2)	1076	(7.0)	1.4	0.1	0.5
Antineoplastic and immunomodulating agents (L)	1944	(4.6)	588	(3.5)	536	(3.5)	525	(3.4)	5.5	0.0	0.4

Table 18. Drug dispensing within the 3 years before index date for rivaroxaban 15 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs. VKA		
	Rivaroxaban 15 mg n = 24529		VKA n = 108639		Rivaroxaban 15 mg n = 23314		VKA n = 23314		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**24423**	**(99.6)**	**107517**	**(99.0)**	**23212**	**(99.6)**	**23159**	**(99.3)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	23266	(94.9)	102078	(94.0)	22090	(94.7)	22083	(94.7)	3.9	1.4	0.1
Alimentary tract and metabolism (A)	22829	(93.1)	100009	(92.1)	21694	(93.1)	21733	(93.2)	3.9	0.8	-0.7
General antiinfectives for systemic use (J)	22280	(90.8)	97410	(89.7)	21161	(90.8)	21191	(90.9)	3.9	-0.3	-0.4
Musculo-skeletal system (M)	19559	(79.7)	84543	(77.8)	18533	(79.5)	18664	(80.1)	4.7	-0.9	-1.4
Cardiovascular system (C)	22543	(91.9)	98796	(90.9)	21464	(92.1)	21505	(92.2)	3.4	1.2	-0.7
C09 - Agents acting on the renin-angiotensin system	*15184*	*(61.9)*	*69551*	*(64.0)*	*14554*	*(62.4)*	*14782*	*(63.4)*	*-4.4*	*-0.1*	*-2*
C10 - Lipid modifying agents	*12587*	*(51.3)*	*56467*	*(52.0)*	*12071*	*(51.8)*	*12119*	*(52.0)*	*-1.3*	*2.0*	*-0.4*
C07 - Beta blocking agents	*11669*	*(47.6)*	*53645*	*(49.4)*	*11143*	*(47.8)*	*11233*	*(48.2)*	*-3.6*	*0.7*	*-0.8*
C03 - Diuretics	*9975*	*(40.7)*	*50030*	*(46.1)*	*9603*	*(41.2)*	*9758*	*(41.9)*	*-10.9*	*0.8*	*-1.3*
C01 - Cardiac therapy	*10657*	*(43.4)*	*42952*	*(39.5)*	*10053*	*(43.1)*	*9818*	*(42.1)*	*7.9*	*3.4*	*2*
C08 - Calcium channel blockers	*8459*	*(34.5)*	*39770*	*(36.6)*	*8085*	*(34.7)*	*8208*	*(35.2)*	*-4.4*	*-1.2*	*-1.1*
C02 - Antihypertensives	*2388*	*(9.7)*	*12943*	*(11.9)*	*2307*	*(9.9)*	*2368*	*(10.2)*	*-7*	*-1.0*	*-0.9*
C04 - Peripheral vasodilators	*1540*	*(6.3)*	*6717*	*(6.2)*	*1468*	*(6.3)*	*1437*	*(6.2)*	*0.4*	*1.0*	*0.6*
C05 - Vasoprotectives	*1067*	*(4.3)*	*3997*	*(3.7)*	*1019*	*(4.4)*	*946*	*(4.1)*	*3.4*	*2.0*	*1.6*
Dermatologicals (D)	18833	(76.8)	82288	(75.7)	17872	(76.7)	17938	(76.9)	2.4	0.0	-0.7
Respiratory system (R)	18033	(73.5)	78783	(72.5)	17084	(73.3)	17122	(73.4)	2.3	-0.5	-0.4
Blood and blood forming organs (B)	17617	(71.8)	78164	(71.9)	16771	(71.9)	16521	(70.9)	-0.3	5	2.4
B01 - Antithrombotic agents	*15999*	*(65.2)*	*69920*	*(64.4)*	*15251*	*(65.4)*	*14897*	*(63.9)*	*1.8*	*6.7*	*3.2*
B03 - Antianemic preparations	*4142*	*(16.9)*	*22196*	*(20.4)*	*3942*	*(16.9)*	*3963*	*(17.0)*	*-9.1*	*0.4*	*-0.2*
B05 - Plasma substitutes and perfusion solutions	*3127*	*(12.7)*	*16329*	*(15.0)*	*2985*	*(12.8)*	*2993*	*(12.8)*	*-6.6*	*0.6*	*-0.1*
B02 - Antihemorrhagics	*291*	*(1.2)*	*1578*	*(1.5)*	*276*	*(1.2)*	*314*	*(1.3)*	*-2.3*	*-1.3*	*-1.5*
Systemic hormonal prep, excluding sex hormones (H)	13123	(53.5)	55792	(51.4)	12412	(53.2)	12379	(53.1)	4.3	0.2	0.3
Sensory organs (S)	14337	(58.4)	58858	(54.2)	13579	(58.2)	13493	(57.9)	8.6	-0.4	0.7
Genito urinary system and sex hormones (G)	7538	(30.7)	30529	(28.1)	7123	(30.6)	6961	(29.9)	5.8	1.9	1.5
Various (V)	6667	(27.2)	31028	(28.6)	6291	(27.0)	6331	(27.2)	-3.1	-1.5	-0.4
Antiparasitic products (P)	1730	(7.1)	7250	(6.7)	1613	(6.9)	1537	(6.6)	1.5	2.2	1.3
Antineoplastic and immunomodulating agents (L)	1621	(6.6)	8051	(7.4)	1557	(6.7)	1682	(7.2)	-3.1	-0.4	-2.1

Table 19. Drug dispensing within the 3 years before index date for rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs. dabigatran 110 mg		
	Rivaroxaban 15 mg n = 24548		Dabigatran 110 mg n = 23665		Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**24442**	**(99.6)**	**23515**	**(99.4)**	**15056**	**(99.5)**	**15036**	**(99.4)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	23285	(94.9)	22323	(94.3)	14309	(94.6)	14259	(94.2)	2.3	0.7	1.4
Alimentary tract and metabolism (A)	22850	(93.1)	21779	(92.0)	14043	(92.8)	14040	(92.8)	4.0	0.8	0.1
General antiinfectives for systemic use (J)	22299	(90.8)	21300	(90.0)	13705	(90.6)	13688	(90.5)	2.8	0.3	0.4
Musculo-skeletal system (M)	19575	(79.7)	18897	(79.9)	12003	(79.3)	12077	(79.8)	-0.3	-1.9	-1.2
Cardiovascular system (C)	22562	(91.9)	21442	(90.6)	13924	(92.0)	13868	(91.7)	4.6	-0.2	1.4
C09 - Agents acting on the renin-angiotensin system	*15188*	*(61.9)*	*14188*	*(60.0)*	*9347*	*(61.8)*	*9215*	*(60.9)*	*3.9*	*0.6*	*1.8*
C10 - Lipid modifying agents	*12595*	*(51.3)*	*11944*	*(50.5)*	*7791*	*(51.5)*	*7688*	*(50.8)*	*1.7*	*-0.3*	*1.4*
C07 - Beta blocking agents	*11677*	*(47.6)*	*10852*	*(45.9)*	*7154*	*(47.3)*	*6965*	*(46.0)*	*3.4*	*0.7*	*2.5*
C03 - Diuretics	*9975*	*(40.6)*	*8842*	*(37.4)*	*5964*	*(39.4)*	*5927*	*(39.2)*	*6.7*	*-0.6*	*0.5*
C01 - Cardiac therapy	*10674*	*(43.5)*	*9297*	*(39.3)*	*6412*	*(42.4)*	*6148*	*(40.6)*	*8.5*	*-0.2*	*3.5*
C08 - Calcium channel blockers	*8461*	*(34.5)*	*7774*	*(32.9)*	*5135*	*(33.9)*	*5021*	*(33.2)*	*3.4*	*0.7*	*1.6*
C02 - Antihypertensives	*2390*	*(9.7)*	*2293*	*(9.7)*	*1492*	*(9.9)*	*1461*	*(9.7)*	*0.2*	*-1.1*	*0.7*
C04 - Peripheral vasodilators	*1542*	*(6.3)*	*1525*	*(6.4)*	*972*	*(6.4)*	*990*	*(6.5)*	*-0.7*	*-2.4*	*-0.5*
C05 - Vasoprotectives	*1071*	*(4.4)*	*1133*	*(4.8)*	*726*	*(4.8)*	*689*	*(4.6)*	*-2.0*	*-3.1*	*1.2*
Dermatologicals (D)	18854	(76.8)	17798	(75.2)	11530	(76.2)	11514	(76.1)	3.7	0.1	0.2
Respiratory system (R)	18047	(73.5)	17441	(73.7)	10990	(72.6)	11103	(73.4)	-0.4	-1.3	-1.7
Blood and blood forming organs (B)	17631	(71.8)	16186	(68.4)	10725	(70.9)	10557	(69.8)	7.5	0.6	2.4
B01 - Antithrombotic agents	*16008*	*(65.2)*	*14621*	*(61.8)*	*9755*	*(64.5)*	*9574*	*(63.3)*	*7.1*	*0.1*	*2.5*
B03 - Antianemic preparations	*4138*	*(16.9)*	*3412*	*(14.4)*	*2433*	*(16.1)*	*2232*	*(14.8)*	*6.7*	*2.0*	*3.7*
B05 - Plasma substitutes and perfusion solutions	*3132*	*(12.8)*	*2855*	*(12.1)*	*1806*	*(11.9)*	*1832*	*(12.1)*	*2.1*	*-0.6*	*-0.5*
B02 - Antihemorrhagics	*291*	*(1.2)*	*288*	*(1.2)*	*165*	*(1.1)*	*172*	*(1.1)*	*-0.3*	*-1.0*	*-0.4*
Systemic hormonal prep, excluding sex hormones (H)	13133	(53.5)	12434	(52.5)	7953	(52.6)	7885	(52.1)	1.9	0.3	0.9
Sensory organs (S)	14360	(58.5)	13592	(57.4)	8748	(57.8)	8858	(58.5)	2.2	-1.0	-1.5
Genito urinary system and sex hormones (G)	7543	(30.7)	6985	(29.5)	4547	(30.1)	4535	(30.0)	2.6	1	0.2
Various (V)	6677	(27.2)	6358	(26.9)	3954	(26.1)	4010	(26.5)	0.7	-1.5	-0.8
Antiparasitic products (P)	1730	(7.0)	1509	(6.4)	1007	(6.7)	911	(6.0)	2.7	2.0	2.6
Antineoplastic and immunomodulating agents (L)	1623	(6.6)	1428	(6.0)	934	(6.2)	932	(6.2)	2.4	0.1	0.1

History of medical visits and lab tests

Nearly all patients had physician visit reimbursements within the 3 years before index date, with a median of 22 in the rivaroxaban 20 mg group, and 27 in the VKA group for the specific population (**Table 20**; Appendix 1-4, Tables 19 to 24). The median number of visits was about one every 2 months (5-6 per year) with general practitioners (GP), only one visit within the 3 years with cardiologists, and about one every year with other specialists in rivaroxaban 20 mg and VKA groups. Lab tests were also largely used (**Table 20**), and the detail by type of lab test (NABM codes) is presented in Appendix 1-4, Tables 26 to 28. The crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching.

For the rivaroxaban 20 mg and dabigatran 150 mg comparison in the specific population, results for history of medical visits and lab tests were similar, with really weak standardized differences after adjustment and matching, (**Table 21**; Appendix 1-5, Tables 19 to 24, and 26 to 28), as well as for reduced dose comparisons, rivaroxaban 15 mg versus VKA, rivaroxaban 15 mg versus dabigatran 110 mg (**Tables 22 and 23**; Appendices 1-6 and 1-7, Tables 19 to 24, and 26 to 28).

Table 20. Medical visits and lab tests in the 3 years before index date for rivaroxaban 20 mg and VKA groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 20 mg vs. VKA		
	Rivaroxaban 20 mg n = 42480	VKA n = 108656	Rivaroxaban 20 mg n = 31171	VKA n = 31171	Crude	Adjusted	Matched
At least one medical visit, n (%)	**42206 (99.4)**	**107894 (99.3)**	**30974 (99.4)**	**30912 (99.2)**			
Number per patient					-23.6	1.9	0.2
Mean (± SD)	26.1 (19.4)	31.2 (23.4)	26.9 (19.4)	26.8 (19.0)			
Median	22.0	27.0	23.0	23.0			
[p25% - p75%]	[14.0;34.0]	[17.0;40.0]	[15.0;35.0]	[15.0;35.0]			
At least one general practitioner visit, n (%)	**41336 (97.3)**	**105716 (97.3)**	**30350 (97.4)**	**30266 (97.1)**			
Number per patient					-29.2	1.3	-0.5
Mean (± SD)	18.8 (14.6)	23.6 (17.5)	19.6 (15.0)	19.7 (14.9)			
Median	16.0	20.0	17.0	17.0			
[p25% - p75%]	[10.0;24.0]	[13.0;31.0]	[11.0;25.0]	[11.0;25.0]			
At least one cardiologist visit, n (%)	**21737 (51.2)**	**52421 (48.2)**	**15596 (50.0)**	**15411 (49.4)**			
Number per patient					-7.4	-1.3	0.2
Mean (± SD)	1.4 (2.3)	1.6 (3.1)	1.4 (2.3)	1.4 (2.5)			
Median	1.0	0.0	1.0	0.0			
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]			
At least one other specialist visit, n (%)	36229 (85.3)	88459 (81.4)	26409 (84.7)	26074 (83.6)			
Number per patient					-1.4	1.9	1.2
Mean (± SD)	5.9 (9.0)	6.1 (13.6)	5.8 (8.4)	5.7 (8.3)			
Median	4.0	3.0	4.0	3.0			
[p25% - p75%]	[1.0;8.0]	[1.0;7.0]	[1.0;8.0]	[1.0;8.0]			
At least one lab test, n (%)	**40830 (96.1)**	**105161 (96.8)**	**30002 (96.2)**	**29983 (96.2)**			

Table 21. Medical visits and lab tests in the 3 years before index date for rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 20 mg vs. dabigatran 150 mg		
	Rivaroxaban 20 mg n = 42514	Dabigatran 150 mg n = 16834	Rivaroxaban 20 mg n = 15323	Dabigatran 150 mg n = 15323	Crude	Adjusted	Matched
At least one medical visit, n (%)	**42240 (99.4)**	**16708 (99.3)**	**15214 (99.3)**	**15213 (99.3)**			
Number per patient					11.2	-1.3	-1.3
Mean (± SD)	26.1 (19.4)	24.0 (18.1)	23.8 (17.2)	24.1 (18.1)			
Median	22.0	21.0	21.0	21.0			
[p25% - p75%]	[14.0;34.0]	[13.0;31.0]	[13.0;31.0]	[13.0;31.0]			
At least one general practitioner visit, n (%)	**41370 (97.3)**	**16416 (97.5)**	**14903 (97.3)**	**14942 (97.5)**			
Number per patient					9.4	-1.0	-1.6
Mean (± SD)	18.8 (14.6)	17.5 (13.4)	17.3 (12.9)	17.5 (13.3)			
Median	16.0	15.0	15.0	15.0			
[p25% - p75%]	[10.0;24.0]	[9.0;22.0]	[9.0;22.0]	[9.0;22.0]			
At least one cardiologist visit, n (%)	**21771 (51.2)**	**7892 (46.9)**	**7486 (48.9)**	**7301 (47.6)**			
Number per patient					10.6	-0.6	3.8
Mean (± SD)	1.4 (2.3)	1.2 (2.0)	1.2 (2.0)	1.2 (2.0)			
Median	1.0	0.0	0.0	0.0			
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]			
At least one other specialist visit, n (%)	36265 (85.3)	14116 (83.9)	12892 (84.1)	12886 (84.1)			
Number per patient					6.4	-0.9	-1.2
Mean (± SD)	5.9 (9.0)	5.3 (8.6)	5.3 (7.9)	5.4 (8.7)			
Median	4.0	3.0	3.0	3.0			
[p25% - p75%]	[1.0;8.0]	[1.0;7.0]	[1.0;7.0]	[1.0;7.0]			
At least one lab test, n (%)	**40864 (96.1)**	**16008 (95.1)**	**14611 (95.4)**	**14627 (95.5)**			

Table 22. Medical visits and lab tests in the 3 years before index date for rivaroxaban 15 mg and VKA groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 15 mg vs. VKA		
	Rivaroxaban 15 mg n = 24529	VKA n = 108639	Rivaroxaban 15 mg n = 23314	VKA n = 23314	Crude	Adjusted	Matched
At least one medical visit, n (%)	**24444 (99.7)**	**107877 (99.3)**	**23232 (99.6)**	**23211 (99.6)**			
Number per patient					2.9	-0.1	1.1
Mean (± SD)	31.8 (20.4)	31.2 (23.4)	31.7 (20.3)	31.5 (20.1)			
Median	28.0	27.0	27.5	27.0			
[p25% - p75%]	[18.0;41.0]	[17.0;40.0]	[18.0;41.0]	[18.0;41.0]			
At least one general practitioner visit, n (%)	**23994 (97.8)**	**105699 (97.3)**	**22797 (97.8)**	**22765 (97.6)**			
Number per patient					0.3	1.0	-0.4
Mean (± SD)	23.6 (16.6)	23.6 (17.5)	23.6 (16.6)	23.6 (16.8)			
Median	20.0	20.0	20.0	20.0			
[p25% - p75%]	[13.0;30.0]	[13.0;31.0]	[13.0;30.0]	[14.0;31.0]			
At least one cardiologist visit, n (%)	**13923 (56.8)**	**52404 (48.2)**	**12997 (55.7)**	**13020 (55.8)**			
Number per patient					10.5	-1.3	1.9
Mean (± SD)	1.9 (3.2)	1.6 (3.1)	1.9 (3.1)	1.8 (3.0)			
Median	1.0	0.0	1.0	1.0			
[p25% - p75%]	[0.0;3.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]			
At least one other specialist visit, n (%)	20892 (85.2)	88442 (81.4)	19781 (84.8)	19754 (84.7)			
Number per patient					2.2	-1.1	2.8
Mean (± SD)	6.3 (8.3)	6.1 (13.6)	6.2 (8.2)	6.0 (7.9)			
Median	4.0	3.0	4.0	4.0			
[p25% - p75%]	[1.0;8.0]	[1.0;7.0]	[1.0;8.0]	[1.0;8.0]			
At least one lab test, n (%)	**24012 (97.9)**	**105144 (96.8)**	**22808 (97.8)**	**22810 (97.8)**			

Table 23. Medical visits and lab tests in the 3 years before index date for rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients		Standardized difference (%) Rivaroxaban 15 mg vs. dabigatran 110 mg		
	Rivaroxaban 15 mg n = 24548	Dabigatran 110 mg n = 23665	Rivaroxaban 15 mg n = 15131	Dabigatran 110 mg n = 15131	Crude	Adjusted	Matched
At least one medical visit, n (%)	**24463 (99.7)**	**23549 (99.5)**	**15081 (99.7)**	**15066 (99.6)**			
Number per patient					6.7	-0.5	1.0
Mean (± SD)	31.8 (20.4)	30.5 (20.2)	31.1 (19.3)	30.9 (19.5)			
Median	28.0	27.0	27.0	27.0			
[p25% - p75%]	[18.0;41.0]	[18.0;39.0]	[18.0;40.0]	[18.0;40.0]			
At least one general practitioner visit, n (%)	**24014 (97.8)**	**23118 (97.7)**	**14794 (97.8)**	**14796 (97.8)**			
Number per patient					5.0	-0.4	0.7
Mean (± SD)	23.6 (16.6)	22.8 (16.1)	23.2 (15.8)	23.1 (16.0)			
Median	20.0	20.0	20.0	20.0			
[p25% - p75%]	[13.0;30.0]	[13.0;29.0]	[13.0;30.0]	[13.0;30.0]			
At least one cardiologist visit, n (%)	**13954 (56.8)**	**12487 (52.8)**	**8399 (55.5)**	**8301 (54.9)**			
Number per patient					8.3	-0.6	0.8
Mean (± SD)	1.9 (3.2)	1.7 (2.9)	1.8 (3.0)	1.8 (3.0)			
Median	1.0	1.0	1.0	1.0			
[p25% - p75%]	[0.0;3.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]			
At least one other specialist visit, n (%)	**20916 (85.2)**	**19968 (84.4)**	**12845 (84.9)**	**12821 (84.7)**			
Number per patient					3.3	-0.3	0.8
Mean (± SD)	6.3 (8.3)	6.0 (8.8)	6.1 (7.7)	6.1 (7.7)			
Median	4.0	4.0	4.0	4.0			
[p25% - p75%]	[1.0;8.0]	[1.0;8.0]	[1.0;8.0]	[1.0;8.0]			
At least one lab test, n (%)	**24032 (97.9)**	**23058 (97.4)**	**14820 (97.9)**	**14819 (97.9)**			

10.2.5. Usage patterns of anticoagulant treatment during the 1-year follow-up period

Modalities of dispensing

For the rivaroxaban 20 mg versus VKA comparison in the specific population, the mean duration of the first drug exposure based on a grace period of 60 days was more than 8 months for both treatment groups for all and matched patients. The number of person-years (PY) during the first drug exposure was 29 391 and 77 480, respectively for all rivaroxaban 20 mg and VKA patients, but close for matched patients, 21 921 and 22 786 PY, respectively, with a medication possession ratio (MPR) greater than 80% for more than 90% for all and matched patients for both treatment groups (**Table 24**; Appendix 1-4, Table 29).

With a grace period of 30 days, the mean duration was about 7.5 months for both treatment groups for all and matched patients, with 27 321 and 67 273 PY, respectively for all patients, and 20 372 and 19 538 PY, respectively for matched patients. MPR was greater than 80% for more than 95% for all and matched patients for both treatment groups (Appendix 1-13, Table 6). Similar results were found for the sensitive population (Appendix 1-9, Table 6).

For the rivaroxaban 20 mg and dabigatran 150 mg comparison in the specific population, the mean duration of the first drug exposure for the dabigatran 150 mg group was also of 8 months for all and matched patients. The number of PY during the first drug exposure was 29 405 and 11 101, respectively for all rivaroxaban 20 mg and dabigatran 150 mg patients, but close for matched patients, 10 613 and 10 160 PY, respectively, with a MPR greater than 80% for more than 95% for all and matched patients for both treatment groups (**Table 25**; Appendix 1-5, Table 29).

With a grace period of 30 days, the mean duration was about 7.5 months for both treatment groups for all and matched patients, with 27 332 and 10 252 PY, respectively, for all patients, and 9 869 and 9 392 PY, respectively for matched patients. MPR was greater than 80% for more than 95% for all and matched patients for both treatment groups (Appendix 1-14, Table 6). Similar results were found for the sensitive population (Appendix 1-10, Table 6).

For the reduced dose comparison, rivaroxaban 15 mg and VKA groups in the specific population, the mean duration of the first drug exposure was slightly less important with rivaroxaban 15 mg than VKA: 8 and 8.5 months for all patients, respectively, and 8 and 9 months for matched patients, respectively. The number of PY was 16 113 and 77 467, respectively for all rivaroxaban 15 mg and VKA patients, and 15 383 and 17 254 PY for matched patients, respectively. MPR was greater than 80% for more than 90% for all and matched patients for both treatment groups (**Table 26**; Appendix 1-6, Table 29).

With a grace period of 30 days, the mean duration was more than 7 months for both treatment groups for all and matched patients, with 14 861 and 67 260 PY, respectively, for all patients, and 14 192 and 15 070 PY, respectively for matched patients. MPR was greater than 80% for more than 95% for all and matched patients for both treatment groups (Appendix 1-15, Table 6). Similar results were found for the sensitive population (Appendix 1-11, Table 6).

For the rivaroxaban 15 mg and dabigatran 110 mg comparison in the specific population, the mean duration of the first drug exposure for the dabigatran 110 mg group was about 8 months for all and matched patients. The number of PY was 16 124 and 15 079, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients, and 10 045 and 9 596 PY for matched patients, respectively. MPR was greater than 80% for more than 90% for all and matched patients for both treatment groups (**Table 27**; Appendix 1-7, Table 29). With a grace period of 30 days, the mean duration was about 7 months for both treatment groups for all and matched patients, with 14 868 and 13 825 PY, respectively, for all patients, and 9 264 and 8 819 PY, respectively for matched patients. MPR was greater than 80% more than 95% for all and matched patients for both treatment groups (Appendix 1-16, Table 6). Similar results were found for the sensitive population (Appendix 1-12, Table 6).

Table 24. Rivaroxaban 20 mg and VKA drug exposure duration during follow-up, with a grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42480	**VKA n = 108656**	**Rivaroxaban 20 mg n = 31171**	**VKA n = 31171**
1st drug exposure duration per patient (in days)				
Mean (± SD)	252.7 (139.5)	260.5 (127.6)	256.9 (138.4)	267.0 (126.8)
Median	365.0	365.0	365.0	365.0
[p25% - p75%]	[101.0;365.0]	[135.0;365.0]	[107.0;365.0]	[146.0;365.0]
[Min - Max]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]
Person-years of the 1st drug exposure, n	29391	77480	21921	22786
Number of drug dispensing* per patient				
Mean (± SD)	9.1 (5.1)	7.9 (4.3)	9.3 (5.1)	8.3 (4.3)
Median	12.0	9.0	12.0	9.0
[p25% - p75%]	[4.0;13.0]	[4.0;12.0]	[4.0;14.0]	[4.0;12.0]
[Min - Max]	[1.0;29.0]	[1.0;27.0]	[1.0;29.0]	[1.0;23.0]
Number of defined daily doses* per patient				
Mean (± SD)	260.5 (145.5)	377.2 (249.8)	265.5 (144.7)	361.4 (238.0)
Median	336.0	360.0	336.0	350.0
[p25% - p75%]	[112.0;392.0]	[173.3;540.0]	[112.0;392.0]	[166.7;510.0]
[Min - Max]	[14.0;1148.0]	[10.0;2340.0]	[14.0;1148.0]	[10.0;1970.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	12 (0.0)	0 (0.0)	1 (0.0)
]20 - 40%]	121 (0.3)	269 (0.2)	94 (0.3)	42 (0.1)
]40 - 60%]	355 (0.8)	2031 (1.9)	246 (0.8)	548 (1.8)
]60 - 80%]	1698 (4.0)	6642 (6.1)	1240 (4.0)	2328 (7.5)
]80 - 100%[	14741 (34.7)	15455 (14.2)	10651 (34.2)	5894 (18.9)
100%	25565 (60.2)	84247 (77.5)	18940 (60.8)	22358 (71.7)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 25. Rivaroxaban 20 mg and dabigatran 150 mg drug exposure duration during follow-up, with a grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42514	**Dabigatran 150 mg n = 16834**	**Rivaroxaban 20 mg n = 15323**	**Dabigatran 150 mg n = 15323**
1st drug exposure duration per patient (in days)				
Mean (± SD)	252.6 (139.5)	240.9 (139.6)	253.0 (139.2)	242.2 (139.4)
Median	365.0	352.0	365.0	365.0
[p25% - p75%]	[101.0;365.0]	[91.0;365.0]	[101.0;365.0]	[92.0;365.0]
[Min - Max]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]
Person-years of the 1st drug exposure, n	29405	11101	10613	10160
Number of drug dispensing* per patient				
Mean (± SD)	9.1 (5.1)	8.3 (4.8)	9.1 (5.1)	8.3 (4.8)
Median	12.0	10.0	12.0	10.0
[p25% - p75%]	[4.0;13.0]	[3.0;13.0]	[4.0;13.0]	[3.0;13.0]
[Min - Max]	[1.0;29.0]	[1.0;30.0]	[1.0;22.0]	[1.0;30.0]
Number of defined daily doses* per patient				
Mean (± SD)	260.4 (145.5)	250.5 (146.6)	259.9 (144.6)	252.0 (146.4)
Median	336.0	300.0	336.0	300.0
[p25% - p75%]	[112.0;392.0]	[90.0;390.0]	[112.0;392.0]	[90.0;390.0]
[Min - Max]	[14.0;1148.0]	[30.0;930.0]	[14.0;764.0]	[30.0;930.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
]20 - 40%]	121 (0.3)	44 (0.3)	40 (0.3)	41 (0.3)
]40 - 60%]	355 (0.8)	150 (0.9)	114 (0.7)	134 (0.9)
]60 - 80%]	1700 (4.0)	622 (3.7)	598 (3.9)	549 (3.6)
]80 - 100%[	14757 (34.7)	4561 (27.1)	5492 (35.8)	4166 (27.2)
100%	25581 (60.2)	11457 (68.1)	9079 (59.3)	10433 (68.1)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 26. Rivaroxaban 15 mg and VKA drug exposure duration during follow-up, with a grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24529	**VKA n = 108639**	**Rivaroxaban 15 mg n = 23314**	**VKA n = 23314**
1st drug exposure duration per patient (in days)				
Mean (± SD)	239.9 (142.4)	260.4 (127.6)	241.0 (142.1)	270.3 (124.0)
Median	365.0	365.0	365.0	365.0
[p25% - p75%]	[82.0;365.0]	[135.0;365.0]	[83.0;365.0]	[154.0;365.0]
[Min - Max]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]
Person-years of the 1st drug exposure, n	16113	77467	15383	17254
Number of drug dispensing* per patient				
Mean (± SD)	8.6 (5.2)	7.9 (4.3)	8.6 (5.2)	8.1 (4.2)
Median	11.0	9.0	11.0	9.0
[p25% - p75%]	[3.0;13.0]	[4.0;12.0]	[3.0;13.0]	[4.0;12.0]
[Min - Max]	[1.0;24.0]	[1.0;27.0]	[1.0;24.0]	[1.0;27.0]
Number of defined daily doses* per patient				
Mean (± SD)	250.4 (151.2)	377.2 (249.8)	251.6 (151.0)	404.5 (253.5)
Median	322.0	360.0	336.0	390.0
[p25% - p75%]	[84.0;392.0]	[173.3;540.0]	[84.0;392.0]	[180.0;600.0]
[Min - Max]	[14.0;1120.0]	[10.0;2340.0]	[14.0;1120.0]	[10.0;2340.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	1 (0.0)	12 (0.0)	1 (0.0)	3 (0.0)
]20 - 40%]	119 (0.5)	269 (0.2)	110 (0.5)	33 (0.1)
]40 - 60%]	356 (1.5)	2030 (1.9)	339 (1.5)	355 (1.5)
]60 - 80%]	1034 (4.2)	6641 (6.1)	973 (4.2)	1283 (5.5)
]80 - 100%[	7328 (29.9)	15453 (14.2)	6969 (29.9)	2947 (12.6)
100%	15691 (64.0)	84234 (77.5)	14922 (64.0)	18693 (80.2)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 27. Rivaroxaban 15 mg and dabigatran 110 mg drug exposure duration during follow-up, with a grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24548	**Dabigatran 110 mg n = 23665**	**Rivaroxaban 15 mg n = 15131**	**Dabigatran 110 mg n = 15131**
1st drug exposure duration per patient (in days)				
Mean (± SD)	239.9 (142.4)	232.7 (142.1)	242.5 (141.7)	231.7 (142.8)
Median	365.0	302.0	365.0	301.0
[p25% - p75%]	[82.0;365.0]	[80.0;365.0]	[84.0;365.0]	[77.0;365.0]
[Min - Max]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]	[1.0;365.0]
Person-years of the 1st drug exposure, n	16124	15079	10045	9596
Number of drug dispensing* per patient				
Mean (± SD)	8.6 (5.2)	8.1 (5.0)	8.7 (5.2)	8.1 (5.0)
Median	11.0	10.0	11.0	10.0
[p25% - p75%]	[3.0;13.0]	[3.0;13.0]	[3.0;13.0]	[3.0;13.0]
[Min - Max]	[1.0;24.0]	[1.0;24.0]	[1.0;24.0]	[1.0;24.0]
Number of defined daily doses* per patient				
Mean (± SD)	250.4 (151.2)	241.2 (148.6)	253.0 (150.9)	240.2 (149.2)
Median	322.0	270.0	336.0	270.0
[p25% - p75%]	[84.0;392.0]	[90.0;390.0]	[84.0;392.0]	[90.0;390.0]
[Min - Max]	[14.0;1120.0]	[5.0;690.0]	[14.0;1120.0]	[5.0;660.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	1 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)
]20 - 40%]	120 (0.5)	80 (0.3)	76 (0.5)	49 (0.3)
]40 - 60%]	356 (1.5)	364 (1.5)	218 (1.4)	255 (1.7)
]60 - 80%]	1038 (4.2)	1243 (5.3)	625 (4.1)	787 (5.2)
]80 - 100%[	7328 (29.9)	5764 (24.4)	4565 (30.2)	3666 (24.2)
100%	15705 (64.0)	16212 (68.5)	9647 (63.8)	10373 (68.6)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Discontinuation and switch

The 1-year cumulative incidence of discontinuation or switch, based on 60-day grace period, was 43.1% (95% CI [42.6; 43.5]) with rivaroxaban 20 mg in the specific population (about 2/3 of discontinuations and 1/3 of switches), and 40.4% [40.1; 40.7] with VKA (3/4 of discontinuations and 1/4 of switches) (**Figure 5** and **Table 28**; Appendix 1-4, Tables 36 and 37, Figures 5 to 10). Switches were mainly towards VKA (48%), heparins (22%), dabigatran (19%), or apixaban (11%) for the rivaroxaban 20 mg group, and towards rivaroxaban (39%), heparins (35%), dabigatran (15%), or apixaban (11%) for the VKA group (**Table 28;** Appendix 1-4, Table 36).

For the specific population with a grace period of 30 days, the 1-year cumulative incidence of discontinuation or switch was more important with 51.1% [50.6; 51.6] for rivaroxaban 20 mg (69% discontinuations and 31% switches) and 58.2% [57.9; 58.5] for VKA (82% discontinuations and 18% switches) (Appendix 1-13, Tables 7 and 8, Figures 8 to 13). Similar results were found for switch drugs whatever the grace period duration (Appendix 1-13, Table 7), as well as for the sensitive population with a 60-day grace period (Appendix 1-9, Tables 7 and 8, Figures 8 to 13).

For rivaroxaban 20 mg and dabigatran 150 mg in the specific population, the 1-year cumulative incidence of discontinuation or switch, based on 60-day grace period, was more important for dabigatran 150 mg with 49.7% [48.9; 50.4] (58% discontinuations and 42% switches) (**Figure 6** and **Table 29**; Appendix 1-5, Tables 36 and 37, Figures 5 to 10). Switches were mainly towards VKA (41%), rivaroxaban (35%), or heparins (17%) for the dabigatran 150 mg group (**Table 29;** Appendix 1-5, Table 36).

With a grace period of 30 days, the 1-year cumulative incidence of discontinuation or switch was more important with 58.1% [57.3; 58.8] for dabigatran 150 mg (about 2/3 discontinuations and 1/3 switches) (Appendix 1-14, Tables 7 and 8, Figures 8 to 13). Similar results were found for switch drugs whatever the grace period duration (Appendix 1-14, Table 7), as well as for the sensitive population with a 60-day grace period (Appendix 1-10, Tables 7 and 8, Figures 8 to 13).

For the reduced dose comparison, rivaroxaban 15 mg and VKA groups in the specific population, the 1-year cumulative incidence of discontinuation or switch, based on 60-day grace period, was 44.6% [44.0; 45.3] with rivaroxaban 15 mg (57% discontinuations and 43% switches), and 40.4% [40.1; 40.7] with VKA (3/4 of discontinuations and 1/4 of switches) (**Figure 7** and **Table 30**; Appendix 1-6, Tables 36 and 37, Figures 5 to 10). Switches were mainly towards VKA (55%), heparins (21%), dabigatran (13%), or apixaban (11%) for the rivaroxaban 15 mg group, and towards rivaroxaban (39%), heparins (35%), dabigatran (15%), or apixaban (11%) for the VKA group (**Table 30;** Appendix 1-6, Table 36).

With a grace period of 30 days, the 1-year cumulative incidence of discontinuation or switch was more important with 53.6% [53.0; 54.3] for rivaroxaban 15 mg (2/3 discontinuations and 1/3 switches) and 58.2% [57.9; 58.5] for VKA (82% discontinuations and 18% switches) (Appendix 1-15, Tables 7 and 8, Figures 8 to 13). Similar results were found for switch drugs whatever the grace period duration (Appendix 1-15, Table 7), as well as for the sensitive population with a 60-day grace period (Appendix 1-11, Table 7, Figures 8 to 13).

For dabigatran 110 mg in the specific population, the 1-year cumulative incidence of discontinuation or switch, based on 60-day grace period, was 49.4% [48.8; 50.1] (50% discontinuations and 50% switches) (**Figure 8** and **Table 31**; Appendix 1-7, Tables 36 and 37, Figures 5 to 10). Switches were mainly towards VKA (48%), rivaroxaban (29%), or heparins (16%) for the dabigatran 110 mg group (**Table 31;** Appendix 1-7, Table 36).

With a grace period of 30 days, the 1-year cumulative incidence of discontinuation or switch was more important with 58.3% [57.6; 58.9] for dabigatran 110 mg (60% discontinuations and 40% switches) (Appendix 1-16, Tables 7 and 8, Figures 8 to 13). Similar results were found for switch drugs whatever the grace period duration (Appendix 1-16, Table 7), as well as for the sensitive population with a 60-day grace period (Appendix 1-12, Table 7, Figures 8 to 13).

Table 28. Discontinuation or switch of initial treatment during the 1-year follow-up period in rivaroxaban 20 mg and VKA groups, grace period of 60 days

	All patients				Matched patients			
	Rivaroxaban 20 mg n = 42480		VKA n = 108656		Rivaroxaban 20 mg n = 31171		VKA n = 31171	
Discontinuation or switch of initial treatment, n (%)	**18074**	**(42.5)**	**40716**	**(37.5)**	**12633**	**(40.5)**	**12641**	**(40.6)**
[95% CI]	[42.1 ; 43.0]		[37.2 ; 37.8]		[40.0 ; 41.1]		[40.0 ; 41.1]	
Discontinuation of initial treatment, n (%)	**11291**	**(26.6)**	**30537**	**(28.1)**	**7449**	**(23.9)**	**8371**	**(26.9)**
[95% CI]	[26.2 ; 27.0]		[27.8 ; 28.4]		[23.4 ; 24.4]		[26.4 ; 27.3]	
Switch of initial treatment, n (%)	**6783**	**(16.0)**	**10179**	**(9.4)**	**5184**	**(16.6)**	**4270**	**(13.7)**
[95% CI]	[15.6 ; 16.3]		[9.2 ; 9.5]		[16.2 ; 17.0]		[13.3 ; 14.1]	
Drugs of switch of initial treatment [1], n (%)								
VKA	3264	(48.1)	0	(0.0)	2586	(49.9)	0	(0.0)
Heparin group	1483	(21.9)	3568	(35.1)	1150	(22.2)	1180	(27.6)
Dabigatran	1272	(18.8)	1509	(14.8)	892	(17.2)	717	(16.8)
Rivaroxaban	0	(0.0)	3960	(38.9)	0	(0.0)	1856	(43.5)
Apixaban	764	(11.3)	1142	(11.2)	556	(10.7)	517	(12.1)

[1] *Among concerned patients*

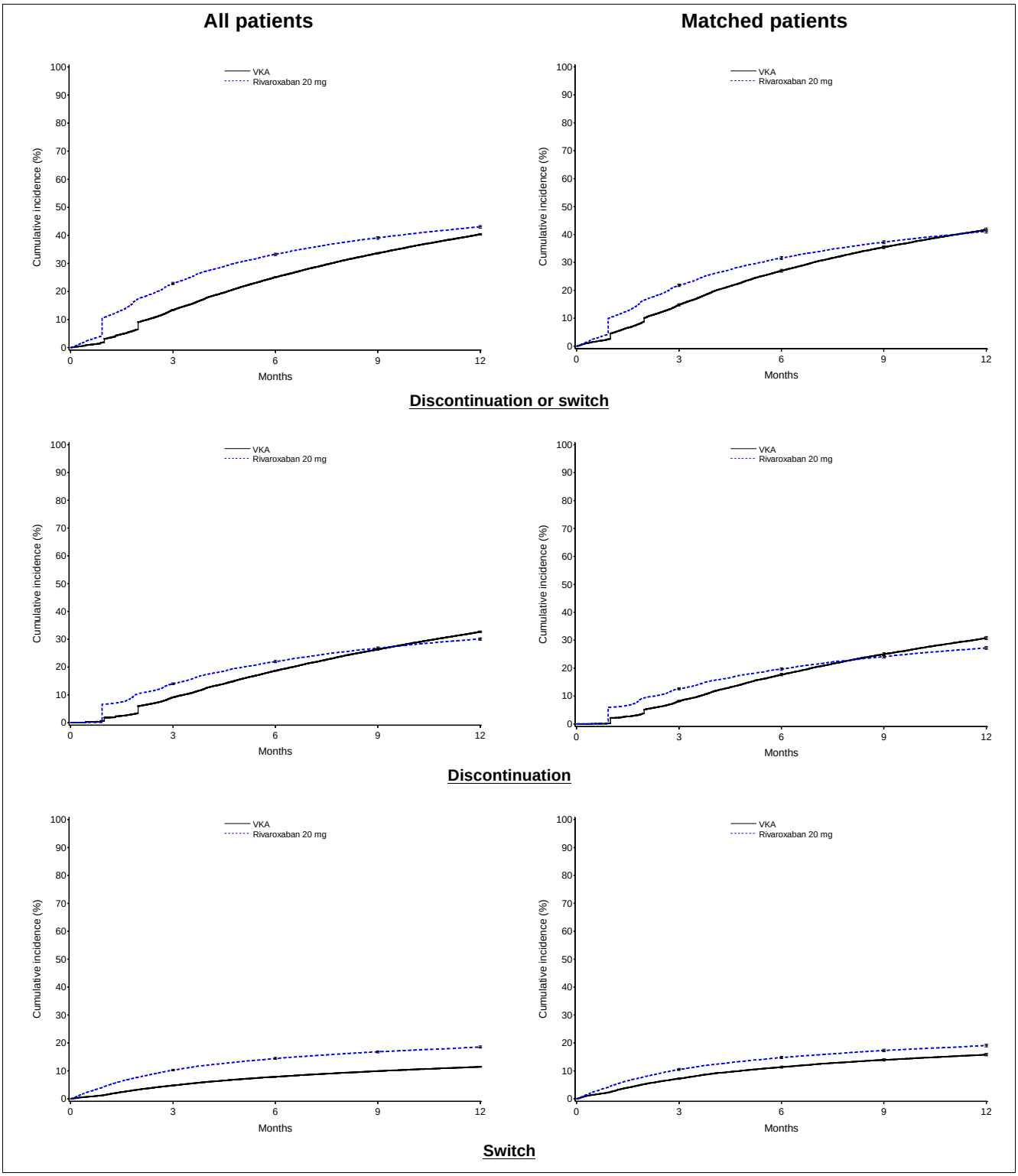


Figure 5. One-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 20 mg and VKA groups, grace period of 60 days

Table 29. Discontinuation or switch of initial treatment during the 1-year follow-up period in rivaroxaban 20 mg and dabigatran 150 mg groups, grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42514	Dabigatran 150 mg n = 16834	Rivaroxaban 20 mg n = 15323	Dabigatran 150 mg n = 15323
Discontinuation or switch of initial treatment, n (%)	**18100 (42.6)**	**8299 (49.3)**	**6620 (43.2)**	**7469 (48.7)**
[95% CI]	[42.1 ; 43.0]	[48.5 ; 50.1]	[42.4 ; 44.0]	[48.0 ; 49.5]
Discontinuation of initial treatment, n (%)	**11312 (26.6)**	**4819 (28.6)**	**4189 (27.3)**	**4265 (27.8)**
[95% CI]	[26.2 ; 27.0]	[27.9 ; 29.3]	[26.6 ; 28.0]	[27.1 ; 28.5]
Switch of initial treatment, n (%)	**6788 (16.0)**	**3480 (20.7)**	**2431 (15.9)**	**3204 (20.9)**
[95% CI]	[15.6 ; 16.3]	[20.1 ; 21.3]	[15.3 ; 16.4]	[20.3 ; 21.6]
Drugs of switch of initial treatment [1], n (%)				
VKA	3266 (48.1)	1435 (41.2)	1142 (47.0)	1329 (41.5)
Heparin group	1483 (21.8)	590 (17.0)	525 (21.6)	539 (16.8)
Dabigatran	1274 (18.8)	0 (0.0)	585 (24.1)	0 (0.0)
Rivaroxaban	0 (0.0)	1214 (34.9)	0 (0.0)	1108 (34.6)
Apixaban	765 (11.3)	241 (6.9)	179 (7.4)	228 (7.1)

[1] *Among concerned patients*

Table 30. Discontinuation or switch of initial treatment during the 1-year follow-up period in rivaroxaban 15 mg and VKA groups, grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24529	VKA n = 108639	Rivaroxaban 15 mg n = 23314	VKA n = 23314
Discontinuation or switch of initial treatment, n (%)	**10543 (43.0)**	**40715 (37.5)**	**9923 (42.6)**	**8370 (35.9)**
[95% CI]	[42.4 ; 43.6]	[37.2 ; 37.8]	[41.9 ; 43.2]	[35.3 ; 36.5]
Discontinuation of initial treatment, n (%)	**5979 (24.4)**	**30537 (28.1)**	**5590 (24.0)**	**6072 (26.0)**
[95% CI]	[23.8 ; 24.9]	[27.8 ; 28.4]	[23.4 ; 24.5]	[25.5 ; 26.6]
Switch of initial treatment, n (%)	**4564 (18.6)**	**10178 (9.4)**	**4333 (18.6)**	**2298 (9.9)**
[95% CI]	[18.1 ; 19.1]	[9.2 ; 9.5]	[18.1 ; 19.1]	[9.5 ; 10.2]
Drugs of switch of initial treatment [1], n (%)				
VKA	2516 (55.1)	0 (0.0)	2395 (55.3)	0 (0.0)
Heparin group	946 (20.7)	3568 (35.1)	897 (20.7)	672 (29.2)
Dabigatran	580 (12.7)	1509 (14.8)	537 (12.4)	369 (16.1)
Rivaroxaban	0 (0.0)	3959 (38.9)	0 (0.0)	952 (41.4)
Apixaban	522 (11.4)	1142 (11.2)	504 (11.6)	305 (13.3)

[1] *Among concerned patients*

Table 31. Discontinuation or switch of initial treatment during the 1-year follow-up period in rivaroxaban 15 mg and dabigatran 110 mg groups, grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24548	Dabigatran 110 mg n = 23665	Rivaroxaban 15 mg n = 15131	Dabigatran 110 mg n = 15131
Discontinuation or switch of initial treatment, n (%)	**10554 (43.0)**	**11322 (47.8)**	**6460 (42.7)**	**7192 (47.5)**
[95% CI]	[42.4 ; 43.6]	[47.2 ; 48.5]	[41.9 ; 43.5]	[46.7 ; 48.3]
Discontinuation of initial treatment, n (%)	**5985 (24.4)**	**5658 (23.9)**	**3609 (23.9)**	**3447 (22.8)**
[95% CI]	[23.8 ; 24.9]	[23.4 ; 24.5]	[23.2 ; 24.5]	[22.1 ; 23.4]
Switch of initial treatment, n (%)	**4569 (18.6)**	**5664 (23.9)**	**2851 (18.8)**	**3745 (24.8)**
[95% CI]	[18.1 ; 19.1]	[23.4 ; 24.5]	[18.2 ; 19.5]	[24.1 ; 25.4]
Drugs of switch of initial treatment [1], n (%)				
VKA	2517 (55.1)	2747 (48.5)	1620 (56.8)	1790 (47.8)
Heparin group	946 (20.7)	923 (16.3)	564 (19.8)	619 (16.5)
Dabigatran	582 (12.7)	0 (0.0)	418 (14.7)	0 (0.0)
Rivaroxaban	0 (0.0)	1641 (29.0)	0 (0.0)	1045 (27.9)
Apixaban	524 (11.5)	353 (6.2)	249 (8.7)	291 (7.8)

[1] *Among concerned patients*

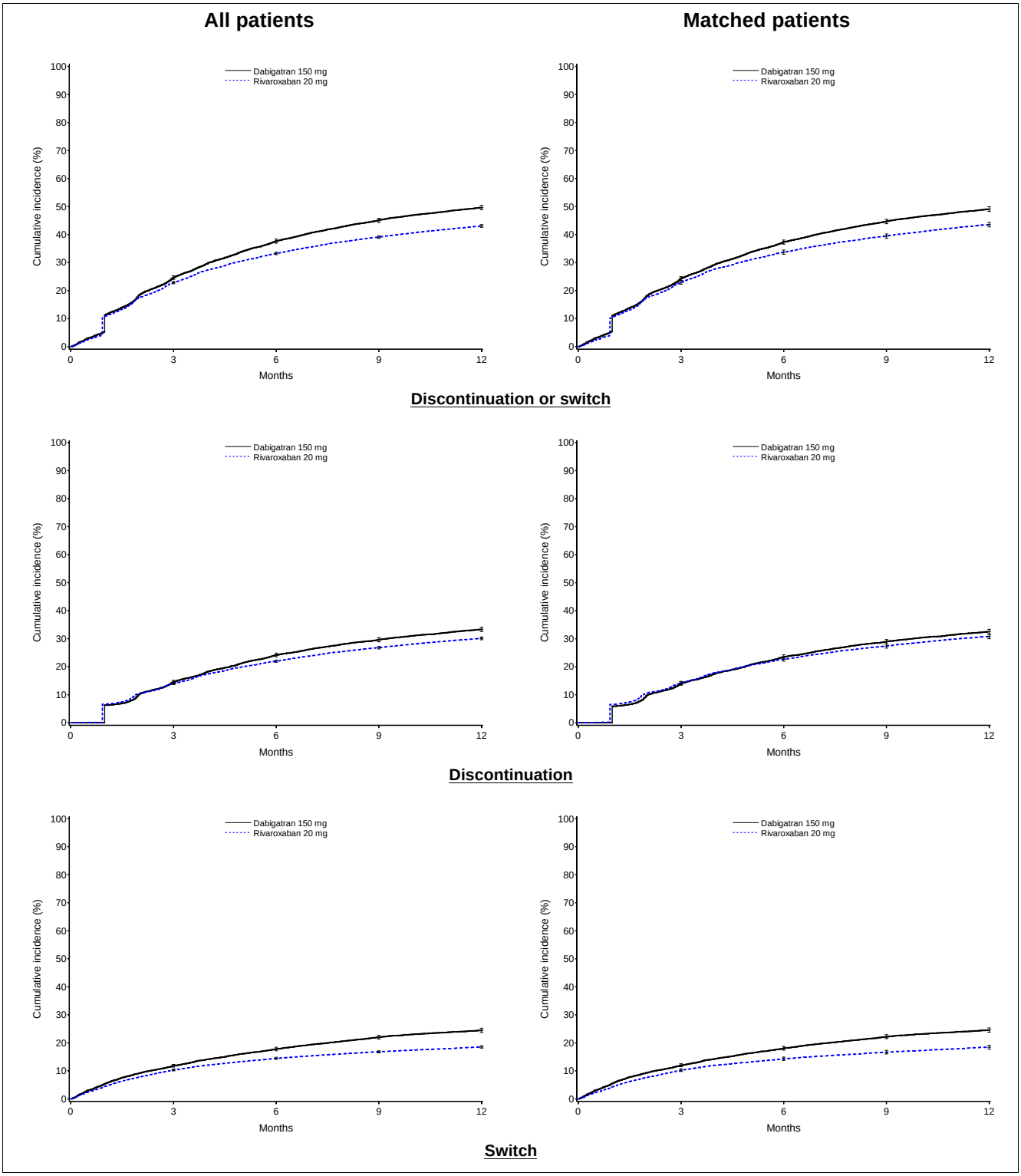


Figure 6. One-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 20 mg and dabigatran 150 mg groups, grace period of 60 days

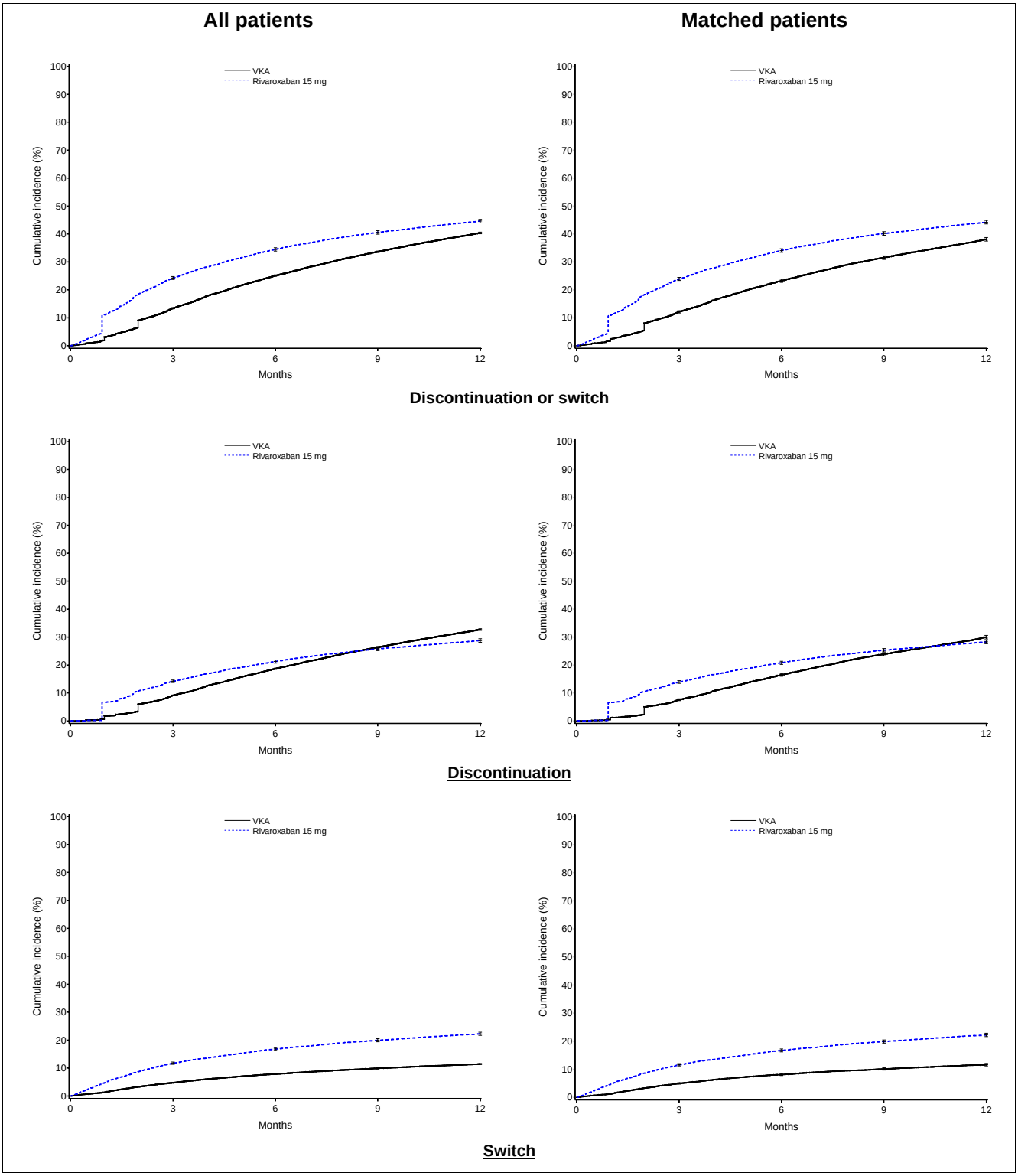


Figure 7. One-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 15 mg and VKA groups, grace period of 60 days

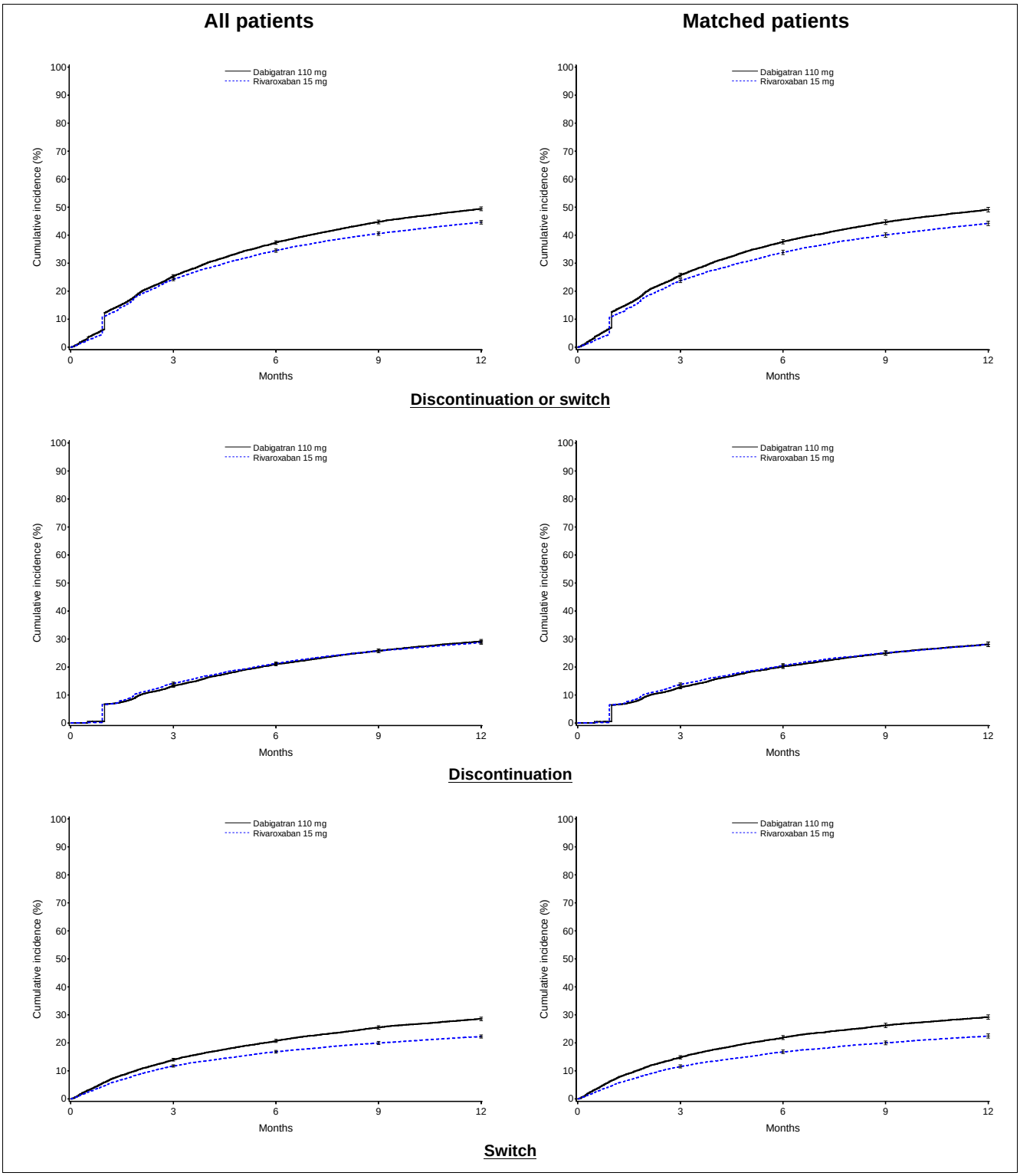


Figure 8. One-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 15 mg and dabigatran 110 mg groups, grace period of 60 days

10.2.6. Healthcare resource use during the drug exposure on the 1-year follow-up period

Hospitalisations, medical visits and lab tests

About 6 patients out of 10 in the rivaroxaban 20 mg group (57%) and in the VKA group (62%) for the specific population had at least one hospitalisation during the drug exposure for rivaroxaban, dabigatran, and VKA on the 1-year follow-up period. The most frequent primary diagnosis was diseases of the circulatory system (38% and 35%, respectively), followed by ill-defined disorders: factors influencing health status and contact with health services (9% and 13%, respectively) or symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (6% and 11%, respectively) (**Table 32**; Appendix 1-4, Table 30).

Nearly all patients had physician visit reimbursements during the drug exposure on the 1-year follow-up period, with a median of 9 visits in the rivaroxaban 20 mg group and 10 in the VKA group: medians of 5 and 8 visits with GP, respectively, of 1 and 0 visit with a cardiologist, and of 1 visit with another specialist (**Table 32**, Appendix 1-4, Tables 33 and 34). Lab tests were also widely used (**Table 32**) and concerned 87% of patients in the rivaroxaban 20 mg group, and 97% of those in the VKA group. The detail by type of lab test (NABM codes) is presented in Appendix 1-4, Table 35.

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, hospitalisations, medical visits and lab tests in the dabigatran 150 mg group during the drug exposure on the 1-year follow-up period were almost the same as for rivaroxaban 20 mg (**Table 33**, Appendix 1-5, Tables 33 to 35).

For the reduced dose comparisons, rivaroxaban 15 mg and VKA groups, rivaroxaban 15 mg and dabigatran 110 mg groups, similar results were found (**Tables 34 and 35**; Appendices 1-6 and 1-7, Tables 33 to 35).

Table 32. Hospitalisations, medicals visits and lab tests during the drug exposure on the 1-year follow-up period in rivaroxaban 20 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42480	**VKA n = 108656**	**Rivaroxaban 20 mg n = 31171**	**VKA n = 31171**
At least one hospitalisation, n (%)	**24233 (57.0)**	**67475 (62.1)**	**17699 (56.8)**	**18975 (60.9)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	16286 (38.3)	37547 (34.6)	11293 (36.2)	12243 (39.3)
Factors influencing health status and contact with health services	3613 (8.5)	14617 (13.5)	2801 (9.0)	3606 (11.6)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2483 (5.8)	11735 (10.8)	1984 (6.4)	2488 (8.0)
At least one medical visit, n (%)	**41047 (96.6)**	**105428 (97.0)**	**30187 (96.8)**	**30557 (98.0)**
Mean per patient, mean (± SD)	10.3 (8.4)	12.1 (10.0)	10.5 (8.2)	11.9 (8.8)
Median per patient	9.0	10.0	9.0	10.0
[p25% - p75%]	[4.0;14.0]	[5.0;16.0]	[5.0;14.0]	[6.0;16.0]
At least one general practitioner visit, n (%)	**38818 (91.4)**	**102172 (94.0)**	**28742 (92.2)**	**29544 (94.8)**
Mean per patient, mean (± SD)	6.7 (6.1)	9.1 (7.6)	7.0 (6.1)	8.4 (6.7)
Median per patient	5.0	8.0	6.0	7.0
[p25% - p75%]	[2.0;9.0]	[4.0;13.0]	[3.0;10.0]	[4.0;12.0]
At least one cardiologist visit, n (%)	**26106 (61.5)**	**46362 (42.7)**	**18102 (58.1)**	**17614 (56.5)**
Mean per patient, mean (± SD)	1.7 (2.4)	1.1 (2.3)	1.6 (2.3)	1.6 (2.5)
Median per patient	1.0	0.0	1.0	1.0
[p25% - p75%]	[0.0;3.0]	[0.0;1.0]	[0.0;2.0]	[0.0;2.0]
At least one other specialist visit, n (%)	**25353 (59.7)**	**55972 (51.5)**	**18270 (58.6)**	**18326 (58.8)**
Mean per patient, mean (± SD)	1.9 (3.2)	1.9 (5.1)	1.9 (3.2)	1.9 (3.4)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]
At least one lab test, n (%)	**36886 (86.8)**	**105618 (97.2)**	**27285 (87.5)**	**30579 (98.1)**

Table 33. Hospitalisations, medicals visits and lab tests during the drug exposure on the 1-year follow-up period in rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42514	**Dabigatran 150 mg n = 16834**	**Rivaroxaban 20 mg n = 15323**	**Dabigatran 150 mg n = 15323**
At least one hospitalisation, n (%)	**24247 (57.0)**	**10070 (59.8)**	**8555 (55.8)**	**9195 (60.0)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	16300 (38.3)	7819 (46.4)	6023 (39.3)	7174 (46.8)
At least one medical visit, n (%)	**41081 (96.6)**	**16251 (96.5)**	**14805 (96.6)**	**14820 (96.7)**
Mean per patient, mean (± SD)	10.3 (8.4)	9.6 (7.6)	9.8 (7.6)	9.6 (7.5)
Median per patient	9.0	8.0	8.0	8.0
[p25% - p75%]	[4.0;14.0]	[4.0;13.0]	[4.0;14.0]	[4.0;13.0]
At least one general practitioner visit, n (%)	**38848 (91.4)**	**15383 (91.4)**	**13974 (91.2)**	**14034 (91.6)**
Mean per patient, mean (± SD)	6.7 (6.1)	6.2 (5.5)	6.3 (5.4)	6.2 (5.4)
Median per patient	5.0	5.0	5.0	5.0
[p25% - p75%]	[2.0;9.0]	[2.0;9.0]	[2.0;9.0]	[2.0;9.0]
At least one cardiologist visit, n (%)	**26140 (61.5)**	**10617 (63.1)**	**9662 (63.1)**	**9834 (64.2)**
Mean per patient, mean (± SD)	1.7 (2.4)	1.8 (2.3)	1.8 (2.4)	1.8 (2.3)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;3.0]	[0.0;3.0]	[0.0;3.0]	[0.0;3.0]
At least one other specialist visit, n (%)	**25371 (59.7)**	**9620 (57.1)**	**9028 (58.9)**	**8810 (57.5)**
Mean per patient, mean (± SD)	1.9 (3.2)	1.6 (2.7)	1.8 (2.7)	1.6 (2.7)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]
At least one lab test, n (%)	**36912 (86.8)**	**14396 (85.5)**	**13262 (86.5)**	**13173 (86.0)**

Table 34. Hospitalisations, medicals visits and lab tests during the drug exposure on the 1-year follow-up period in rivaroxaban 15 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24529	**VKA n = 108639**	**Rivaroxaban 15 mg n = 23314**	**VKA n = 23314**
At least one hospitalisation, n (%)	**13574 (55.3)**	**67467 (62.1)**	**12901 (55.3)**	**14240 (61.1)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	7300 (29.8)	37543 (34.6)	6887 (29.5)	8117 (34.8)
Factors influencing health status and contact with health services	2020 (8.2)	14617 (13.5)	1930 (8.3)	2465 (10.6)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1997 (8.1)	11734 (10.8)	1914 (8.2)	2309 (9.9)
At least one medical visit, n (%)	**23686 (96.6)**	**105411 (97.0)**	**22504 (96.5)**	**22834 (97.9)**
Mean per patient, mean (± SD)	10.6 (8.6)	12.1 (10.0)	10.6 (8.6)	12.8 (9.5)
Median per patient	9.0	10.0	9.0	11.0
[p25% - p75%]	[4.0;15.0]	[5.0;16.0]	[4.0;15.0]	[6.0;17.0]
At least one general practitioner visit, n (%)	**22642 (92.3)**	**102153 (94.0)**	**21532 (92.4)**	**22173 (95.1)**
Mean per patient, mean (± SD)	7.4 (6.7)	9.1 (7.6)	7.5 (6.7)	9.4 (7.6)
Median per patient	6.0	8.0	6.0	8.0
[p25% - p75%]	[3.0;11.0]	[4.0;13.0]	[3.0;11.0]	[4.0;13.0]
At least one cardiologist visit, n (%)	**13002 (53.0)**	**46347 (42.7)**	**12127 (52.0)**	**12553 (53.8)**
Mean per patient, mean (± SD)	1.4 (2.4)	1.1 (2.3)	1.4 (2.3)	1.5 (2.6)
Median per patient	1.0	0.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;1.0]	[0.0;2.0]	[0.0;2.0]
At least one other specialist visit, n (%)	**13051 (53.2)**	**55962 (51.5)**	**12323 (52.9)**	**13227 (56.7)**
Mean per patient, mean (± SD)	1.7 (3.0)	1.9 (5.1)	1.7 (3.0)	1.9 (3.5)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]
At least one lab test, n (%)	**21534 (87.8)**	**105601 (97.2)**	**20477 (87.8)**	**22836 (97.9)**

Table 35. Hospitalisations, medicals visits and lab tests during the drug exposure on the 1-year follow-up period in rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24548	Dabigatran 110 mg n = 23665	Rivaroxaban 15 mg n = 15131	Dabigatran 110 mg n = 15131
At least one hospitalisation, n (%)	**13586 (55.3)**	**13000 (54.9)**	**8246 (54.5)**	**8366 (55.3)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	7303 (29.7)	7467 (31.6)	4347 (28.7)	4789 (31.7)
At least one medical visit, n (%)	**23705 (96.6)**	**22838 (96.5)**	**14608 (96.5)**	**14641 (96.8)**
Mean per patient, mean (± SD)	10.6 (8.6)	10.1 (8.1)	10.5 (8.4)	10.1 (8.2)
Median per patient	9.0	8.0	9.0	8.0
[p25% - p75%]	[4.0;15.0]	[4.0;14.0]	[4.0;15.0]	[4.0;14.0]
At least one general practitioner visit, n (%)	**22660 (92.3)**	**21793 (92.1)**	**13983 (92.4)**	**13968 (92.3)**
Mean per patient, mean (± SD)	7.4 (6.7)	7.1 (6.3)	7.4 (6.5)	7.1 (6.2)
Median per patient	6.0	6.0	6.0	6.0
[p25% - p75%]	[3.0;11.0]	[2.0;10.0]	[3.0;11.0]	[2.0;10.0]
At least one cardiologist visit, n (%)	**13026 (53.1)**	**12156 (51.4)**	**7947 (52.5)**	**8051 (53.2)**
Mean per patient, mean (± SD)	1.4 (2.4)	1.4 (2.2)	1.4 (2.3)	1.4 (2.2)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]
At least one other specialist visit, n (%)	**13073 (53.3)**	**12152 (51.4)**	**8054 (53.2)**	**7815 (51.6)**
Mean per patient, mean (± SD)	1.7 (3.0)	1.6 (3.1)	1.7 (3.0)	1.6 (3.1)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]	[0.0;2.0]
At least one lab test, n (%)	**21554 (87.8)**	**20483 (86.6)**	**13289 (87.8)**	**13127 (86.8)**

Drug dispensing

The four most frequent drugs dispensed (first level of the ATC classification) during the drug exposure on the 1-year follow-up period for the specific population were for: blood and blood forming organs, cardiovascular system, nervous system, and alimentary tract and metabolism. All patients in rivaroxaban 20 mg and VKA groups had a dispensing of antithrombotic agents (first anticoagulant dispensing included) (**Table 36**; Appendix 1-4, Table 31). Specific drug dispensing (antithrombotic agents and antiarrhythmics) were more frequent in the rivaroxaban 20 mg group than the VKA group: median number of specific drug dispensing of 12 and 9, respectively, with more than half of patients and more than one third with at least 11 dispensing, respectively (Appendix 1-4, Table 32).

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, similar results were found for two groups (**Table 37**; Appendix 1-5, Table 31). The median number of specific drug dispensing was slightly more important in the rivaroxaban 20 mg group than the dabigatran 150 mg group, 12 and 10, respectively (Appendix 1-5, Table 32).

For the reduced dose comparison, rivaroxaban 15 mg and VKA groups, the four most frequent drugs dispensed (first level of the ATC classification) were also for: blood and blood forming organs, cardiovascular system, nervous system, and alimentary tract and metabolism (**Table 38**; Appendix 1-6, Table 31). Antithrombotic agent and antiarrhythmic dispensing were more frequent in the rivaroxaban 15 mg group than the VKA group: median number of specific drug dispensing of 11 and 9, respectively, with more than half of patients and more than one third with at least 11 dispensing, respectively (Appendix 1-6, Table 32).

For the rivaroxaban 15 mg and dabigatran 110 mg comparison, similar results were found for two groups (**Table 39**; Appendix 1-7, Table 31), and about half of patient had at least 11 specific drug dispensing (Appendix 1-7, Table 32).

Table 36. Drug dispensing during the drug exposure on the 1-year follow-up period in rivaroxaban 20 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42480	VKA n = 108656	Rivaroxaban 20 mg n = 31171	VKA n = 31171
At least one dispensing of drugs*, n (%)	**42480 (100.0)**	**108656 (100.0)**	**31171 (100.0)**	**31171 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	42480 (100.0)	108656 (100.0)	31171 (100.0)	31171 (100.0)
B01 - Antithrombotic agents	*42480 (100.0)*	*108656 (100.0)*	*31171 (100.0)*	*31171 (100.0)*
B03 - Antianemic preparations	*2658 (6.3)*	*19211 (17.7)*	*2253 (7.2)*	*3064 (9.8)*
B05 - Plasma substitutes and perfusion solutions	*2191 (5.2)*	*12425 (11.4)*	*1791 (5.7)*	*2298 (7.4)*
B02 - Antihemorrhagics	*371 (0.9)*	*6076 (5.6)*	*283 (0.9)*	*1474 (4.7)*
Cardiovascular system (C)	41028 (96.6)	105973 (97.5)	30146 (96.7)	30268 (97.1)
C07 - Beta blocking agents	*27680 (65.2)*	*71226 (65.6)*	*20323 (65.2)*	*20899 (67.0)*
C09 - Agents acting on the renin-angiotensin system	*22720 (53.5)*	*62241 (57.3)*	*17720 (56.8)*	*18120 (58.1)*
C01 - Cardiac therapy	*29505 (69.5)*	*67156 (61.8)*	*21055 (67.5)*	*20681 (66.3)*
C10 - Lipid modifying agents	*17340 (40.8)*	*49302 (45.4)*	*13762 (44.2)*	*14548 (46.7)*
C03 - Diuretics	*13244 (31.2)*	*64629 (59.5)*	*11153 (35.8)*	*13262 (42.5)*
C08 - Calcium channel blockers	*8896 (20.9)*	*31273 (28.8)*	*7129 (22.9)*	*7915 (25.4)*
C02 - Antihypertensives	*1749 (4.1)*	*7104 (6.5)*	*1467 (4.7)*	*1584 (5.1)*
Nervous system (N)	30939 (72.8)	92201 (84.9)	23327 (74.8)	24668 (79.1)
Alimentary tract and metabolism (A)	31030 (73.0)	94721 (87.2)	23683 (76.0)	24770 (79.5)
General antiinfectives for systemic use (J)	24501 (57.7)	73504 (67.6)	18694 (60.0)	19594 (62.9)
Dermatologicals (D)	17365 (40.9)	53631 (49.4)	13122 (42.1)	14103 (45.2)
Respiratory system (R)	18008 (42.4)	49076 (45.2)	13524 (43.4)	13841 (44.4)
Musculo-skeletal system (M)	16495 (38.8)	40879 (37.6)	12528 (40.2)	11620 (37.3)
Systemic hormonal prep, excluding sex hormones (H)	11759 (27.7)	33902 (31.2)	8910 (28.6)	8847 (28.4)
Sensory organs (S)	10493 (24.7)	32803 (30.2)	8120 (26.0)	8606 (27.6)
Genito urinary system and sex hormones (G)	7156 (16.8)	20676 (19.0)	5554 (17.8)	5570 (17.9)
Various (V)	6981 (16.4)	17590 (16.2)	4979 (16.0)	5496 (17.6)
Antineoplastic and immunomodulating agents (L)	1284 (3.0)	5562 (5.1)	1035 (3.3)	1323 (4.2)
Antiparasitic products (P)	1022 (2.4)	2781 (2.6)	728 (2.3)	698 (2.2)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 37. Drug dispensing during the drug exposure on the 1-year follow-up period in rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 42514	Dabigatran 150 mg n = 16834	Rivaroxaban 20 mg n = 15323	Dabigatran 150 mg n = 15323
At least one dispensing of drugs*, n (%)	**42514 (100.0)**	**16834 (100.0)**	**15323 (100.0)**	**15323 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	42514 (100.0)	16834 (100.0)	15323 (100.0)	15323 (100.0)
B01 - Antithrombotic agents	*42514 (100.0)*	*16834 (100.0)*	*15323 (100.0)*	*15323 (100.0)*
B03 - Antianemic preparations	*2659 (6.3)*	*721 (4.3)*	*760 (5.0)*	*633 (4.1)*
B05 - Plasma substitutes and perfusion solutions	*2190 (5.2)*	*778 (4.6)*	*662 (4.3)*	*709 (4.6)*
B02 - Antihemorrhagics	*371 (0.9)*	*109 (0.6)*	*119 (0.8)*	*99 (0.6)*
Cardiovascular system (C)	41061 (96.6)	16338 (97.1)	14846 (96.9)	14890 (97.2)
C07 - Beta blocking agents	*27695 (65.1)*	*11696 (69.5)*	*10131 (66.1)*	*10640 (69.4)*
C09 - Agents acting on the renin-angiotensin system	*22725 (53.5)*	*8935 (53.1)*	*8176 (53.4)*	*8164 (53.3)*
C01 - Cardiac therapy	*29538 (69.5)*	*12056 (71.6)*	*10821 (70.6)*	*11042 (72.1)*
C10 - Lipid modifying agents	*17339 (40.8)*	*6537 (38.8)*	*6196 (40.4)*	*6036 (39.4)*
C03 - Diuretics	*13242 (31.1)*	*4981 (29.6)*	*4342 (28.3)*	*4496 (29.3)*
C08 - Calcium channel blockers	*8897 (20.9)*	*3292 (19.6)*	*2961 (19.3)*	*3027 (19.8)*
C02 - Antihypertensives	*1747 (4.1)*	*661 (3.9)*	*594 (3.9)*	*613 (4.0)*
Nervous system (N)	30964 (72.8)	11594 (68.9)	10775 (70.3)	10528 (68.7)
Alimentary tract and metabolism (A)	31049 (73.0)	11596 (68.9)	10740 (70.1)	10580 (69.0)
General antiinfectives for systemic use (J)	24512 (57.7)	8682 (51.6)	8446 (55.1)	7952 (51.9)
Dermatologicals (D)	17376 (40.9)	6284 (37.3)	5951 (38.8)	5747 (37.5)
Respiratory system (R)	18021 (42.4)	6614 (39.3)	6299 (41.1)	5994 (39.1)
Musculo-skeletal system (M)	16505 (38.8)	6095 (36.2)	5761 (37.6)	5584 (36.4)
Systemic hormonal prep, excluding sex hormones (H)	11766 (27.7)	4145 (24.6)	3946 (25.8)	3754 (24.5)
Sensory organs (S)	10495 (24.7)	3635 (21.6)	3450 (22.5)	3355 (21.9)
Genito urinary system and sex hormones (G)	7161 (16.8)	2443 (14.5)	2273 (14.8)	2258 (14.7)
Various (V)	6991 (16.4)	2522 (15.0)	2490 (16.3)	2282 (14.9)
Antineoplastic and immunomodulating agents (L)	1284 (3.0)	386 (2.3)	361 (2.4)	341 (2.2)
Antiparasitic products (P)	1023 (2.4)	326 (1.9)	369 (2.4)	301 (2.0)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 38. Drug dispensing during the drug exposure on the 1-year follow-up period in rivaroxaban 15 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24529	**VKA n = 108639**	**Rivaroxaban 15 mg n = 23314**	**VKA n = 23314**
At least one dispensing of drugs*, n (%)	**24529 (100.0)**	**108639 (100.0)**	**23314 (100.0)**	**23314 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	24529 (100.0)	108639 (100.0)	23314 (100.0)	23314 (100.0)
B01 - Antithrombotic agents	*24529 (100.0)*	*108639 (100.0)*	*23314 (100.0)*	*23314 (100.0)*
B03 - Antianemic preparations	*2852 (11.6)*	*19208 (17.7)*	*2729 (11.7)*	*3384 (14.5)*
B05 - Plasma substitutes and perfusion solutions	*1813 (7.4)*	*12419 (11.4)*	*1736 (7.4)*	*2122 (9.1)*
B02 - Antihemorrhagics	*239 (1.0)*	*6075 (5.6)*	*229 (1.0)*	*1275 (5.5)*
Cardiovascular system (C)	23693 (96.6)	105956 (97.5)	22537 (96.7)	22763 (97.6)
C07 - Beta blocking agents	*14761 (60.2)*	*71215 (65.6)*	*14098 (60.5)*	*14973 (64.2)*
C09 - Agents acting on the renin-angiotensin system	*13678 (55.8)*	*62226 (57.3)*	*13102 (56.2)*	*13801 (59.2)*
C01 - Cardiac therapy	*15945 (65.0)*	*67145 (61.8)*	*15093 (64.7)*	*15161 (65.0)*
C10 - Lipid modifying agents	*10092 (41.1)*	*49297 (45.4)*	*9704 (41.6)*	*10357 (44.4)*
C03 - Diuretics	*11924 (48.6)*	*64617 (59.5)*	*11460 (49.2)*	*12897 (55.3)*
C08 - Calcium channel blockers	*6339 (25.8)*	*31267 (28.8)*	*6089 (26.1)*	*6752 (29.0)*
C02 - Antihypertensives	*1331 (5.4)*	*7104 (6.5)*	*1285 (5.5)*	*1458 (6.3)*
Nervous system (N)	19184 (78.2)	92183 (84.9)	18271 (78.4)	19590 (84.0)
Alimentary tract and metabolism (A)	19853 (80.9)	94702 (87.2)	18915 (81.1)	19859 (85.2)
General antiinfectives for systemic use (J)	15095 (61.5)	73487 (67.6)	14410 (61.8)	16014 (68.7)
Dermatologicals (D)	10960 (44.7)	53619 (49.4)	10435 (44.8)	11396 (48.9)
Respiratory system (R)	10248 (41.8)	49072 (45.2)	9756 (41.8)	10618 (45.5)
Musculo-skeletal system (M)	9744 (39.7)	40868 (37.6)	9266 (39.7)	9256 (39.7)
Systemic hormonal prep, excluding sex hormones (H)	7430 (30.3)	33890 (31.2)	7050 (30.2)	7341 (31.5)
Sensory organs (S)	7483 (30.5)	32792 (30.2)	7108 (30.5)	7843 (33.6)
Genito urinary system and sex hormones (G)	4676 (19.1)	20672 (19.0)	4455 (19.1)	4600 (19.7)
Various (V)	3069 (12.5)	17587 (16.2)	2898 (12.4)	3369 (14.5)
Antineoplastic and immunomodulating agents (L)	1025 (4.2)	5561 (5.1)	984 (4.2)	1190 (5.1)
Antiparasitic products (P)	497 (2.0)	2780 (2.6)	466 (2.0)	543 (2.3)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

Table 39. Drug dispensing during the drug exposure on the 1-year follow-up period in rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 24548	**Dabigatran 110 mg n = 23665**	**Rivaroxaban 15 mg n = 15131**	**Dabigatran 110 mg n = 15131**
At least one dispensing of drugs*, n (%)	**24548 (100.0)**	**23665 (100.0)**	**15131 (100.0)**	**15131 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	24548 (100.0)	23665 (100.0)	15131 (100.0)	15131 (100.0)
B01 - Antithrombotic agents	*24548 (100.0)*	*23665 (100.0)*	*15131 (100.0)*	*15131 (100.0)*
B03 - Antianemic preparations	*2852 (11.6)*	*2338 (9.9)*	*1685 (11.1)*	*1549 (10.2)*
B05 - Plasma substitutes and perfusion solutions	*1813 (7.4)*	*1607 (6.8)*	*1047 (6.9)*	*1019 (6.7)*
B02 - Antihemorrhagics	*239 (1.0)*	*139 (0.6)*	*158 (1.0)*	*91 (0.6)*
Cardiovascular system (C)	23711 (96.6)	22956 (97.0)	14662 (96.9)	14662 (96.9)
C07 - Beta blocking agents	*14771 (60.2)*	*14494 (61.2)*	*9095 (60.1)*	*9246 (61.1)*
C09 - Agents acting on the renin-angiotensin system	*13687 (55.8)*	*13249 (56.0)*	*8573 (56.7)*	*8518 (56.3)*
C01 - Cardiac therapy	*15968 (65.0)*	*15418 (65.2)*	*9774 (64.6)*	*9858 (65.2)*
C10 - Lipid modifying agents	*10096 (41.1)*	*9955 (42.1)*	*6341 (41.9)*	*6238 (41.2)*
C03 - Diuretics	*11928 (48.6)*	*10931 (46.2)*	*7258 (48.0)*	*7209 (47.6)*
C08 - Calcium channel blockers	*6338 (25.8)*	*6032 (25.5)*	*3925 (25.9)*	*3857 (25.5)*
C02 - Antihypertensives	*1332 (5.4)*	*1261 (5.3)*	*829 (5.5)*	*815 (5.4)*
Nervous system (N)	19201 (78.2)	18438 (77.9)	11811 (78.1)	11760 (77.7)
Alimentary tract and metabolism (A)	19871 (80.9)	18951 (80.1)	12214 (80.7)	12065 (79.7)
General antiinfectives for systemic use (J)	15115 (61.6)	13927 (58.9)	9251 (61.1)	9003 (59.5)
Dermatologicals (D)	10966 (44.7)	10029 (42.4)	6731 (44.5)	6391 (42.2)
Respiratory system (R)	10253 (41.8)	9674 (40.9)	6219 (41.1)	6010 (39.7)
Musculo-skeletal system (M)	9753 (39.7)	9011 (38.1)	6030 (39.9)	5768 (38.1)
Systemic hormonal prep, excluding sex hormones (H)	7434 (30.3)	6879 (29.1)	4515 (29.8)	4330 (28.6)
Sensory organs (S)	7492 (30.5)	6987 (29.5)	4590 (30.3)	4563 (30.2)
Genito urinary system and sex hormones (G)	4676 (19.0)	4347 (18.4)	2854 (18.9)	2831 (18.7)
Various (V)	3071 (12.5)	2793 (11.8)	1797 (11.9)	1724 (11.4)
Antineoplastic and immunomodulating agents (L)	1026 (4.2)	915 (3.9)	600 (4.0)	585 (3.9)
Antiparasitic products (P)	497 (2.0)	463 (2.0)	279 (1.8)	294 (1.9)

** Drug dispensing occurred the last date of the drug exposure period were not considered*

10.3. Outcome data

The main analysis of the outcomes (clinical events) was assessed during the drug exposure (rivaroxaban, dabigatran or VKA) on the 1-year follow-up period (on treatment) for the specific NVAF population with a grace period of 60 days, for all patients included in each treatment group (rivaroxaban 20 mg, dabigatran 150 mg, rivaroxaban 15 mg, dabigatran 110 mg, and VKA), and for patients matched (1:1) on the date of the first drug dispensing, gender, age at index date, and logit of the hdPS. It was the same for sensitivity analyses: specific population with a grace period of 30 days, and sensitive NVAF population with a 60-day grace period.

10.4. Main results

10.4.1. Incidence rate of outcomes (all patients)

The incidence rates of different outcomes (first event) per 100 person-years (PY) for all patients during the drug exposure period are presented in **Table 40** for all patients of the rivaroxaban 20 mg and VKA groups of the specific population and a grace period of 60 days (Appendix 1-4, Tables 46, 54, 60, 66, 86, 94, 102, 122, 140, 146, 152, 158, 164, 178, 184, and 190). For SSE, it was 1.5 [95%CI: 1.4; 1.6] per 100 PY for the rivaroxaban 20 mg group, and 3.1 [3.0; 3.2] for the VKA group, 1.4 [1.3; 1.5] and 3.8 [3.7; 3.9] for major bleeds, respectively, 3.4 [3.2; 3.6] and 15.6 [15.3; 15.9] for death, respectively, and 5.8 [5.5; 6.1] and 20.6 [20.3; 20.9], respectively for the composite criterion (SSE, major bleeding, death). Death was the most frequent event; patient with several events were counted only once for the first event for the composite criterion.

The overall incidence rates of the 6 main outcomes per 100 PY were similar with a grace period of 30 days (Appendix 1-13, Tables 14, 20, 26, 32, 38 and 44), as well as for the sensitive population with a 60-day grace period (Appendix 1-9, Tables 14, 20, 26, 32, 38 and 44).

For all patients in the dabigatran 150 mg group of the specific population and a grace period of 60 days, the overall incidence was 1.4 [1.2; 1.6] per 100 PY for SSE, 0.6 [0.5; 0.7] for major bleeds, 1.9 [1.6; 2.2] for death, and 3.7 [3.3; 4.1] for the composite (**Table 41**, Appendix 1-5, Tables 46, 54, 60, 66, 86, 94, 102, 122, 140, 146, 152, 158, 164, 178, 184, and 190).

The overall incidence rates of the 6 main outcomes per 100 PY were similar with a grace period of 30 days (Appendix 1-14, Tables 14, 20, 26, 32, 38 and 44), as well as for the sensitive population with a 60-day grace period (Appendix 1-10, Tables 14, 20, 26, 32, 38 and 44).

Table 40. Incidence rate of different outcomes per 100 person-years (PY) during the drug exposure period for all patients in the rivaroxaban 20 mg and VKA groups

	Rivaroxaban 20 mg			VKA		
	n evt	Person-years	Inc./100 PY [95%CI]	n evt	Person-years	Inc./100 PY [95%CI]
Stroke and systemic embolism (SSE)	**447**	**29 270**	**1.5 [1.4; 1.6]**	**2372**	**76 682**	**3.1 [3.0; 3.2]**
Ischemic or undefined stroke	280	29 334	1.0 [0.9; 1.1]	1345	77 066	1.7 [1.6; 1.8]
Other SE or surgical procedure for SE	168	29 327	0.6 [0.5; 0.7]	1050	77 093	1.4 [1.3; 1.5]
Major bleeding	**414**	**29 338**	**1.4 [1.3; 1.5]**	**2904**	**76 835**	**3.8 [3.7; 3.9]**
Clinically relevant bleeding (CRB)	**957**	**29 162**	**3.3 [3.1; 3.5]**	**4824**	**76 047**	**6.3 [6.1; 6.5]**
Haemorrhagic stroke	116	29 385	0.4 [0.3; 0.5]	718	77 406	0.9 [0.8; 1.0]
Other critical organ or site bleeding	77	29 379	0.3 [0.2; 0.4]	664	77 348	0.9 [0.8; 1.0]
Gastro-intestinal bleeding	367	29 300	1.3 [1.2; 1.4]	1535	76 999	2.0 [1.9; 2.1]
Urogenital bleeding	199	29 323	0.7 [0.6; 0.8]	674	77 202	0.9 [0.8; 1.0]
Other bleeding	226	29 336	0.8 [0.7; 0.9]	1485	76 946	1.9 [1.8; 2.0]
Death (all causes)	**992**	**29 391**	**3.4 [3.2; 3.6]**	**12057**	**77 480**	**15.6 [15.3; 15.9]**
Composite criterion (SSE, major bleeding, and death)	**1694**	**29 218**	**5.8 [5.5; 6.1]**	**15633**	**76 063**	**20.6 [20.3; 20.9]**
Acute coronary syndrome (ACS)	**345**	**29 268**	**1.2 [1.1; 1.3]**	**1551**	**76 811**	**2.0 [1.9; 2.1]**
ST-segment elevation MI (STEMI)	70	29 375	0.2 [0.1; 0.3]	460	77 313	0.6 [0.5; 0.7]
Non-ST-segment elevation MI (NSTEMI)	49	29 376	0.2 [0.1; 0.3]	280	77 368	0.4 [0.4; 0.4]
Unstable angina (I20.0 codes)	247	29 295	0.8 [0.7; 0.9]	950	77 048	1.2 [1.1; 1.3]

Table 41. Incidence rate of different outcomes per 100 person-years (PY) during the drug exposure period for all patients in the rivaroxaban 20 mg and dabigatran 150 mg groups

	Rivaroxaban 20 mg			Dabigatran 150 mg		
	n evt	Person-years	Inc./100 PY [95%CI]	n evt	Person-years	Inc./100 PY [95%CI]
Stroke and systemic embolism (SSE)	**447**	**29 284**	**1.5 [1.4; 1.6]**	**155**	**11 054**	**1.4 [1.2; 1.6]**
Ischemic or undefined stroke	280	29 348	1.0 [0.9; 1.1]	96	11 076	0.9 [0.7; 1.1]
Other SE or surgical procedure for SE	168	29 341	0.6 [0.5; 0.7]	60	11 079	0.5 [0.4; 0.6]
Major bleeding	**414**	**29 351**	**1.4 [1.3; 1.5]**	**71**	**11 089**	**0.6 [0.5; 0.7]**
Clinically relevant bleeding (CRB)	**957**	**29 176**	**3.3 [3.1; 3.5]**	**175**	**11 055**	**1.6 [1.4; 1.8]**
Haemorrhagic stroke	116	29 399	0.4 [0.3; 0.5]	16	11 100	0.1 [0.0; 0.2]
Other critical organ or site bleeding	77	29 393	0.3 [0.2; 0.4]	23	11 095	0.2 [0.1; 0.3]
Gastro-intestinal bleeding	367	29 314	1.3 [1.2; 1.4]	78	11 079	0.7 [0.5; 0.9]
Urogenital bleeding	199	29 337	0.7 [0.6; 0.8]	32	11 093	0.3 [0.2; 0.4]
Other bleeding	226	29 350	0.8 [0.7; 0.9]	31	11 090	0.3 [0.2; 0.4]
Death (all causes)	**992**	**29 405**	**3.4 [3.2; 3.6]**	**214**	**11 101**	**1.9 [1.6; 2.2]**
Composite criterion (SSE, major bleeding, and death)	**1694**	**29 232**	**5.8 [5.5; 6.1]**	**412**	**11 043**	**3.7 [3.3; 4.1]**
Acute coronary syndrome (ACS)	**344**	**29 282**	**1.2 [1.1; 1.3]**	**109**	**11 067**	**1.0 [0.8; 1.2]**
ST-segment elevation MI (STEMI)	70	29 389	0.2 [0.1; 0.3]	35	11 091	0.3 [0.2; 0.4]
Non-ST-segment elevation MI (NSTEMI)	49	29 390	0.2 [0.1; 0.3]	13	11 099	0.1 [0.0; 0.2]
Unstable angina (I20.0 codes)	246	29 309	0.8 [0.7; 0.9]	69	11 078	0.6 [0.5; 0.7]

For the reduced dose comparison of the specific population and a grace period of 60 days, the incidence rate of SSE was 2.6 [2.4; 2.8] per 100 PY for the rivaroxaban 15 mg group, and 3.1 [3.0; 3.2] for the VKA group, 2.8 [2.5; 3.1] and 3.8 [3.7; 3.9] for major bleeds, respectively, 10.1 [9.6; 10.6] and 15.6 [15.3; 15.9] for death, respectively, and 14.3 [13.8; 14.8], and 20.6 [20.3; 20.9] for the composite criterion, respectively (**Table 42**, Appendix 1-6, Tables 46, 54, 60, 66, 86, 94, 102, 122, 140, 146, 152, 158, 164, 178, 184, and 190).

The overall incidence rates of the 6 main outcomes per 100 PY were similar with a grace period of 30 days (Appendix 1-15, Tables 14, 20, 26, 32, 38 and 44), as well as for the sensitive population with a 60-day grace period (Appendix 1-11, Tables 14, 20, 26, 32, 38 and 44).

For the dabigatran 110 mg group of the specific population and a grace period of 60 days, the incidence rate was 2.1 [1.9; 2.3] per 100 PY for SSE, 2.0 [1.8; 2.2] for major bleeds, 8.5 [8.1; 8.9] for death, and 11.7 [11.2; 12.2] for the composite criterion (**Table 43**, Appendix 1-7, Tables 46, 54, 60, 66, 86, 94, 102, 122, 140, 146, 152, 158, 164, 178, 184, and 190).

The overall incidence rates of the 6 main outcomes per 100 PY were similar with a grace period of 30 days (Appendix 1-16, Tables 14, 20, 26, 32, 38 and 44), as well as for the sensitive population with a 60-day grace period (Appendix 1-12, Tables 14, 20, 26, 32, 38 and 44).

Table 42. Incidence rate of different outcomes per 100 person-years (PY) during the drug exposure period for all patients in the rivaroxaban 15 mg and VKA groups

	Rivaroxaban 15 mg			VKA		
	n evt	Person-years	Inc./100 PY [95%CI]	n evt	Person-years	Inc./100 PY [95%CI]
Stroke and systemic embolism (SSE)	**422**	**16 011**	**2.6 [2.4; 2.8]**	**2370**	**76 669**	**3.1 [3.0; 3.2]**
Ischemic or undefined stroke	268	16 054	1.7 [1.5; 1.9]	1344	77 052	1.7 [1.6; 1.8]
Other SE or surgical procedure for SE	158	16 071	1.0 [0.8; 1.2]	1049	77 080	1.4 [1.3; 1.5]
Major bleeding	**446**	**16 064**	**2.8 [2.5; 3.1]**	**2904**	**76 822**	**3.8 [3.7; 3.9]**
Clinically relevant bleeding (CRB)	**820**	**15 960**	**5.1 [4.8; 5.4]**	**4823**	**76 034**	**6.3 [6.1; 6.5]**
Haemorrhagic stroke	118	16 107	0.7 [0.6; 0.8]	718	77 392	0.9 [0.8; 1.0]
Other critical organ or site bleeding	91	16 102	0.6 [0.5; 0.7]	664	77 334	0.9 [0.8; 1.0]
Gastro-intestinal bleeding	295	16 062	1.8 [1.6; 1.2]	1535	76 985	2.0 [1.9; 2.1]
Urogenital bleeding	111	16 080	0.7 [0.6; 0.8]	673	77 190	0.9 [0.8; 1.0]
Other bleeding	228	16 060	1.4 [1.2; 1.6]	1485	76 932	1.9 [1.8; 2.0]
Death (all causes)	**1629**	**16 113**	**10.1 [9.6; 10.6]**	**12053**	**77 467**	**15.6 [15.3; 15.9]**
Composite criterion (SSE, major bleeding, and death)	**2279**	**15 964**	**14.3 [13.8; 14.8]**	**15629**	**76 049**	**20.6 [20.3; 20.9]**
Acute coronary syndrome (ACS)	**281**	**16 035**	**1.8 [1.6; 2.0]**	**1551**	**76 798**	**2.0 [1.9; 2.1]**
ST-segment elevation MI (STEMI)	82	16 102	0.5 [0.4; 0.6]	460	77 299	0.6 [0.5; 0.7]
Non-ST-segment elevation MI (NSTEMI)	29	16 104	0.2 [0.1; 0.3]	280	77 354	0.4 [0.4; 0.4]
Unstable angina (I20.0 codes)	196	16 050	1.2 [1.0; 1.4]	950	77 034	1.2 [1.1; 1.3]

Table 43. Incidence rate of different outcomes per 100 person-years (PY) during the drug exposure period for all patients in the rivaroxaban 15 mg and dabigatran 110 mg groups

	Rivaroxaban 15 mg			Dabigatran 110 mg		
	n evt	Person-years	Inc./100 PY [95%CI]	n evt	Person-years	Inc./100 PY [95%CI]
Stroke and systemic embolism (SSE)	**422**	**16 022**	**2.6 [2.4; 2.8]**	**318**	**15 008**	**2.1 [1.9; 2.3]**
Ischemic or undefined stroke	268	16 065	1.7 [1.5; 1.9]	223	15 040	1.5 [1.3; 1.7]
Other SE or surgical procedure for SE	158	16 081	1.0 [0.8; 1.2]	99	15 047	0.7 [0.6; 0.8]
Major bleeding	**448**	**16 075**	**2.8 [2.5; 3.1]**	**308**	**15 045**	**2.0 [1.8; 2.2]**
Clinically relevant bleeding (CRB)	**822**	**15 971**	**5.1 [4.8; 5.4]**	**546**	**14 984**	**3.6 [3.3; 3.9]**
Haemorrhagic stroke	119	16 118	0.7 [0.6; 0.8]	54	15 076	0.4 [0.3; 0.5]
Other critical organ or site bleeding	91	16 113	0.6 [0.5; 0.7]	59	15 069	0.4 [0.3; 0.5]
Gastro-intestinal bleeding	295	16 072	1.8 [1.6; 1.2]	265	15 035	1.8 [1.6; 2.0]
Urogenital bleeding	112	16 091	0.7 [0.6; 0.8]	70	15 059	0.5 [0.4; 0.6]
Other bleeding	228	16 071	1.4 [1.2; 1.6]	117	15 060	0.8 [0.7; 0.9]
Death (all causes)	**1628**	**16 124**	**10.1 [9.6; 10.6]**	**1276**	**15 079**	**8.5 [8.1; 8.9]**
Composite criterion (SSE, major bleeding, and death)	**2278**	**15 975**	**14.3 [13.8; 14.8]**	**1751**	**14 975**	**11.7 [11.2; 12.2]**
Acute coronary syndrome (ACS)	**280**	**16 046**	**1.7 [1.5; 1.9]**	**266**	**15 014**	**1.8 [1.6; 2.0]**
ST-segment elevation MI (STEMI)	82	16 113	0.5 [0.4; 0.6]	82	15 067	0.5 [0.4; 0.6]
Non-ST-segment elevation MI (NSTEMI)	29	16 114	0.2 [0.1; 0.3]	46	15 070	0.3 [0.2; 0.4]
Unstable angina (I20.0 codes)	195	16 061	1.2 [1.0; 1.4]	163	15 030	1.1 [0.9; 1.3]

10.4.1.1. Crude cumulative incidence of outcomes (all patients)

The 1-year cumulative incidences of each outcome during the drug exposure period for the specific population and a grace period of 60 days are presented in Appendix 1-4 for all patients for rivaroxaban 20 mg and VKA groups, in Appendix 1-5 for rivaroxaban 20 mg and dabigatran 150 mg groups, in Appendix 1-6 for rivaroxaban 15 mg and VKA groups, and in Appendix 1-7 for rivaroxaban 15 mg and dabigatran 110 mg groups (Tables 47, 55, 61, 67, 87, 95, 103, 123, 141, 147, 153, 159, 165, 179, 185, 191, and Figures 14, 14b, 16, 16b, 18, 18b, 20, 20b, 26, 26b, 27, 27b, 28, 28b, 34, 34b, 40, 40b, 42, 42b, 44, 44b, 46, 46b, 48, 48b, 52, 52b, 54, 54b, 56, 56b).

Results were similar for the 6 main outcomes with a grace period of 30 days (Appendices 1-13 to 1-16, Tables 15, 21, 27, 33, 39, 45, and Figures 15, 15b, 17, 17b, 19, 19b, 21, 21b, 23, 23b, 25, 25b), as well as for the sensitive population with a 60-day grace period (Appendices 1-9 to 1-12, Tables 15, 21, 27, 33, 39, 45, and Figures 15, 15b, 17, 17b, 19, 19b, 21, 21b, 23, 23b, 25, 25b).

10.4.1.2. Cumulative incidence of outcomes for matched patients

The 1-year cumulative incidence of outcomes during the drug exposure for the specific population and a grace period of 60 days was lower for rivaroxaban 20 mg than for matched VKA patients for all events (**Table 44**, **Figure 9**; Appendix 1-4, Tables 48, 68, 88, 96, 104, 166, and Figures 15, 15b, 21, 21b, 27, 27b, 29, 29b, 31, 31b, 51, 51b).

Results were similar with a 30-day grace period (Appendix 1-13, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b), as well as for the sensitive population and a 60-day grace period (Appendix 1-9, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b).

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, the 1-year cumulative incidence of outcomes during the drug exposure for the specific population and a grace period of 60 days was slightly lower for rivaroxaban 20 mg than for matched dabigatran 150 mg patients for SSE, and higher for all other outcomes (major bleeding, CRB, death, composite, and ACS) (**Table 45**, **Figure 10**; Appendix 1-5, Tables 48, 68, 88, 96, 104, 166, and Figures 15, 15b, 21, 21b, 27, 27b, 29, 29b, 31, 31b, 51, 51b).

Results were similar with a 30-day grace period (Appendix 1-14, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b), as well as for the sensitive population and a 60-day grace period (Appendix 1-10, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b).

Table 44. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 31 171		**VKA n = 31 171**	
	n evt	**% [95%CI]**	**n evt**	**% [95%CI]**
60-day grace period for treatment discontinuation				
Stroke and systemic embolism (SSE)	**372**	**1.5 [1.4; 1.7]**	**494**	**1.9 [1.8; 2.1]**
Major bleeding	**359**	**1.5 [1.4; 1.7]**	**560**	**2.2 [2.1; 2.4]**
Clinically relevant bleeding (CRB)	798	3.3 [3.1; 3.6]	1001	4.0 [3.7; 4.2]
Death (all causes)	**902**	**3.9 [3.7; 4.2]**	**1414**	**5.8 [5.5; 6.1]**
Composite criterion (SSE, major bleeding, and death)	**1489**	**6.3 [6.0; 6.6]**	**2217**	**8.9 [8.5; 9.2]**
Acute coronary syndrome (ACS)	**286**	**1.2 [1.0; 1.3]**	**374**	**1.4 [1.3; 1.6]**
30-day grace period for treatment discontinuation				
SSE	**335**	**1.4 [1.3; 1.6]**	**428**	**1.9 [1.7; 2.1]**
Major bleeding	**325**	**1.5 [1.3; 1.6]**	**487**	**2.2 [2.0; 2.4]**
CRB	739	3.3 [3.0; 3.5]	885	3.9 [3.6; 4.2]
Death (all causes)	**694**	**3.2 [3.0; 3.4]**	**1127**	**5.2 [4.9; 5.5]**
Composite criterion (SSE, major bleeding, and death)	**1246**	**5.6 [5.3; 5.9]**	**1842**	**8.2 [7.9; 8.6]**
ACS	**265**	**1.1 [1.0; 1.3]**	**346**	**1.5 [1.3; 1.6]**

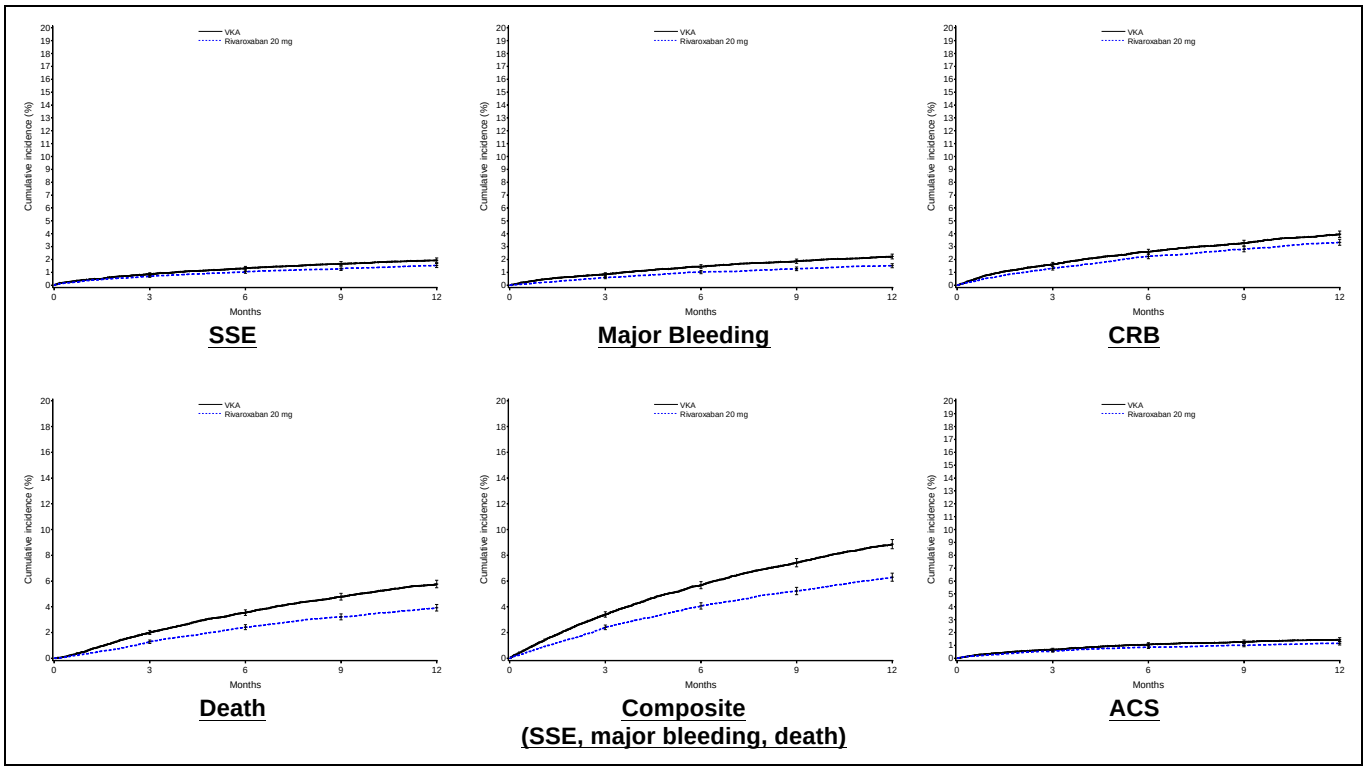


Figure 9. One-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 20 mg and VKA matched patients

Table 45. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 15 323		Dabigatran 150 mg n = 15 323	
	n evt	% [95%CI]	n evt	% [95%CI]
60-day grace period for treatment discontinuation				
Stroke and systemic embolism (SSE)	**132**	**1.1 [0.9; 1.3]**	**143**	**1.3 [1.1; 1.5]**
Major bleeding	**119**	**1.1 [0.9; 1.3]**	**66**	**0.6 [0.5; 0.7]**
Clinically relevant bleeding (CRB)	288	2.5 [2.2; 2.8]	157	1.4 [1.2; 1.6]
Death (all causes)	**253**	**3.2 [3.0; 3.4]**	**191**	**1.8 [1.6; 2.0]**
Composite criterion (SSE, major bleeding, and death)	**467**	**4.1 [3.8; 4.5]**	**375**	**3.4 [3.0; 3.7]**
Acute coronary syndrome (ACS)	**139**	**1.2 [1.0; 1.4]**	**100**	**0.9 [0.7; 1.1]**
30-day grace period for treatment discontinuation				
SSE	**116**	**1.0 [0.9; 1.2]**	**128**	**1.2 [1.0; 1.4]**
Major bleeding	**108**	**1.0 [0.8; 1.2]**	**60**	**0.6 [0.4; 0.7]**
CRB	265	2.4 [2.1; 2.7]	147	1.4 [1.2; 1.6]
Death (all causes)	**194**	**1.9 [1.6; 2.1]**	**150**	**1.4 [1.2; 1.7]**
Composite criterion (SSE, major bleeding, and death)	**395**	**3.7 [3.3; 4.0]**	**314**	**3.0 [2.7; 3.3]**
ACS	**132**	**1.2 [1.0; 1.4]**	**92**	**0.8 [0.7; 1.0]**

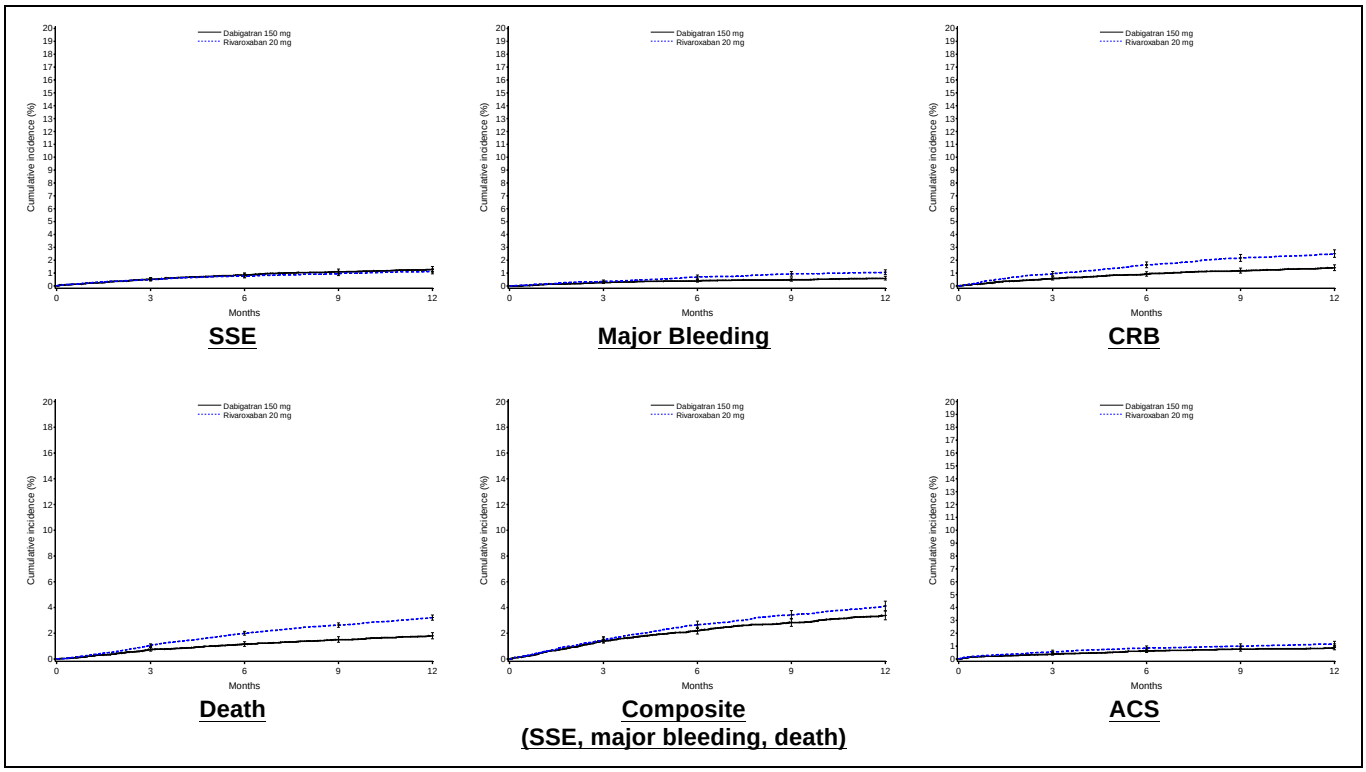


Figure 10. One-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 20 mg and dabigatran 150 mg matched patients

The 1-year cumulative incidence of death and composite criterion during the drug exposure for the specific population and a grace period of 60 days was lower for rivaroxaban 15 mg than for matched VKA patients, while there was an overlap of 95%CI for the other outcomes (**Table 46**, **Figure 11**; Appendix 1-6, Tables 48, 68, 88, 96, 104, 166, and Figures 15, 15b, 21, 21b, 27, 27b, 29, 29b, 31, 31b, 51, 51b).

Results were similar with a 30-day grace period (Appendix 1-15, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b). For the sensitive population and a 60-day grace period, the 1-year cumulative incidence of major bleeding and CRB during the drug exposure was also lower for rivaroxaban 15 mg than for matched VKA patients, while there was an overlap of 95%CI for the other outcomes (SSE and ACS) with a similar point estimate (Appendix 1-11, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b).

The 1-year cumulative incidence of SSE, major bleeding, and CRB during the drug exposure for the specific population and a grace period of 60 days was higher for rivaroxaban 15 mg than for matched dabigatran 110 mg patients, while 95%CI of the other outcomes overlapped, with a similar point estimate for ACS (**Table 47**, **Figure 12**; Appendix 1-7, Tables 48, 68, 88, 96, 104, 166, and Figures 15, 15b, 21, 21b, 27, 27b, 29, 29b, 31, 31b, 51, 51b).

With a 30-day grace period, only the 1-year cumulative incidence of major bleeding and CRB remained higher for rivaroxaban 15 mg (**Table 47;** Appendix 1-16, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b). For the sensitive population and a 60-day grace period, only the 1-year cumulative incidence of CRB during the drug exposure was higher for rivaroxaban 15 mg than for matched dabigatran 110 mg patients, while 95%CI of the other outcomes overlapped, with a similar point estimate for ACS (Appendix 1-12, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b).

Table 46. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 23 314		VKA n = 23 314	
	n evt	% [95%CI]	n evt	% [95%CI]
60-day grace period for treatment discontinuation				
Stroke and systemic embolism (SSE)	**399**	**2.3 [2.0; 2.5]**	**419**	**2.1 [1.9; 2.3]**
Major bleeding	**426**	**2.4 [2.2; 2.6]**	**560**	**2.9 [2.6; 3.1]**
Clinically relevant bleeding (CRB)	787	4.4 [4.1; 4.7]	975	4.9 [4.6; 5.3]
Death (all causes)	**1565**	**9.1 [8.6; 9.5]**	**2069**	**10.8 [10.3; 11.2]**
Composite criterion (SSE, major bleeding, and death)	**2189**	**12.5 [12.0; 13.0]**	**2738**	**14.0 [13.5; 14.5]**
Acute coronary syndrome (ACS)	**270**	**1.5 [1.3; 1.7]**	**347**	**1.7 [1.6; 1.9]**
30-day grace period for treatment discontinuation				
SSE	**343**	**2.1 [1.9; 2.3]**	**384**	**2.2 [1.9; 2.4]**
Major bleeding	**388**	**2.3 [2.1; 2.6]**	**508**	**2.9 [2.6; 3.1]**
CRB	722	4.3 [4.0; 4.6]	886	5.0 [4.6; 5.3]
Death (all causes)	**1262**	**7.7 [7.3; 8.2]**	**1710**	**9.8 [9.4; 10.3]**
Composite criterion (SSE, major bleeding, and death)	**1834**	**11.0 [10.6; 11.5]**	**2349**	**13.2 [12.7; 13.8]**
ACS	**247**	**1.4 [1.3; 1.6]**	**323**	**1.8 [1.6; 2.0]**

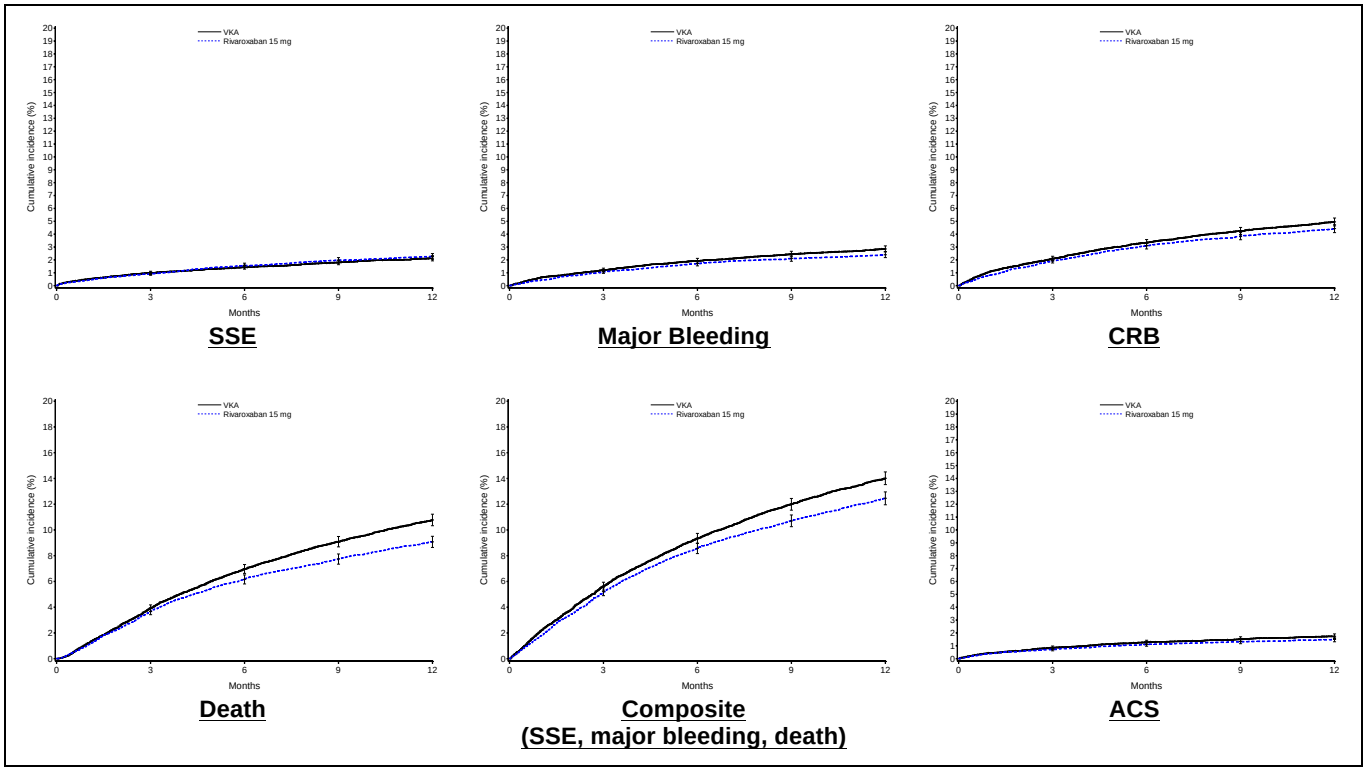


Figure 11. One-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 15 mg and VKA matched patients

Table 47. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 15 131		Dabigatran 110 mg n = 15 131	
	n evt	% [95%CI]	n evt	% [95%CI]
60-day grace period for treatment discontinuation				
Stroke and systemic embolism (SSE)	**266**	**2.3 [2.0; 2.6]**	**202**	**1.9 [1.6; 2.1]**
Major bleeding	**284**	**2.5 [2.2; 2.8]**	**215**	**1.9 [1.7; 2.2]**
Clinically relevant bleeding (CRB)	525	4.5 [4.1; 4.9]	370	3.3 [3.0; 3.6]
Death (all causes)	**934**	**8.3 [7.8; 8.8]**	**868**	**8.1 [7.6; 8.7]**
Composite criterion (SSE, major bleeding, and death)	**1339**	**11.7 [11.1; 12.3]**	**1185**	**10.9 [10.3; 11.5]**
Acute coronary syndrome (ACS)	**180**	**1.5 [1.3; 1.8]**	**180**	**1.6 [1.4; 1.8]**
30-day grace period for treatment discontinuation				
SSE	**226**	**2.0 [1.8; 2.3]**	**179**	**1.8 [1.5; 2.0]**
Major bleeding	**257**	**2.4 [2.1; 2.7]**	**193**	**1.8 [1.6; 2.1]**
CRB	482	4.4 [4.0; 4.8]	335	3.1 [2.8; 3.5]
Death (all causes)	**737**	**6.9 [6.4; 7.4]**	**692**	**6.9 [6.4; 7.4]**
Composite criterion (SSE, major bleeding, and death)	**1109**	**10.2 [9.6; 10.8]**	**987**	**9.6 [9.0; 10.2]**
ACS	**168**	**1.5 [1.3; 1.7]**	**162**	**1.5 [1.3; 1.8]**

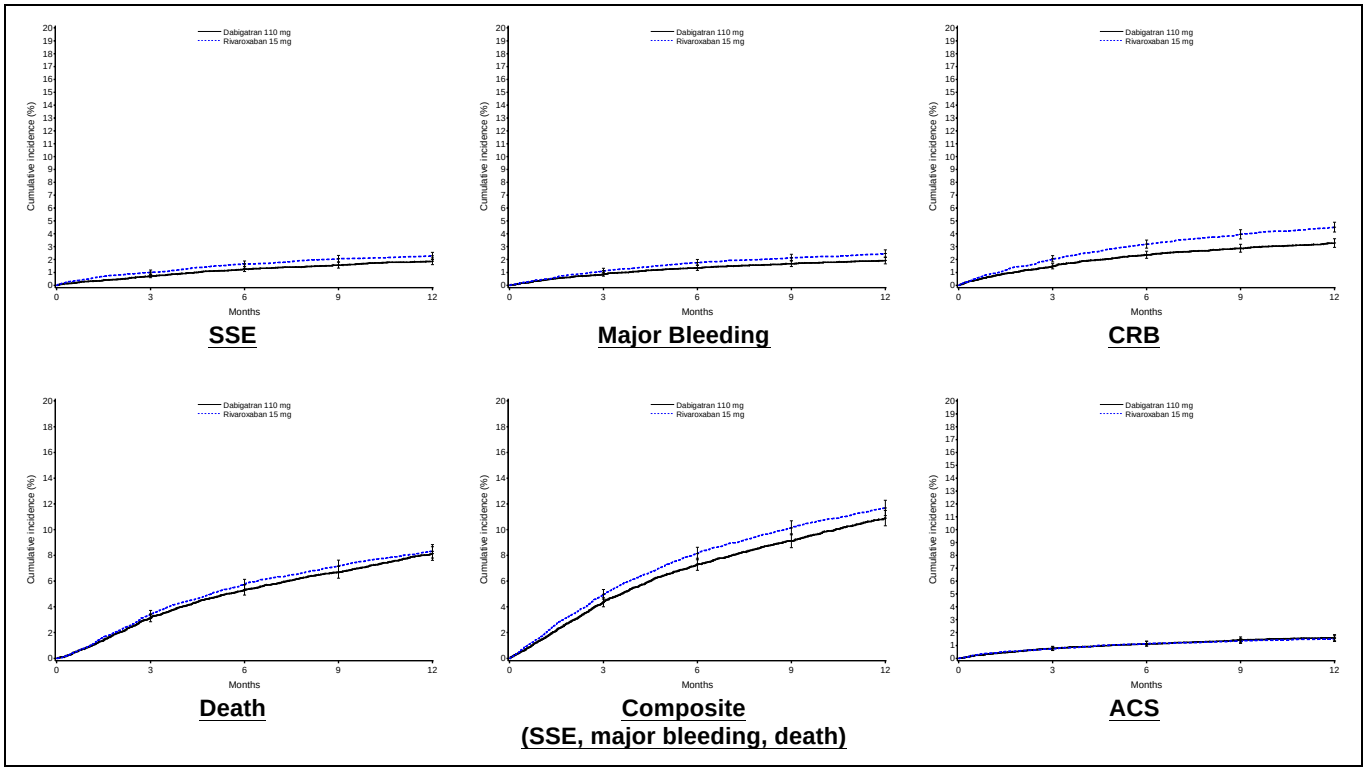


Figure 12. One-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 15 mg and dabigatran 110 mg matched patients

10.4.2. Rivaroxaban 20 mg versus VKA comparison of the 1-year risk of outcomes during the exposure period (on treatment)

For matched patients of the specific population and a 60-day grace period for drug discontinuation definition, the risk of all main outcomes, SSE, major bleeding and death, as well as the composite of these three events was significantly lower with rivaroxaban 20 mg compared to VKA: 21% [10% to 31%], 33% [23% to 41%], 33% [27% to 39%], and 30% [26% to 35%], respectively (**Figure 13**; Appendix 1-4, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101).

The risk was also significantly lower with rivaroxaban 20 mg for individual SSE outcomes, 20% [5% to 33%] for ischemic or undefined stroke, and 24% [5% to 39%] for other SE or surgical procedure for SE (**Figure 14)**. That was also the case for ACS (20% [7% to 31%]), including STEMI (38% [15% to 55%]) and NSTEMI (43% [15% to 62%]), as well as for most bleeding subgroups: 17% [9% to 24%] for CRB, 33% [14% to 48%] for haemorrhagic stroke, 50% [33% to 62%] for other critical organ or site bleeding, and 32% [19% to 43%] for other bleeding; without difference for GI bleeding and urogenital bleeding risks (HR: 1.11 [0.95 to 1.31] and 1.01 [0.81 to 1.26], respectively) (**Figures 13 and 14**).

For all outcomes, hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figures 13 and 14**).

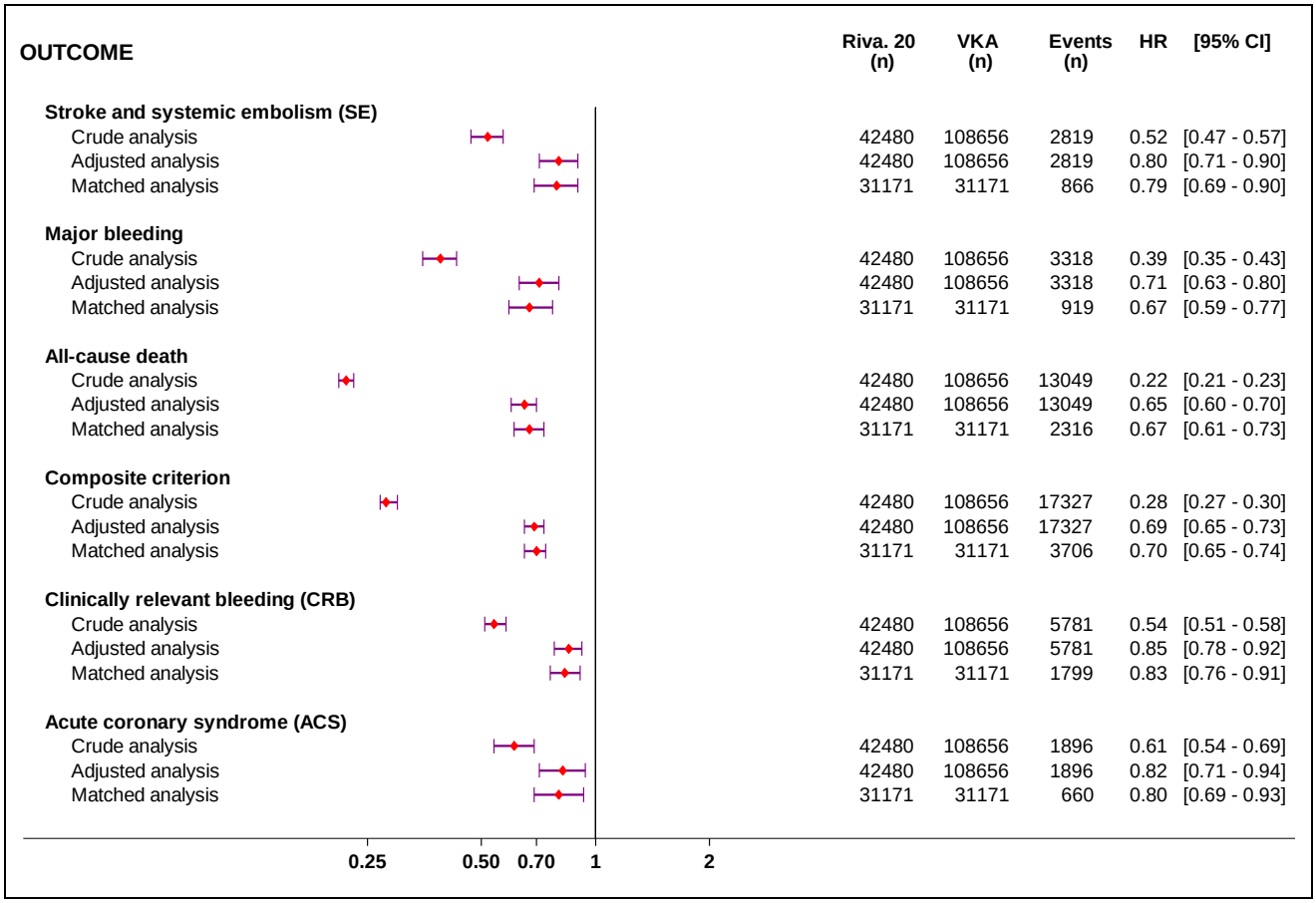


Figure 13. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation (main analysis)

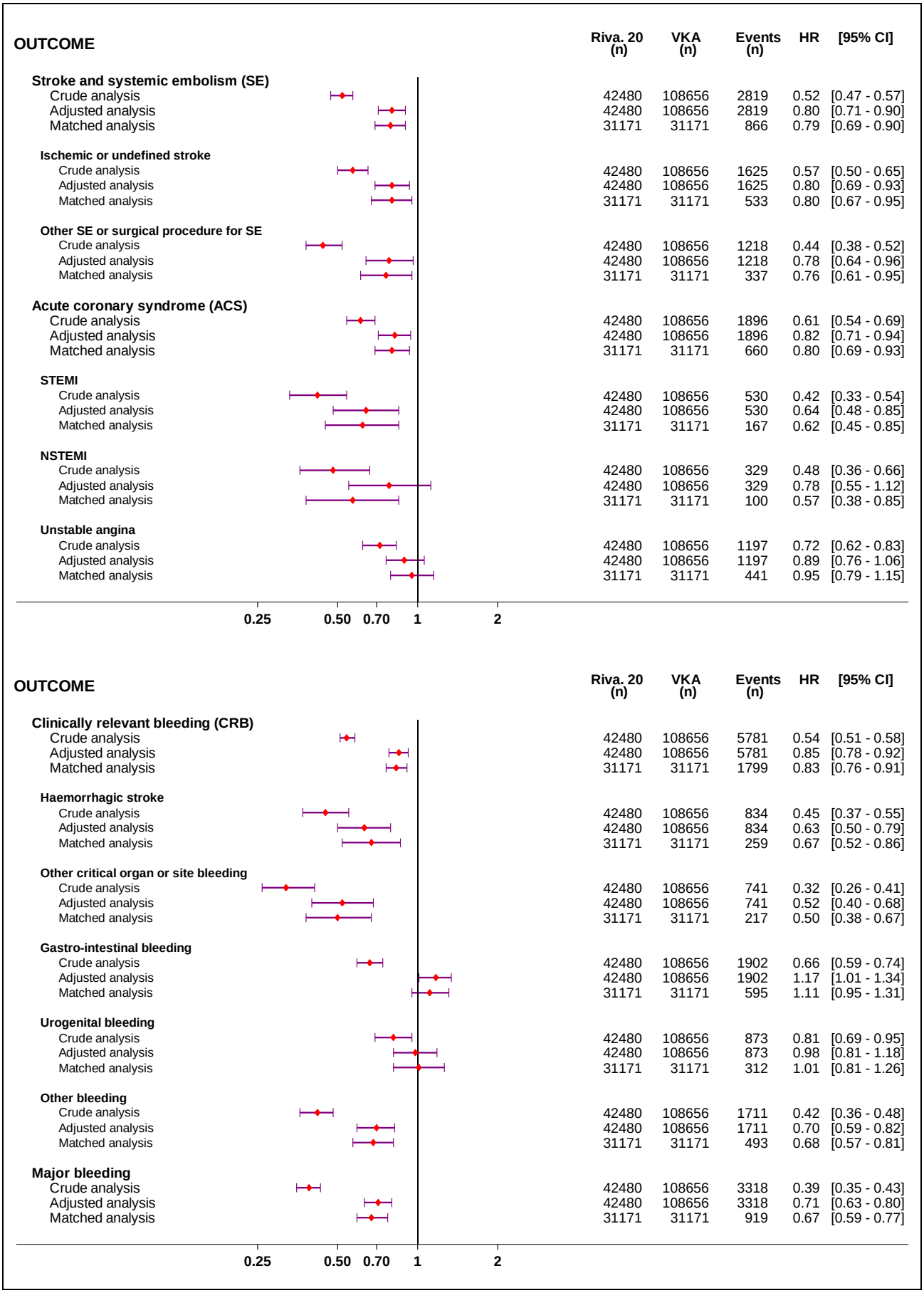
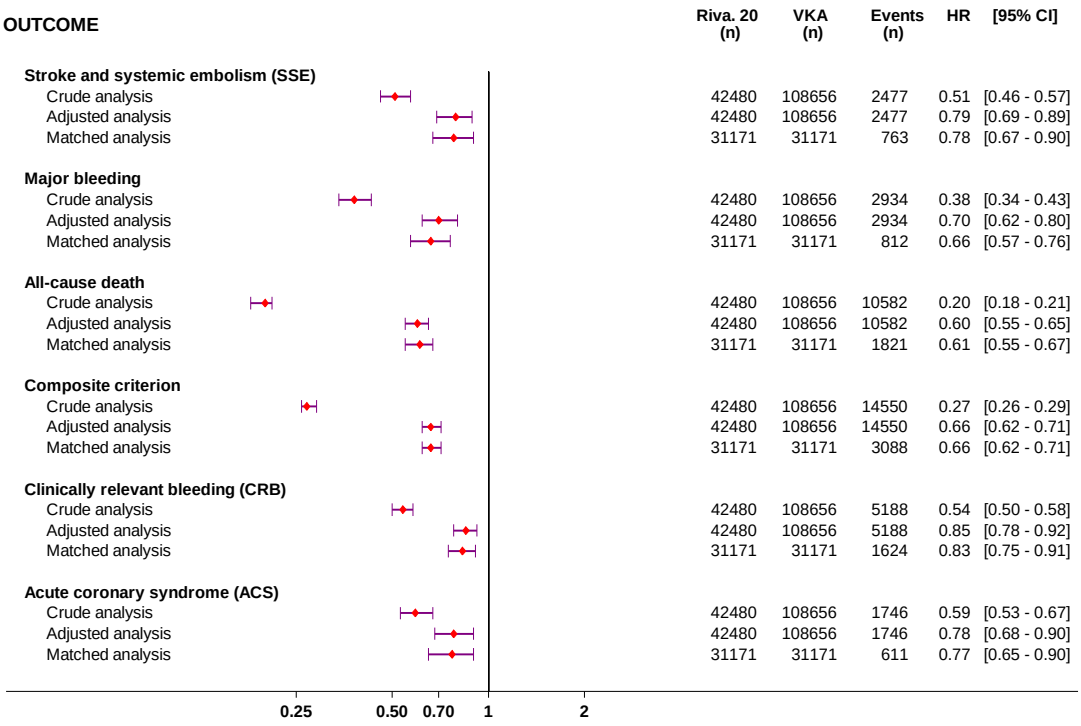


Figure 14. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of outcome details for the specific population and a 60-day grace period for drug discontinuation (main analysis)

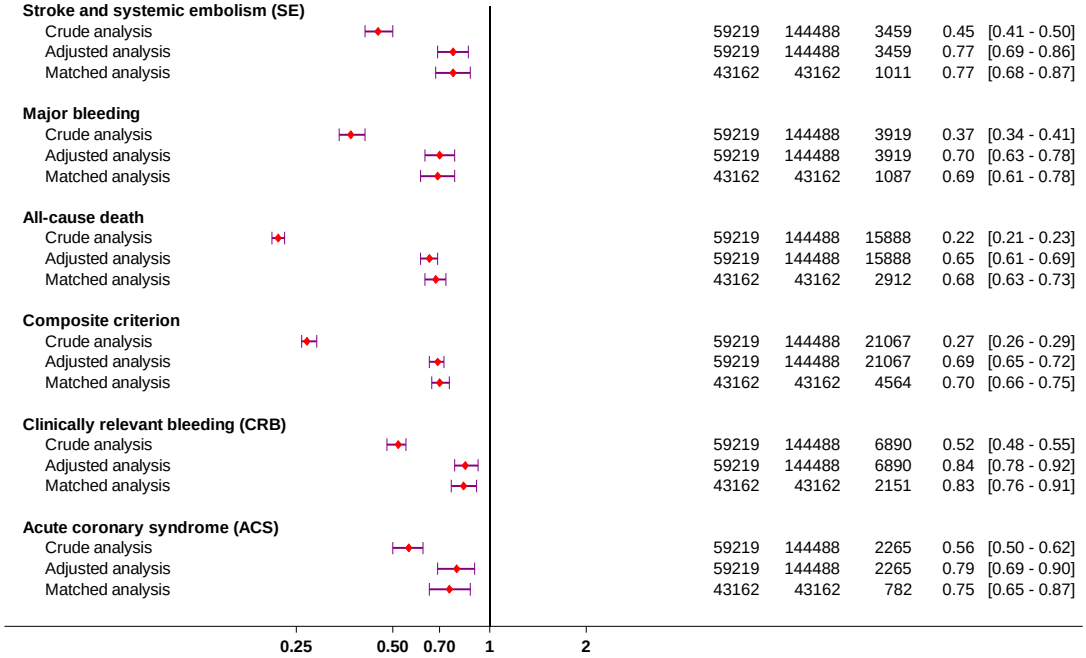
For the sensitivity analyses, results for main and secondary outcomes (SSE, major bleeding, death, composite, CRB, and ACS) remained essentially unchanged with a 30-day grace period (**Figure 15**; Appendix 1-13, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), as well as for the sensitive population and a 60-day grace period (**Figure 15**; Appendix 1-9, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49).

Specific population and a 30-day grace period



OUTCOME	Riva. 20 (n)	VKA (n)	Events (n)	HR	[95% CI]
Stroke and systemic embolism (SSE)					
Crude analysis	42480	108656	2477	0.51	[0.46 - 0.57]
Adjusted analysis	42480	108656	2477	0.79	[0.69 - 0.89]
Matched analysis	31171	31171	763	0.78	[0.67 - 0.90]
Major bleeding					
Crude analysis	42480	108656	2934	0.38	[0.34 - 0.43]
Adjusted analysis	42480	108656	2934	0.70	[0.62 - 0.80]
Matched analysis	31171	31171	812	0.66	[0.57 - 0.76]
All-cause death					
Crude analysis	42480	108656	10582	0.20	[0.18 - 0.21]
Adjusted analysis	42480	108656	10582	0.60	[0.55 - 0.65]
Matched analysis	31171	31171	1821	0.61	[0.55 - 0.67]
Composite criterion					
Crude analysis	42480	108656	14550	0.27	[0.26 - 0.29]
Adjusted analysis	42480	108656	14550	0.66	[0.62 - 0.71]
Matched analysis	31171	31171	3088	0.66	[0.62 - 0.71]
Clinically relevant bleeding (CRB)					
Crude analysis	42480	108656	5188	0.54	[0.50 - 0.58]
Adjusted analysis	42480	108656	5188	0.85	[0.78 - 0.92]
Matched analysis	31171	31171	1624	0.83	[0.75 - 0.91]
Acute coronary syndrome (ACS)					
Crude analysis	42480	108656	1746	0.59	[0.53 - 0.67]
Adjusted analysis	42480	108656	1746	0.78	[0.68 - 0.90]
Matched analysis	31171	31171	611	0.77	[0.65 - 0.90]

Sensitive population and a 60-day grace period



OUTCOME	Riva. 20 (n)	VKA (n)	Events (n)	HR	[95% CI]
Stroke and systemic embolism (SE)					
Crude analysis	59219	144488	3459	0.45	[0.41 - 0.50]
Adjusted analysis	59219	144488	3459	0.77	[0.69 - 0.86]
Matched analysis	43162	43162	1011	0.77	[0.68 - 0.87]
Major bleeding					
Crude analysis	59219	144488	3919	0.37	[0.34 - 0.41]
Adjusted analysis	59219	144488	3919	0.70	[0.63 - 0.78]
Matched analysis	43162	43162	1087	0.69	[0.61 - 0.78]
All-cause death					
Crude analysis	59219	144488	15888	0.22	[0.21 - 0.23]
Adjusted analysis	59219	144488	15888	0.65	[0.61 - 0.69]
Matched analysis	43162	43162	2912	0.68	[0.63 - 0.73]
Composite criterion					
Crude analysis	59219	144488	21067	0.27	[0.26 - 0.29]
Adjusted analysis	59219	144488	21067	0.69	[0.65 - 0.72]
Matched analysis	43162	43162	4564	0.70	[0.66 - 0.75]
Clinically relevant bleeding (CRB)					
Crude analysis	59219	144488	6890	0.52	[0.48 - 0.55]
Adjusted analysis	59219	144488	6890	0.84	[0.78 - 0.92]
Matched analysis	43162	43162	2151	0.83	[0.76 - 0.91]
Acute coronary syndrome (ACS)					
Crude analysis	59219	144488	2265	0.56	[0.50 - 0.62]
Adjusted analysis	59219	144488	2265	0.79	[0.69 - 0.90]
Matched analysis	43162	43162	782	0.75	[0.65 - 0.87]

Figure 15. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period (sensitivity analyses)

Stratified analyses were performed for the specific population and a 60-day grace period according to index date, gender, age classes, CHA_2DS_2-VASc score and its individual risk factors (congestive heart failure, hypertension, diabetes mellitus, stroke or TIA history, vascular disease history, age 65-74 years, age ≥ 75 years), HAS-BLED score and quintiles of logit hdPS (**Table 48**; Appendix 1-8). The risk point estimate with rivaroxaban 20 mg compared to VKA showed substantial variations of the HR point estimate according to the different subgroups:

- **For stroke and systemic embolism,**
  - At least 25% significantly lower for 2014 index date (32%), 65-69 and 75-79 years old (30% and 39%, respectively), CHA_2DS_2-VASc scores 2 and 3 (38% and 33%, respectively), and the two last quintiles of logit hdPS (34% and 40%, respectively),
  - Between 10% and 24% lower for all matched patients (21%), 2013 index date (10%), male and female (20% and 23%, respectively), < 65 and 70-74 years old (17% and 11%, respectively), CHA_2DS_2-VASc scores ≥ 4 (11%), congestive heart failure (21%), stroke or TIA history (18%), vascular disease history (15%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (20% and 23%, respectively), HAS-BLED scores 0-1 and 2-3 (24% and 22%, respectively), the first and third quintiles (12% and 17%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 48**),
  - Relatively similar with HR between 0.91 and 1.10 (symmetric of 0.91) for ≥ 80 years old (0.92), CHA_2DS_2-VASc scores 0-1 (1.04), hypertension (0.93), diabetes mellitus (0.94), HAS-BLED scores > 3 (0.92), and the second quintile (0.94),
  - None were lower with VKA,
  - With a gradient for HAS-BLED, from 0.76 to 0.92 for scores 0-1 to scores > 3 HR, and no clear systematic variation for the other factors;
- **For major bleeding,**
  - At least 25% significantly lower for all matched patients (33%), 2013 and 2014 index date (30% and 36%, respectively), male and female (28% and 43%, respectively), 65-69, 70-74, and 75-79 years old (56%, 31% and 42%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and 3 (32%, 46% and 33%, respectively), congestive heart failure (27%), hypertension (26%), diabetes mellitus (30%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (42% and 31%, respectively), HAS-BLED scores 0-1, 2-3 and > 3 (34%, 32% and 28%, respectively), and the four last quintiles of logit hdPS (27%, 36%, 34% and 60%, respectively),
  - Between 10% and 24% lower for < 65 and ≥ 80 years old (11% and 21%, respectively), and CHA_2DS_2-VASc scores ≥ 4 (23%), stroke or TIA history (20%), the first quintile (17%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 48**),
  - Relatively similar with HR between 0.91 and 1.10 for vascular disease history (1.04),
  - None lower with VKA,
  - With a gradient for HAS-BLED, from 0.66 to 0.72 for scores 0-1 to > 3 HR, and for quintiles from 0.40 to 0.83 for the last to the first quintile HR, and no clear systematic variation for the other factors;
- **For clinically relevant bleeding,**
  - At least 25% significantly lower for 65-69 and 70-74 years old (35% and 30%, respectively), CHA_2DS_2-VASc score 2 (28%), age 65-74 years as CHA_2DS_2-VASc risk factor (32%) and the last quintile of logit hdPS (36%),
  - Between 10% and 24% lower for all matched patients (17%), 2013 and 2014 index date (10% and 23%, respectively), male and female (13% and 23%, respectively), 75-79 years old (21%), CHA_2DS_2-VASc scores 0-1 and 3 (20% and 12%, respectively), hypertension (13%), diabetes mellitus (12%), stroke or TIA history (16%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (10%), all HAS-BLED scores (12%, 16% and 23%, respectively), the third and fourth quintiles (23% and 22%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 48**),
  - Relatively similar with HR between 0.91 and 1.10 for < 65 and ≥ 80 years old (1.0 and 1.0, respectively), CHA_2DS_2-VASc scores ≥ 4 (0.91), congestive heart failure (0.94), vascular disease history (0.98), and the two first quintiles (0.99 and 0.95, respectively),

- None lower with VKA,
- With a weak gradient for HAS-BLED, from 0.77 to 0.88 for scores > 3 to scores 0-1 HR (inverse that of major bleeding), and for quintiles, from 0.64 to 0.99 for the first to the last quintiles HR, and no clear systematic variation for the other factors;

– **For death,**
- At least 25% significantly lower for all matched patients (33%), 2013 and 2014 index date (32% and 35%, respectively), male and female (33% and 34%, respectively), all age classes (30%, 31%, 26%, 46% and 28%, respectively), all CHA_2DS_2-VASc score classes (27%, 29%, 40% and 30%, respectively), congestive heart failure (42%), hypertension (30%), diabetes mellitus (31%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (28% and 34%, respectively), all HAS-BLED score classes (39%, 31% and 26%, respectively), and all quintiles of logit hdPS (27%, 26%, 42%, 28%, 37%, respectively),
- Between 10% and 24% non-significantly lower for stroke or TIA history (18%), and significantly for vascular disease history (20%),
- All were at least 18% lower with rivaroxaban, and all significantly, except one with upper 95%CI close to 1 (1.02),
- With a gradient for HAS-BLED, from 0.61 to 0.74 for scores 0-1 to scores > 3 HR, and no clear systematic variation for the other covariates;

– **For the composite criterion (stroke and systemic embolism, major bleeding and death),**
- At least 25% significantly lower for all matched patients (30%), 2013 and 2014 index date (27% and 34%, respectively), male and female (28% and 34%, respectively), 65-69 and 75-79 years old (36% and 44%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (35%, 36% and 25%, respectively), congestive heart failure (36%), hypertension (25%), diabetes mellitus (25%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (29% and 32%, respectively), HAS-BLED scores 0-1 and 2-3 (34% and 29%, respectively), and the three last quintiles of logit hdPS (35%, 33% and 41%, respectively),
- Between 10% and 24% significantly lower for < 65 years, 70-74 and ≥ 80 years old (20%, 23% and 24%, respectively), CHA_2DS_2-VASc scores 0-1 (19%), stroke or TIA history (18%) and vascular disease history (15%), HAS-BLED scores > 3 (24%), and the two first quintiles (22% for both),
- None lower than 15% with rivaroxaban, and all significantly,
- With a gradient for HAS-BLED, from 0.66 to 0.76 for scores 0-1 to scores > 3 HR, and for quintiles, from 0.59 to 0.78 for the last to the first quintiles HR, and no clear systematic variation for the other factors;

– **For ACS,**
- At least 25% lower for < 65, 70-74 and ≥ 80 years old (42%, 28% and 41%, respectively), CHA_2DS_2-VASc scores 0-1 (30%), stroke or TIA history (27%), and the fourth quintile of logit hdPS (36%), and significantly when there were enough patients and events to reach statistical power,
- Between 10% and 24% lower for all matched patients (20%), 2013 and 2014 index date (23% and 16%, respectively), male and female (23% and 12%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (20%, 20% and 14%, respectively), hypertension (21%), diabetes mellitus (14%), vascular disease history (21%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (15% and 13%, respectively), all HAS-BLED score classes (16%, 19% and 23%, respectively), the two first and last quintiles (21%, 23% and 16%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 48**),
- Relatively similar with HR between 0.91 and 1.10 for 65-79 years old (1.05), for congestive heart failure (0.99), and the third quintile (1.10),
- Non-significantly higher risk for 75-79 years old (18%),
- With a weak gradient for HAS-BLED, from 0.77 to 0.84 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors.

Table 48. Rivaroxaban 20 mg versus VKA stratified analyses of main and secondary outcomes for matched patients, hazard ratio (HR and 95%CI)

	Rivaroxaban 20 mg	**VKA**	Stroke and systemic embolism	Major bleeding	Clinically relevant bleeding	Death (all causes)	Composite criterion	Acute coronary syndrome
	n	n	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
All matched patients	31 171	31 171	0.79 [0.69 ; 0.90]	0.67 [0.59 ; 0.77]	0.83 [0.76 ; 0.91]	0.67 [0.61 ; 0.73]	0.70 [0.65 ; 0.74]	0.80 [0.69 ; 0.93]
Index date								
2013	15 712	15 712	0.90 [0.74 ; 1.08]	0.70 [0.58 ; 0.85]	0.90 [0.79 ; 1.03]	0.68 [0.61 ; 0.77]	0.73 [0.67 ; 0.80]	0.77 [0.62 ; 0.95]
2014	15 459	15 459	0.68 [0.56 ; 0.83]	0.64 [0.53 ; 0.78]	0.77 [0.67 ; 0.88]	0.65 [0.58 ; 0.73]	0.66 [0.60 ; 0.73]	0.84 [0.67 ; 1.05]
Gender								
Male	19 329	19 329	0.80 [0.67 ; 0.94]	0.72 [0.62 ; 0.85]	0.87 [0.77 ; 0.97]	0.67 [0.61 ; 0.74]	0.72 [0.66 ; 0.78]	0.77 [0.64 ; 0.93]
Female	11 842	11 842	0.77 [0.61 ; 0.97]	0.57 [0.45 ; 0.73]	0.77 [0.66 ; 0.90]	0.66 [0.57 ; 0.76]	0.66 [0.59 ; 0.74]	0.88 [0.67 ; 1.16]
Age (years)								
<65	7 305	7 278	0.83 [0.59 ; 1.16]	0.89 [0.61 ; 1.31]	1.00 [0.78 ; 1.28]	0.70 [0.54 ; 0.90]	0.80 [0.67 ; 0.96]	0.58 [0.40 ; 0.84]
65-69	5 309	5 470	0.70 [0.49 ; 1.00]	0.44 [0.30 ; 0.66]	0.65 [0.50 ; 0.84]	0.69 [0.53 ; 0.89]	0.64 [0.53 ; 0.77]	1.05 [0.70 ; 1.55]
70-74	5 733	5 493	0.89 [0.65 ; 1.23]	0.69 [0.51 ; 0.95]	0.70 [0.56 ; 0.88]	0.74 [0.59 ; 0.91]	0.77 [0.66 ; 0.91]	0.72 [0.51 ; 1.02]
75-79	6 284	6 587	0.61 [0.46 ; 0.82]	0.58 [0.44 ; 0.75]	0.79 [0.66 ; 0.96]	0.54 [0.45 ; 0.65]	0.56 [0.49 ; 0.65]	1.22 [0.89 ; 1.65]
≥ 80	6 540	6 343	0.92 [0.72 ; 1.18]	0.79 [0.63 ; 0.99]	1.00 [0.84 ; 1.18]	0.72 [0.63 ; 0.81]	0.76 [0.68 ; 0.84]	0.59 [0.42 ; 0.83]
CHA_2DS_2-VASc score								
0-1	7 618	7 423	1.04 [0.72 ; 1.51]	0.68 [0.46 ; 1.00]	0.80 [0.63 ; 1.03]	0.73 [0.57 ; 0.95]	0.81 [0.66 ; 0.98]	0.70 [0.46 ; 1.07]
2	7 513	7 262	0.62 [0.46 ; 0.85]	0.54 [0.41 ; 0.73]	0.72 [0.59 ; 0.87]	0.71 [0.58 ; 0.86]	0.65 [0.56 ; 0.75]	0.80 [0.57 ; 1.12]
3	7 245	7 173	0.67 [0.50 ; 0.90]	0.67 [0.52 ; 0.88]	0.88 [0.73 ; 1.06]	0.60 [0.50 ; 0.71]	0.64 [0.55 ; 0.73]	0.80 [0.60 ; 1.07]
≥ 4	8 795	9 313	0.89 [0.73 ; 1.09]	0.77 [0.62 ; 0.94]	0.91 [0.78 ; 1.05]	0.70 [0.62 ; 0.79]	0.75 [0.68 ; 0.82]	0.86 [0.67 ; 1.11]
Risk factors								
Congestive heart failure	4 853	4 949	0.79 [0.58 ; 1.09]	0.73 [0.55 ; 0.97]	0.94 [0.76 ; 1.16]	0.58 [0.49 ; 0.67]	0.64 [0.57 ; 0.73]	0.99 [0.71 ; 1.37]
Hypertension	11 908	12 354	0.93 [0.77 ; 1.13]	0.74 [0.61 ; 0.89]	0.87 [0.76 ; 0.99]	0.70 [0.62 ; 0.78]	0.75 [0.69 ; 0.83]	0.79 [0.64 ; 0.99]
Diabetes mellitus	12 824	12 930	0.94 [0.73 ; 1.21]	0.70 [0.55 ; 0.88]	0.88 [0.74 ; 1.05]	0.69 [0.60 ; 0.81]	0.75 [0.66 ; 0.84]	0.86 [0.67 ; 1.10]
Stroke or TIA history	7 016	7 285	0.82 [0.62 ; 1.08]	0.80 [0.58 ; 1.11]	0.84 [0.66 ; 1.08]	0.82 [0.66 ; 1.02]	0.82 [0.70 ; 0.96]	0.73 [0.43 ; 1.24]
Vascular disease history	3 329	3 521	0.85 [0.66 ; 1.09]	1.04 [0.76 ; 1.42]	0.98 [0.78 ; 1.21]	0.80 [0.66 ; 0.97]	0.85 [0.73 ; 0.97]	0.79 [0.60 ; 1.03]
Age 65-74 years	4 098	4 315	0.80 [0.63 ; 1.02]	0.58 [0.46 ; 0.74]	0.68 [0.58 ; 0.81]	0.72 [0.61 ; 0.85]	0.71 [0.63 ; 0.81]	0.85 [0.66 ; 1.10]
Age ≥ 75 years	11 042	10 963	0.77 [0.64 ; 0.93]	0.69 [0.58 ; 0.82]	0.90 [0.79 ; 1.02]	0.66 [0.59 ; 0.73]	0.68 [0.62 ; 0.74]	0.87 [0.70 ; 1.10]
HAS-BLED score								
0-1	11 453	10 821	0.76 [0.58 ; 0.99]	0.66 [0.49 ; 0.89]	0.88 [0.73 ; 1.07]	0.61 [0.51 ; 0.72]	0.66 [0.57 ; 0.75]	0.84 [0.61 ; 1.17]
2-3	18 137	18 731	0.78 [0.66 ; 0.93]	0.68 [0.58 ; 0.80]	0.84 [0.75 ; 0.94]	0.69 [0.62 ; 0.76]	0.71 [0.66 ; 0.77]	0.81 [0.67 ; 0.97]
>3	1 581	1 619	0.92 [0.63 ; 1.34]	0.72 [0.49 ; 1.07]	0.77 [0.57 ; 1.04]	0.74 [0.57 ; 0.95]	0.76 [0.62 ; 0.93]	0.77 [0.45 ; 1.31]
Quintiles of logit hdPS								
Quintile 1	6 151	6 317	0.88 [0.69 ; 1.12]	0.83 [0.66 ; 1.04]	0.99 [0.83 ; 1.17]	0.73 [0.64 ; 0.82]	0.78 [0.70 ; 0.86]	0.79 [0.59 ; 1.07]
Quintile 2	5 987	6 482	0.94 [0.71 ; 1.23]	0.73 [0.56 ; 0.95]	0.95 [0.79 ; 1.15]	0.74 [0.63 ; 0.88]	0.78 [0.68 ; 0.89]	0.77 [0.56 ; 1.06]
Quintile 3	5 878	6 590	0.83 [0.61 ; 1.14]	0.64 [0.48 ; 0.87]	0.77 [0.62 ; 0.95]	0.58 [0.46 ; 0.73]	0.65 [0.55 ; 0.76]	1.10 [0.78 ; 1.55]
Quintile 4	6 316	6 153	0.66 [0.46 ; 0.94]	0.66 [0.46 ; 0.95]	0.78 [0.61 ; 1.00]	0.72 [0.55 ; 0.95]	0.67 [0.55 ; 0.82]	0.64 [0.44 ; 0.93]
Quintile 5	6 839	5 629	0.60 [0.41 ; 0.88]	0.40 [0.25 ; 0.64]	0.64 [0.49 ; 0.84]	0.63 [0.45 ; 0.89]	0.59 [0.47 ; 0.74]	0.84 [0.55 ; 1.28]

10.4.3. Rivaroxaban 20 mg versus dabigatran 150 mg comparison of the 1-year risk of outcomes during the exposure period (on treatment)

For matched patients of the specific population and a 60-day grace period for drug discontinuation definition, the risk of SSE was not different between rivaroxaban 20 mg and dabigatran 150 mg (HR: 0.90 [0.71 to 1.13]) while the risk of major bleeding, death, and the composite of the three main outcomes (SSE, major bleeding and death) was significantly lower with dabigatran: 43% [22% to 58%], 22% [6% to 35%] and 17% [5% to 28%], respectively (**Figure 16**; Appendix 1-5, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101).

The lack of SSE risk difference persisted for individual outcomes, ischemic or undefined stroke, and other SE or surgical procedure for SE (**Figure 17)**. The risk was also significantly lower with dabigatran for ACS (26% [5% to 43%]) including unstable angina (32% [7% to 51%), but not for STEMI (0.76 [0.45 to 1.28]) and NSTEMI (1.87 [0.95 to 3.66]) (**Figures 16 and 17)**. It was also significantly lower with dabigatran for most bleeding subgroups: 44% [32% to 54%] for CRB, 57% [24% to 76%] for haemorrhagic stroke, 30% [4% to 48%] for GI bleeding, 59% [36% to 74%] for urogenital bleeding, 53% [28% to 69%] for other bleeding, but not for other critical organ or site bleeding (HR: 0.96 [0.53 to 1.74]) (**Figures 16 and 17)**.

For all outcomes, hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figures 16 and 17)**.

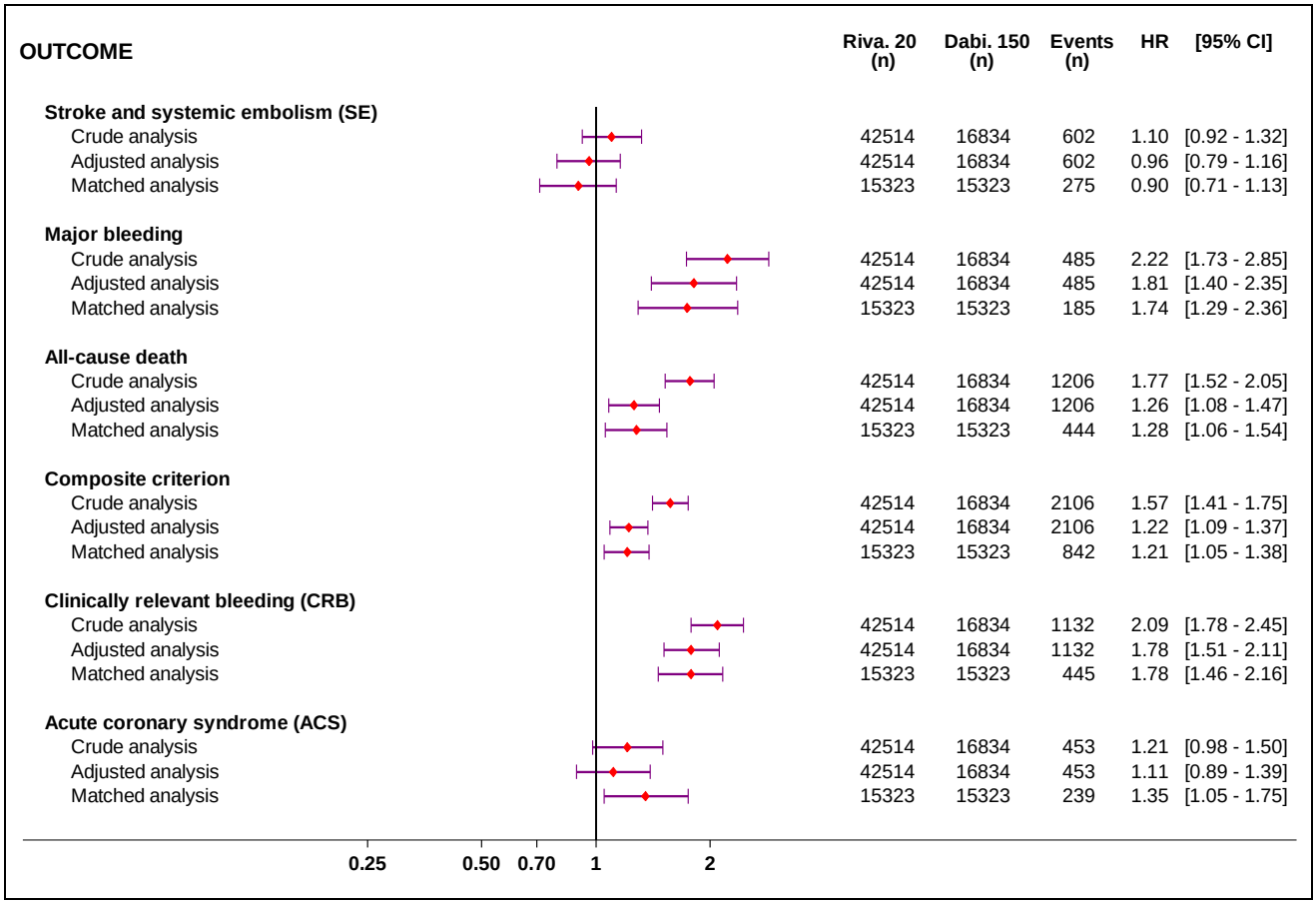


Figure 16. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation (main analysis)

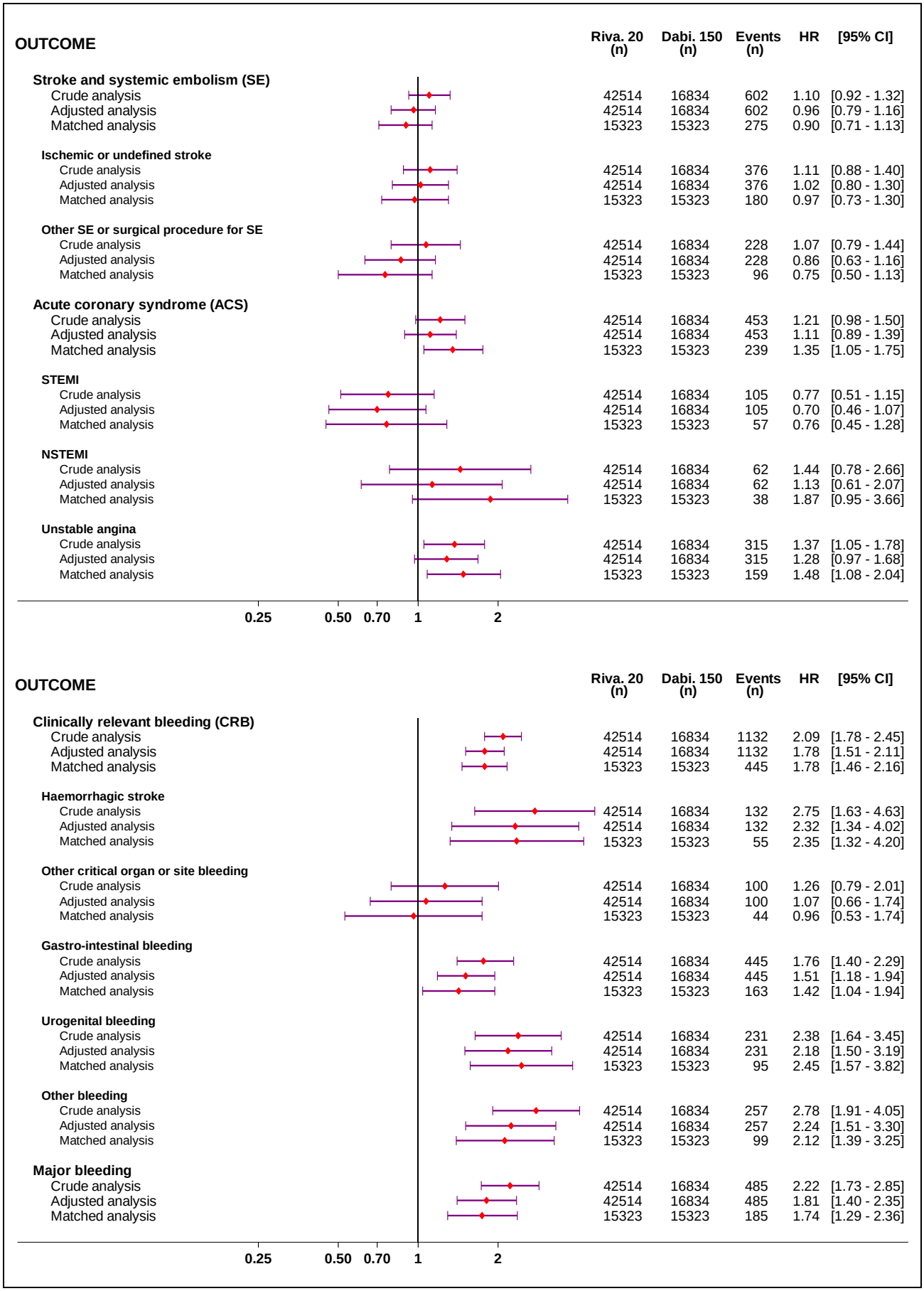


Figure 17. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95% CI of outcome details for the specific population and a 60-day grace period for drug discontinuation (main analysis)

For the sensitivity analyses, results for main and secondary outcomes remained essentially unchanged with a 30-day grace period (**Figure 18**; Appendix 1-14, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), as well as for the sensitive population and a 60-day grace period (**Figure 18**; Appendix 1-10, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), except for the risk of SSE (significantly lower with rivaroxaban 20 mg, 23% [3% to 93%]), and for the risk of ACS (without significant increase, 1.27 [0.99 to 1.64]) for the sensitive population and a 60-day grace period.

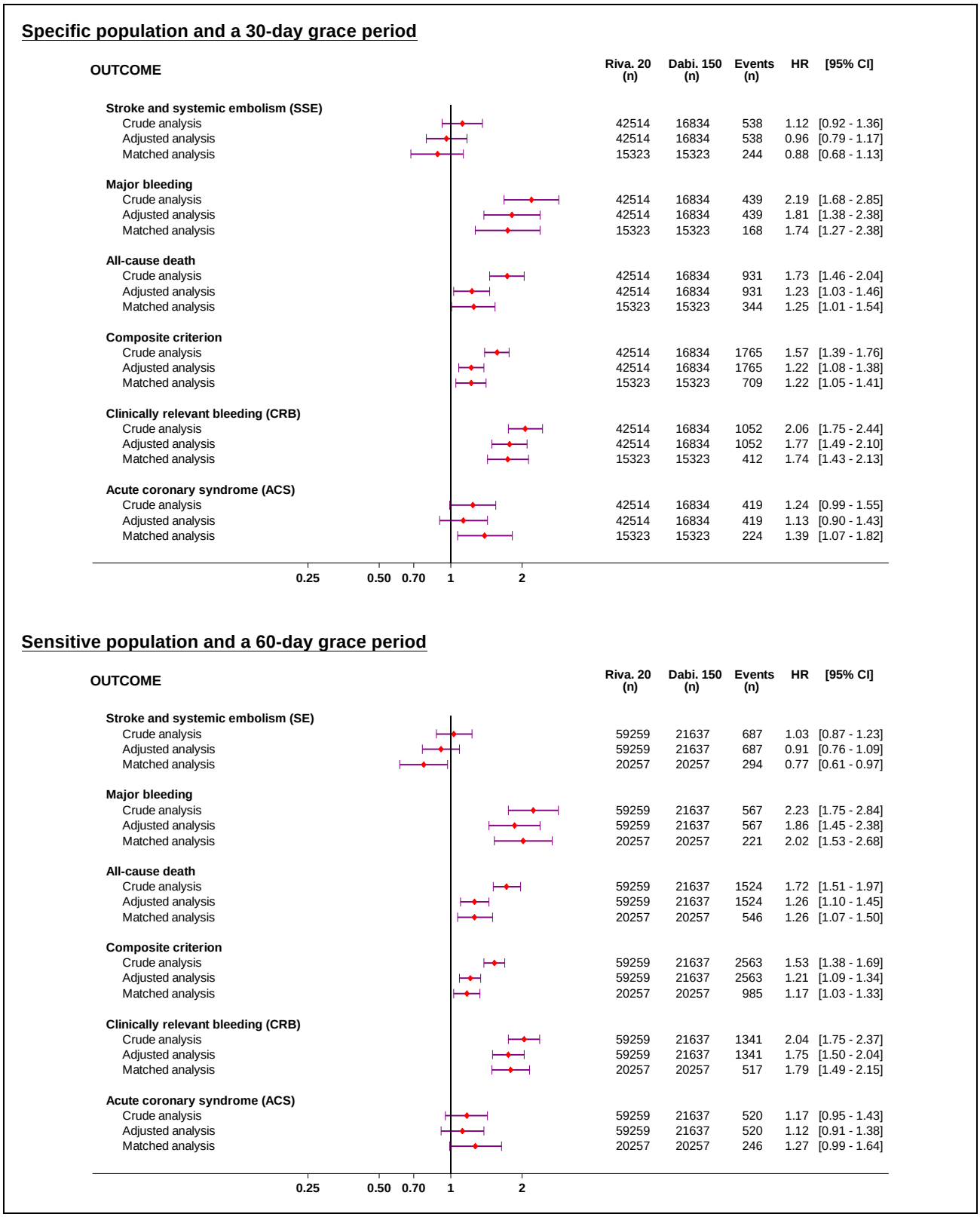


Figure 18. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period (sensitivity analyses)

For the rivaroxaban 20 mg versus dabigatran 150 mg comparison, stratified analyses for the specific population and a 60-day grace period (**Table 49**) showed substantial variations of the HR point estimate according to the different subgroups:

- **For stroke and systemic embolism,**
  - At least 25% significantly lower with rivaroxaban for < 65 years old (43%), vascular disease history (46%), and non-significantly for 2014 index date (26%), CHA_2DS_2-VASc score 3 (31%), and diabetes mellitus (25%),
  - Between 10% and 24% non-significantly lower with rivaroxaban for all matched patients (10%), male (13%), CHA_2DS_2-VASc score 2 (19%), congestive heart failure (16%), hypertension (23%), stroke or TIA history (10%), HAS-BLED scores 0-1 and 2-3 (15% and 13%, respectively), the second and last quintiles of logit hdPS (22% and 17%, respectively),
  - Relatively similar with HR between 0.91 and 1.10 for 2013 index date (0.96), female (0.98), 65-69, 70-74 and 75-79 years old (1.03, 1.10 and 0.95, respectively), CHA_2DS_2-VASc scores ≥ 4 (0.92), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (1.06 and 1.08, respectively), and the three and fourth quintiles (1.10 and 1.02, respectively),
  - Between 10% and 24% non-significantly lower with dabigatran for CHA_2DS_2-VASc scores 0-1 (12%, i.e. inverse of 1.14; [1-(1/1.14)]), and HAS-BLED scores > 3 (18%) with very few patients and large 95%CI,
  - At least 25% non-significantly lower with dabigatran for ≥ 80 years old (31%) with very few patients and large 95%CI,
  - Without clear systematic variation;
- **For major bleeding,**
  - Relatively similar with HR between 0.91 and 1.10 for ≥ 80 years old (1.08),
  - Between 10% and 24% non-significantly lower with dabigatran for 2014 index date (10%), female (23%), and the first quintile of logit hdPS (22%),
  - At least 25% lower with dabigatran for all matched patients (43%, i.e. inverse of 1.74; [1-(1/1.74)]), 2013 index date (55%), male (47%), < 65, 65-69, 70-74, and 75-79 years old (59%, 36%, 56% and 34%, respectively), all CHA_2DS_2-VASc scores (56%, 47%, 32% and 38%, respectively), congestive heart failure (37%), hypertension (45%), diabetes mellitus (47%), stroke or TIA history (31%), vascular disease history (61%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (47% and 25%, respectively), all HAS-BLED scores (43%, 45% and 25%, respectively), the four last quintiles (76%, 53%, 39% and 35%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - None lower with rivaroxaban,
  - Without clear systematic variation;
- **For clinically relevant bleeding,**
  - Between 10% and 24% non-significantly lower with dabigatran for 75-79 years old (23%), and age ≥ 75 years as CHA_2DS_2-VASc risk factor (24%),
  - At least 25% lower with dabigatran for all matched patients (44%), 2013 and 2014 index date (49% and 32%, respectively), male and female (46% and 36%, respectively), < 65, 65-69, 70-74, ≥ 80 years old (58%, 44%, 50% and 25%, respectively), all CHA_2DS_2-VASc scores (62%, 35%, 40%, and 32%, respectively), congestive heart failure (44%), hypertension (35%), diabetes mellitus (41%), stroke or TIA history (30%), vascular disease history (53%), age 65-74 years as CHA_2DS_2-VASc risk factor (47%), all HAS-BLED scores (54%, 38% and 32%, respectively), all quintiles of logit hdPS (31%, 52%, 64%, 35% and 39%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - None lower than with rivaroxaban,
  - With a gradient for HAS-BLED, from 1.46 to 2.18 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;

- **For death,**
  - Between 10% and 24% non-significantly lower with rivaroxaban for < 65 years old (19%), HAS-BLED scores > 3 (17%), and stroke or TIA history (18%), and the first quintile of logit hdPS (11%),
  - Relatively similar with HR between 0.91 and 1.10 for CHA_2DS_2-VASc scores 2 and 3 (1.09 and 1.10, respectively), and vascular disease history (0.99),
  - Between 10% and 24% lower with dabigatran for all matched patients (22%), 2014 index date (12%), male (16%), CHA_2DS_2-VASc scores 0-1 (24%), congestive heart failure (24%), hypertension (24%), HAS-BLED scores 0-1 (17%), the two last quintiles (19% and 21%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - At least 25% lower with dabigatran for 2013 index date (26%), female (41%), 65-69, 70-74, 75-79 and ≥ 80 years old (40%, 32%, 28% and 37%, respectively), CHA_2DS_2-VASc scores ≥ 4 (38%), diabetes mellitus (32%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (35% and 31%, respectively), HAS-BLED scores 2-3 (29%), the second and third quintiles (50% and 25%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - Without clear systematic variation;
- **For the composite criterion (stroke and systemic embolism, major bleeding and death),**
  - Between 10% and 24% non-significantly lower with rivaroxaban for < 65 years old (13%), and vascular disease history (12%),
  - Relatively similar with HR between 0.91 and 1.10 for 2014 index date (1.01), CHA_2DS_2-VASc scores 2 and 3 (1.10 and 1.05, respectively), stroke or TIA history (0.96), HAS-BLED scores > 3 (1.03), and the first quintile of logit hdPS (0.97),
  - Between 10% and 24% lower with dabigatran for all matched patients (17%), 2013 index date (24%), male (14%), 75-79 years old (18%), CHA_2DS_2-VASc scores ≥ 4 (23%), congestive heart failure (20%), hypertension (16%), diabetes mellitus (19%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (20%), HAS-BLED scores 0-1 and 2-3 (14% and 21%, respectively), the two last quintiles (14% and 13%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - At least 25% lower with dabigatran for female (28%), 65-69, 70-74 and ≥ 80 years (29%, 32% and 25%, respectively), CHA_2DS_2-VASc scores 0-1 (26%), age 65-74 years as CHA_2DS_2-VASc risk factor (30%), the second and third quintiles (27% and 34%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - Without clear systematic variation;
- **For ACS,**
  - At least 25% non-significantly lower with rivaroxaban for ≥ 80 years (58%), stroke or TIA history (49%), HAS-BLED scores > 3 (88%),
  - Relatively similar with HR between 0.91 and 1.10 for 2014 index date (0.98), and the first quintile of logit hdPS (0.95),
  - Between 10% and 24% non-significantly lower with dabigatran for male (18%), < 65 years old (19%), CHA_2DS_2-VASc scores 0-1, 2 and 3 (22%, 20% and 24%, respectively), vascular disease history (15%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (16%), the second and last quintiles (15% and 17%, respectively),
  - At least 25% lower with dabigatran for all patients (26%), 2013 index date (36%), female (44%), 65-69, 70-74 and 75-79 years old (32%, 38% and 32%, respectively), CHA_2DS_2-VASc scores ≥ 4 (40%), congestive heart failure (52%), hypertension (26%), diabetes mellitus (31%), age 65-74 years as CHA_2DS_2-VASc risk factor (35%), HAS-BLED scores 0-1 and 2 (39% and 27%, respectively), the third and fourth quintiles (49% and 38%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - With a gradient for HAS-BLED, from 0.12 to 1.63 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors.

Table 49. Rivaroxaban 20 mg versus dabigatran 150 mg stratified analyses of main and secondary outcomes for matched patients, hazard ratio (HR and 95%CI)

	Rivaroxaban 20 mg n	**Dabigatran 150 mg** n	Stroke and systemic embolism HR [95%CI]	Major bleeding HR [95%CI]	Clinically relevant bleeding HR [95%CI]	Death (all causes) HR [95%CI]	Composite criterion HR [95%CI]	Acute coronary syndrome HR [95%CI]
All matched patients	15 323	15 323	0.90 [0.71 ; 1.13]	1.74 [1.29 ; 2.36]	1.78 [1.46 ; 2.16]	1.28 [1.06 ; 1.54]	1.21 [1.05 ; 1.38]	1.35 [1.05 ; 1.75]
Index date								
2013	10 402	10 402	0.96 [0.73 ; 1.26]	2.24 [1.53 ; 3.30]	1.95 [1.54 ; 2.47]	1.36 [1.08 ; 1.71]	1.31 [1.11 ; 1.54]	1.57 [1.15 ; 2.14]
2014	4 921	4 921	0.74 [0.46 ; 1.19]	1.11 [0.68 ; 1.83]	1.47 [1.05 ; 2.06]	1.13 [0.81 ; 1.56]	1.01 [0.79 ; 1.29]	0.98 [0.62 ; 1.56]
Gender								
Male	10 724	10 724	0.87 [0.67 ; 1.14]	1.89 [1.35 ; 2.66]	1.86 [1.48 ; 2.32]	1.19 [0.96 ; 1.47]	1.16 [1.00 ; 1.36]	1.22 [0.91 ; 1.65]
Female	4 599	4 599	0.98 [0.60 ; 1.60]	1.30 [0.69 ; 2.48]	1.57 [1.06 ; 2.33]	1.69 [1.12 ; 2.54]	1.38 [1.03 ; 1.84]	1.79 [1.08 ; 2.98]
Age (years)								
<65	5 970	6 005	0.57 [0.36 ; 0.90]	2.41 [1.19 ; 4.85]	2.36 [1.58 ; 3.52]	0.81 [0.56 ; 1.18]	0.87 [0.66 ; 1.13]	1.23 [0.77 ; 1.97]
65-69	3 583	3 513	1.03 [0.64 ; 1.66]	1.57 [0.82 ; 2.97]	1.80 [1.15 ; 2.83]	1.66 [1.08 ; 2.54]	1.40 [1.04 ; 1.88]	1.48 [0.89 ; 2.45]
70-74	2 930	2 981	1.10 [0.66 ; 1.83]	2.29 [1.17 ; 4.50]	1.99 [1.33 ; 2.99]	1.46 [0.98 ; 2.18]	1.47 [1.10 ; 1.97]	1.61 [0.90 ; 2.91]
75-79	2 187	2 162	0.95 [0.54 ; 1.68]	1.52 [0.83 ; 2.78]	1.30 [0.87 ; 1.95]	1.38 [0.90 ; 2.13]	1.22 [0.90 ; 1.67]	1.46 [0.82 ; 2.60]
≥ 80	653	662	1.45 [0.62 ; 3.38]	1.08 [0.48 ; 2.45]	1.33 [0.72 ; 2.45]	1.58 [0.91 ; 2.73]	1.33 [0.87 ; 2.02]	0.42 [0.11 ; 1.64]
CHA_2DS_2-VASc score								
0-1	6 396	6 417	1.14 [0.72 ; 1.80]	2.26 [1.15 ; 4.44]	2.66 [1.79 ; 3.94]	1.32 [0.91 ; 1.92]	1.35 [1.03 ; 1.77]	1.28 [0.79 ; 2.08]
2	3 933	3 823	0.81 [0.48 ; 1.36]	1.90 [0.98 ; 3.70]	1.55 [1.04 ; 2.29]	1.09 [0.74 ; 1.61]	1.10 [0.82 ; 1.47]	1.25 [0.75 ; 2.08]
3	2 584	2 641	0.69 [0.39 ; 1.19]	1.46 [0.77 ; 2.74]	1.68 [1.09 ; 2.59]	1.10 [0.74 ; 1.63]	1.05 [0.78 ; 1.41]	1.32 [0.80 ; 2.19]
≥ 4	2 410	2 442	0.92 [0.61 ; 1.39]	1.62 [0.99 ; 2.67]	1.46 [1.02 ; 2.08]	1.61 [1.13 ; 2.30]	1.30 [1.02 ; 1.66]	1.68 [0.95 ; 2.96]
Risk factors								
Congestive heart failure	1 837	1 854	0.84 [0.44 ; 1.59]	1.59 [0.86 ; 2.93]	1.80 [1.15 ; 2.82]	1.31 [0.92 ; 1.87]	1.25 [0.94 ; 1.66]	2.08 [1.04 ; 4.16]
Hypertension	4 792	4 788	0.77 [0.53 ; 1.11]	1.81 [1.14 ; 2.86]	1.53 [1.12 ; 2.07]	1.32 [1.00 ; 1.76]	1.19 [0.97 ; 1.47]	1.35 [0.89 ; 2.04]
Diabetes mellitus	3 207	3 190	0.75 [0.49 ; 1.13]	1.87 [1.11 ; 3.13]	1.70 [1.18 ; 2.45]	1.47 [1.04 ; 2.07]	1.23 [0.97 ; 1.57]	1.44 [0.92 ; 2.26]
Stroke or TIA history	1 191	1 260	0.90 [0.57 ; 1.43]	1.44 [0.73 ; 2.86]	1.43 [0.87 ; 2.34]	0.82 [0.47 ; 1.42]	0.96 [0.69 ; 1.34]	0.51 [0.19 ; 1.37]
Vascular disease history	1 455	1 411	0.54 [0.33 ; 0.90]	2.54 [1.23 ; 5.24]	2.12 [1.30 ; 3.47]	0.99 [0.63 ; 1.58]	0.88 [0.64 ; 1.20]	1.17 [0.69 ; 2.01]
Age 65-74 years	6 513	6 494	1.06 [0.75 ; 1.50]	1.88 [1.18 ; 2.98]	1.89 [1.40 ; 2.56]	1.54 [1.15 ; 2.07]	1.43 [1.17 ; 1.76]	1.54 [1.05 ; 2.26]
Age ≥ 75 years	2 840	2 824	1.08 [0.68 ; 1.74]	1.34 [0.83 ; 2.18]	1.31 [0.94 ; 1.83]	1.44 [1.03 ; 2.02]	1.25 [0.97 ; 1.60]	1.19 [0.71 ; 1.99]
HAS-BLED score								
0-1	8 068	8 089	0.85 [0.57 ; 1.25]	1.74 [1.02 ; 2.97]	2.18 [1.57 ; 3.03]	1.21 [0.89 ; 1.66]	1.16 [0.93 ; 1.46]	1.63 [1.06 ; 2.51]
2-3	6 826	6 803	0.87 [0.62 ; 1.21]	1.83 [1.23 ; 2.73]	1.60 [1.24 ; 2.07]	1.40 [1.09 ; 1.80]	1.26 [1.05 ; 1.52]	1.37 [0.98 ; 1.91]
>3	429	431	1.22 [0.62 ; 2.40]	1.33 [0.54 ; 3.29]	1.46 [0.70 ; 3.02]	0.83 [0.42 ; 1.67]	1.03 [0.66 ; 1.62]	0.12 [0.02 ; 0.97]
Quintiles of logit hdPS								
Quintile 1	2 969	3 160	0.93 [0.52 ; 1.64]	1.28 [0.69 ; 2.39]	1.44 [0.93 ; 2.23]	0.89 [0.56 ; 1.40]	0.97 [0.70 ; 1.34]	0.95 [0.49 ; 1.82]
Quintile 2	3 083	3 046	0.78 [0.47 ; 1.28]	4.12 [1.38 ; 12.3]	2.07 [1.24 ; 3.43]	2.02 [1.18 ; 3.44]	1.37 [0.98 ; 1.92]	1.18 [0.64 ; 2.16]
Quintile 3	3 110	3 020	1.10 [0.59 ; 2.03]	2.13 [1.08 ; 4.19]	2.74 [1.65 ; 4.55]	1.34 [0.83 ; 2.17]	1.52 [1.08 ; 2.14]	1.97 [1.04 ; 3.72]
Quintile 4	3 095	3 034	1.02 [0.55 ; 1.87]	1.65 [0.77 ; 3.54]	1.55 [1.00 ; 2.42]	1.24 [0.80 ; 1.92]	1.16 [0.83 ; 1.62]	1.61 [0.94 ; 2.76]
Quintile 5	3 066	3 063	0.83 [0.54 ; 1.29]	1.53 [0.90 ; 2.60]	1.64 [1.15 ; 2.33]	1.27 [0.93 ; 1.75]	1.15 [0.91 ; 1.46]	1.21 [0.73 ; 2.00]

10.4.4. Rivaroxaban 15 mg versus VKA comparison of the 1-year risk of outcomes during the exposure period (on treatment)

For matched patients of the specific population and a 60-day grace period for drug discontinuation definition, the risk of SSE was not different between rivaroxaban 15 mg and VKA (HR: 1.05 [0.92 to 1.21]), and a significant lower risk for the two other outcomes of the main objective, major bleeding and death, as well as for the composite of these three events: 16% [4% to 26%], 15% [10% to 21%], and 11% [6% to 16%], respectively (**Figure 19**; Appendix 1-6, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101).

The lack of SSE risk difference persisted for individual outcomes, ischemic or undefined stroke, and other SE or surgical procedure for SE (**Figure 20).** The risk of ACS was at the significant threshold (HR: 0.85 [0.73 to 1.00]) (**Figure 19**), and the risk for most bleeding subgroups was in favour of rivaroxaban: CRB (11% [2% to 19%]), haemorrhagic stroke (26% [5% to 42%]), urogenital bleeding (26% [5% to 42%]), other bleeding (17% [2% to 30%]), at the significant threshold for other critical organ or site bleeding (HR: 0.76 [0.58 to 1.00]), without significant increase for GI bleeding (HR: 1.13 [0.96 to 1.33]) (**Figures 19 and 20)**.

For all outcomes, hazard ratios were similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figures 19 and 20**).

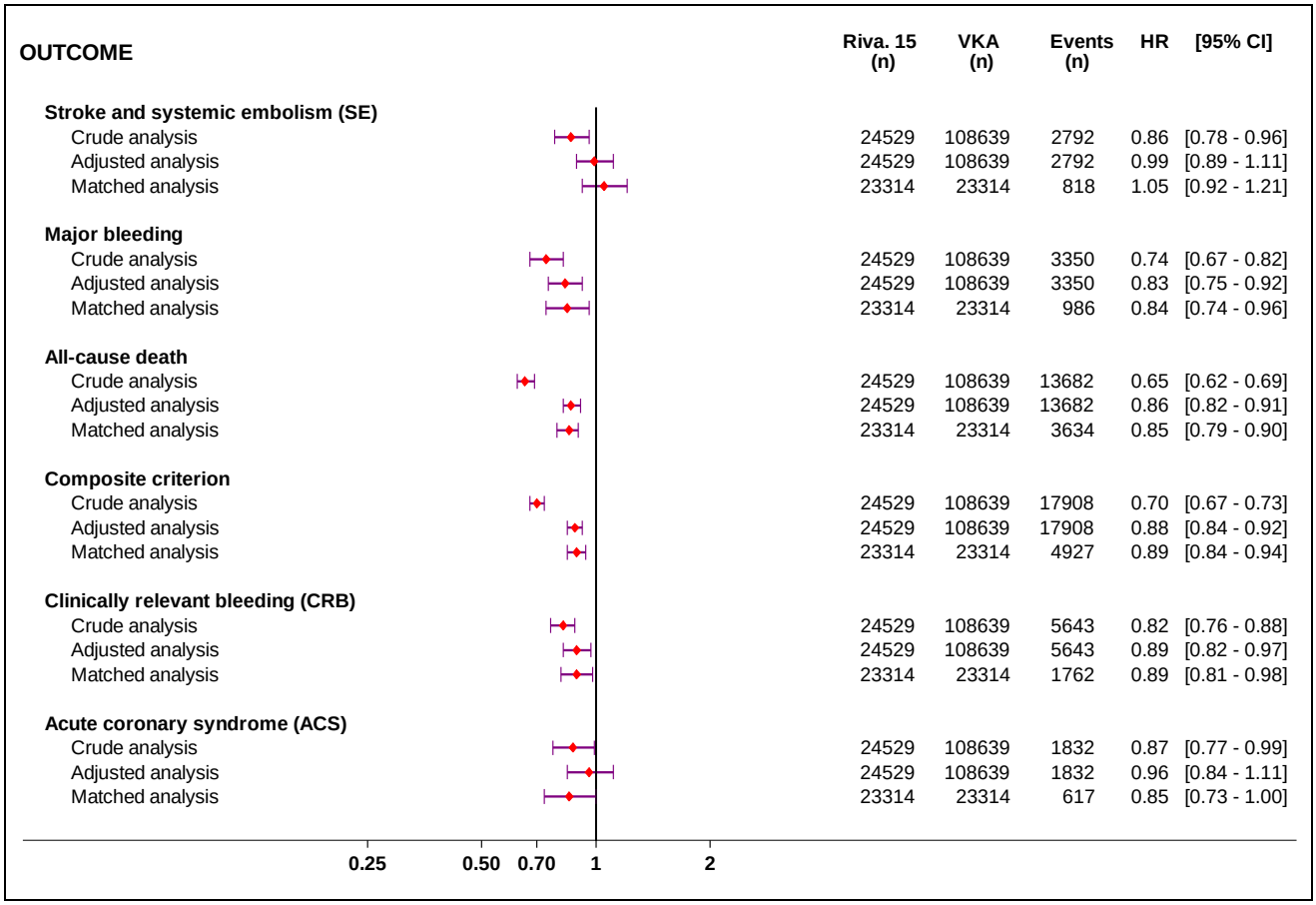


Figure 19. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation (main analysis)

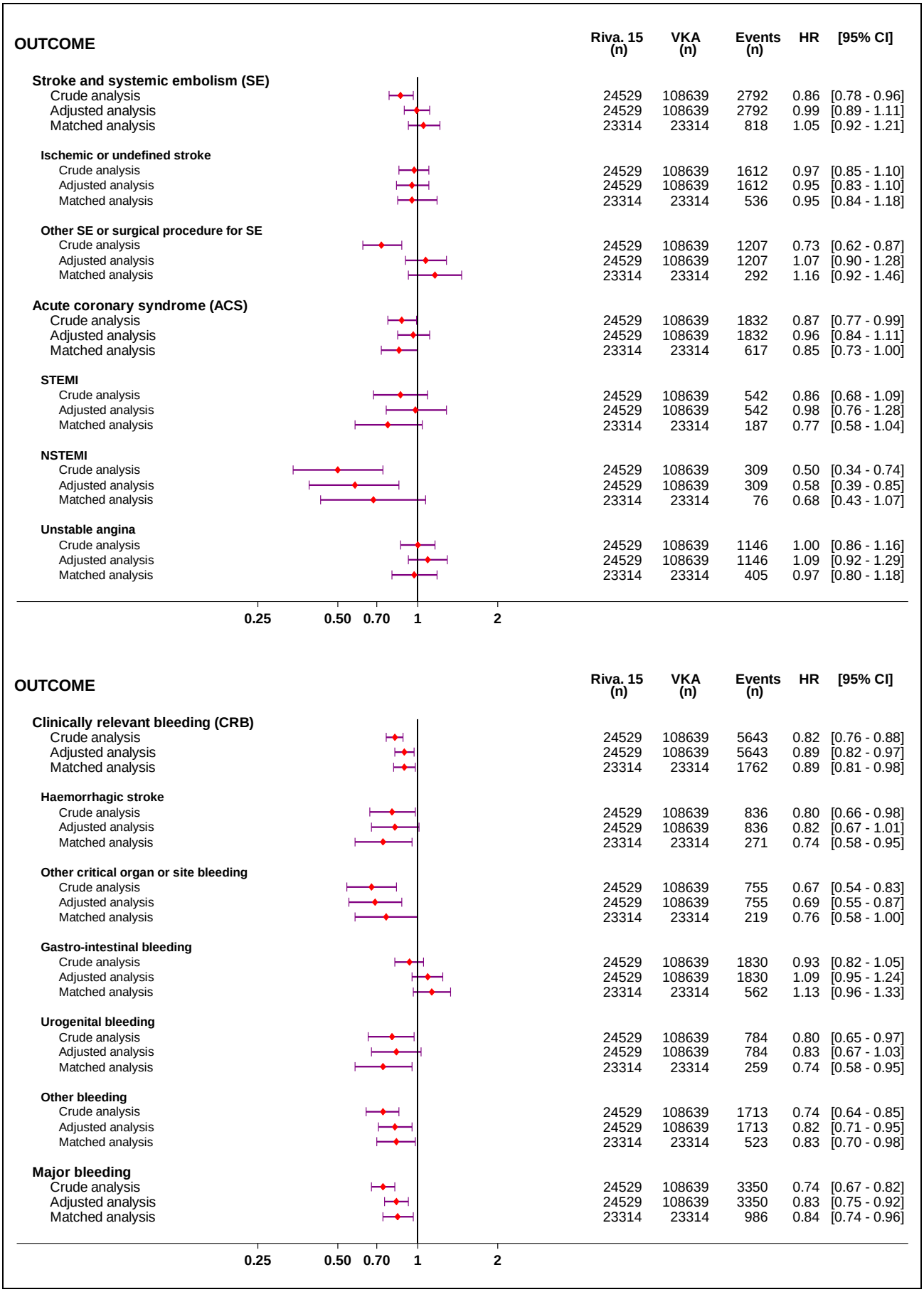


Figure 20. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95% CI of outcome details for the specific population and a 60-day grace period for drug discontinuation (main analysis)

For the sensitivity analyses, results for main and secondary outcomes remained essentially unchanged with a 30-day grace period (**Figure 21**; Appendix 1-15, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), as well as for the sensitive population and a 60-day grace period (**Figure 21**; Appendix 1-11, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), except for the risk of ACS: significantly lower with rivaroxaban 15 mg and a 30-day grace period (18% [3% to 31%]), and with no difference for the sensitive population and a 60-day grace period (0.92 [0.79 to 1.06]).

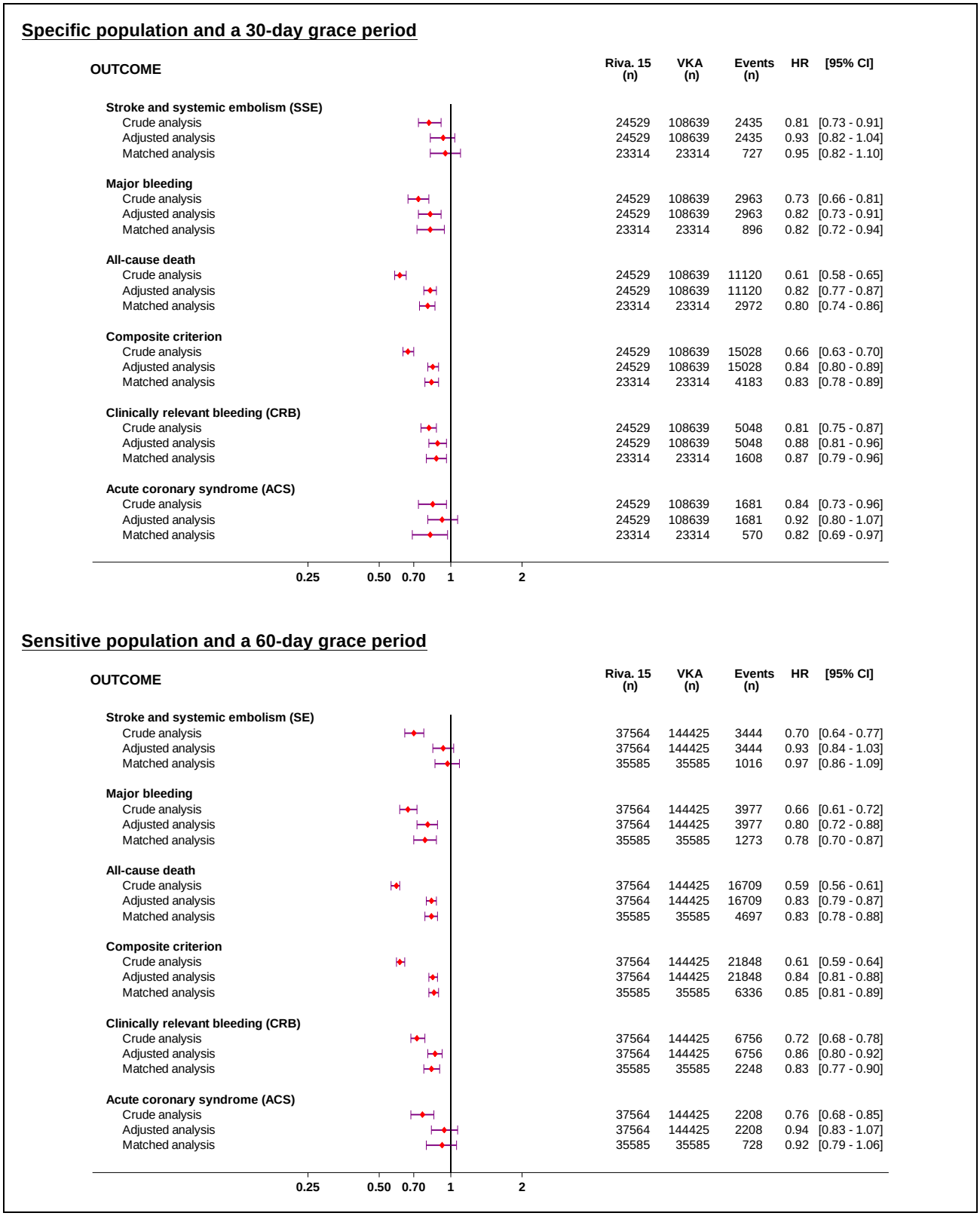


Figure 21. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period (sensitivity analyses)

For the rivaroxaban 15 mg versus VKA comparison, stratified analyses for the specific population and a 60-day grace period (**Table 50**) showed substantial variations of the HR point estimate according to the different subgroups:

- **For stroke and systemic embolism,**
  - At least 25% non-significantly lower with rivaroxaban for the last quintile of logit hdPS (26%),
  - Between 10% and 24% non-significantly lower with rivaroxaban for < 65 years old (14%), and CHA_2DS_2-VASc score 3 (11%),
  - Similar with HR between 0.91 and 1.10 for all matched patients (1.05), 2014 index date (0.92), female (0.94), 75-79 and ≥ 80 years old (0.95 and 1.07, respectively), CHA_2DS_2-VASc score 2 (1.04), hypertension (1.08), stroke or TIA history (1.05), age ≥ 75 years as CHA_2DS_2-VASc risk factor (1.05), all HAS-BLED scores (1.04, 1.06 and 1.10, respectively), and the fourth quintile (1.07),
  - Between 10% and 24% non-significantly lower with VKA for 2013 index date (15%), male (15%), 65-69 and 70-74 years old (12% and 22%, respectively), CHA_2DS_2-VASc scores 0-1 and ≥ 4 (24% and 10%, respectively), congestive heart failure (16%), diabetes mellitus (18%), vascular disease history (15%), age 65-74 years as CHA_2DS_2-VASc risk factor (18%), and the three first quintiles (14%, 17% and 12%, respectively),
  - With a weak gradient for quintiles, from 0.74 to 1.16 for the last to the first quintile, relatively stable for HAS-BLED scores and no clear systematic variation for the other factors.
- **For major bleeding,**
  - At least 25% lower with rivaroxaban for 65-69 years old (47%), CHA_2DS_2-VASc score 2 (32%), and HAS-BLED > 3 (46%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 50**),
  - Between 10% and 24% lower with rivaroxaban for all matched patients (16%), 2013 and 2014 index date (10% and 21%, respectively), male and female (10% and 21%, respectively), < 65, 75-79 and ≥ 80 years old (23%, 17% and 16%, respectively), CHA_2DS_2-VASc scores 3 and ≥ 4 (18% and 11%, respectively), hypertension (19%), vascular disease history (10%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (13% and 16%, respectively), HAS-BLED scores 2-3 (13%), the four last quintiles of logit hdPS (19%, 24%, 10% and 20%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 50**),
  - Similar with HR between 0.91 and 1.10 for 70-74 years old (1.09), congestive heart failure (0.96), diabetes mellitus (0.96), stroke or TIA history (0.96), and the first quintile (0.94),
  - Between 10% and 24% non-significantly lower with VKA for CHA_2DS_2-VASc scores 0-1 (24%) and HAS-BLED scores 0-1 (10%),
  - With a gradient for HAS-BLED, from 0.54 to 1.11 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For clinically relevant bleeding,**
  - At least 25% significantly lower with rivaroxaban for HAS-BLED scores > 3 (38%), and non-significantly lower for < 65 years old (27%),
  - Between 10% and 24% lower with rivaroxaban for all matched patients (11%), 2014 index date (14%), female (18%), 65-69 and ≥ 80 years old (22% and 12%, respectively), CHA_2DS_2-VASc scores 2 and 3 (23% and 15%, respectively), hypertension (13%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (11%), the three last quintiles of logit hdPS (21%, 11% and 16%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 50**),
  - Similar with HR between 0.91 and 1.10 for 2013 index date (0.92), male (0.96), 70-74 and 75-79 years old (0.98 and 0.96, respectively), CHA_2DS_2-VASc scores 0-1 and ≥ 4 (1.02 and 0.94, respectively), congestive heart failure (1.07), diabetes mellitus (1.01), stroke or TIA history (0.93), vascular disease history (0.92), age 65-74 years as CHA_2DS_2-VASc risk factor (0.91), HAS-BLED scores 0-1 and 2-3 (1.02 and 0.93, respectively), and the two first quintiles (0.95 and 0.98, respectively),
  - With a gradient for HAS-BLED, from 0.62 to 1.02 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;

- **For death,**
  - Between 10% and 24% lower with rivaroxaban for all matched patients (15%), 2013 and 2014 index date (16% and 14%, respectively), male and female (14% and 16%, respectively), 75-79 and ≥ 80 years old (11% and 18%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (13%, 13% and 17%, respectively), congestive heart failure (16%), hypertension (16%), diabetes mellitus (17%), vascular disease history (13%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (17%), all HAS-BLED scores (15%, 14% and 19%, respectively), the fourth last quintiles of logit hdPS (12%, 21%, 20% and 24%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 50**),
  - Similar with HR between 0.91 and 1.10 for < 65 and 65-69 years old (1.02 and 1.08, respectively), stroke or TIA history (0.94), and the first quintile (0.95),
  - Between 10% and 24% non-significantly lower with VKA for 70-74 years old (13%), CHA_2DS_2-VASc scores 0-1 (19%), and age 65-74 years as CHA_2DS_2-VASc risk factor (11%),
  - With a gradient for CHA_2DS_2-VASc, from 0.83 to 1.23 for scores ≥ 4 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For the composite criterion (stroke and systemic embolism, major bleeding and death),**
  - Between 10% and 24% significantly lower with rivaroxaban for all matched patients (11%), 2013 and 2014 index date (10% and 13%, respectively), female (14%), ≥ 80 years old (13%), CHA_2DS_2-VASc scores 3 and ≥ 4 (12% and 11%, respectively), congestive heart failure (10%), hypertension (12%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (13%), HAS-BLED scores 2-3 and > 3 (10% and 17%, respectively), the three last quintiles of logit hdPS (14%, 13% and 22%, respectively), and non-significantly lower for CHA_2DS_2-VASc score 2 (14%),
  - Similar with HR between 0.91 and 1.10 for male (0.92), < 65, 65-69 and 75-79 years old (0.93, 1.0 and 0.91, respectively), diabetes mellitus (0.91), stroke or TIA history (0.97), vascular disease history (0.94), age 65-74 years as CHA_2DS_2-VASc risk factor (1.09), HAS-BLED scores 0-1 (0.91) and the two first quintiles (0.98 and 0.91, respectively),
  - Between 10% and 24% non-significantly lower with VKA for 70-74 years old (13%) and CHA_2DS_2-VASc scores 0-1 (21%),
  - With a weak gradient for HAS-BLED, from 0.83 to 0.91 for scores > 3 to scores 0-1 HR, and for CHA_2DS_2-VASc, from 0.89 to 1.26 for scores ≥ 4 to scores 0-1, and no clear systematic variation for the other factors;
- **For ACS,**
  - At least 25% significantly lower with rivaroxaban for CHA_2DS_2-VASc score 3 (32%), HAS-BLED scores > 3 (48%), and the fourth quintile of logit hdPS (32%),
  - Between 10% and 24% lower with rivaroxaban for all matched patients (15%), 2014 index date (22%), female (23%), 75-79 and ≥ 80 years old (18% and 20%, respectively), CHA_2DS_2-VASc scores ≥ 4 (10%), congestive heart failure (22%), hypertension (19%), diabetes mellitus (17%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (20%), HAS-BLED scores 0-1 (23%), the third and last quintiles (15% and 19%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 50**),
  - Similar with HR between 0.91 and 1.10 for 2013 index date (0.92), male (0.92), 65-69 and 70-74 years old (1.08 and 1.09, respectively), CHA_2DS_2-VASc score 2 (0.96), stroke or TIA history (0.94), vascular disease history (1.06), age 65-74 years as CHA_2DS_2-VASc risk factor (1.08), HAS-BLED scores 2-3 (0.94), the two first quintiles (0.98 and 0.96, respectively),
  - Between 10% and 24% non-significantly lower with VKA for < 65 years old (12%) and CHA_2DS_2-VASc scores 0-1 (22%),
  - Without clear systematic variation.

Table 50. Rivaroxaban 15 mg versus VKA stratified analyses of main and secondary outcomes for matched patients, hazard ratio (HR and 95%CI)

	Rivaroxaban 15 mg	**VKA**	Stroke and systemic embolism	Major bleeding	Clinically relevant bleeding	Death (all causes)	Composite criterion	Acute coronary syndrome
	n	n	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
All matched patients	23 314	23 314	1.05 [0.92 ; 1.21]	0.84 [0.74 ; 0.96]	0.89 [0.81 ; 0.98]	0.85 [0.79 ; 0.90]	0.89 [0.84 ; 0.94]	0.85 [0.73 ; 1.00]
Index date								
2013	12 037	12 037	1.18 [0.98 ; 1.42]	0.90 [0.75 ; 1.07]	0.92 [0.81 ; 1.05]	0.84 [0.77 ; 0.92]	0.90 [0.83 ; 0.97]	0.92 [0.74 ; 1.15]
2014	11 277	11 277	0.92 [0.75 ; 1.13]	0.79 [0.66 ; 0.95]	0.86 [0.75 ; 0.98]	0.86 [0.78 ; 0.94]	0.87 [0.80 ; 0.95]	0.78 [0.62 ; 0.99]
Gender								
Male	11 070	11 070	1.18 [0.97 ; 1.44]	0.90 [0.75 ; 1.07]	0.96 [0.84 ; 1.09]	0.86 [0.79 ; 0.95]	0.92 [0.85 ; 0.99]	0.92 [0.75 ; 1.13]
Female	12 244	12 244	0.94 [0.78 ; 1.14]	0.79 [0.66 ; 0.95]	0.82 [0.71 ; 0.94]	0.84 [0.76 ; 0.92]	0.86 [0.79 ; 0.93]	0.77 [0.60 ; 0.99]
Age (years)								
<65	1 369	1 380	0.86 [0.43 ; 1.73]	0.77 [0.24 ; 2.44]	0.73 [0.34 ; 1.58]	1.02 [0.65 ; 1.61]	0.93 [0.64 ; 1.36]	1.14 [0.59 ; 2.22]
65-69	1 412	1 358	1.13 [0.61 ; 2.11]	0.53 [0.26 ; 1.08]	0.78 [0.48 ; 1.26]	1.08 [0.72 ; 1.64]	1.00 [0.73 ; 1.37]	1.08 [0.54 ; 2.18]
70-74	2 189	2 251	1.28 [0.73 ; 2.25]	1.09 [0.70 ; 1.70]	0.98 [0.71 ; 1.37]	1.15 [0.85 ; 1.54]	1.15 [0.91 ; 1.46]	1.09 [0.66 ; 1.81]
75-79	4 250	4 159	0.95 [0.68 ; 1.34]	0.83 [0.62 ; 1.13]	0.96 [0.77 ; 1.20]	0.89 [0.73 ; 1.08]	0.91 [0.78 ; 1.06]	0.82 [0.57 ; 1.18]
≥ 80	14 094	14 166	1.07 [0.91 ; 1.27]	0.84 [0.73 ; 0.98]	0.88 [0.78 ; 0.98]	0.82 [0.76 ; 0.89]	0.87 [0.81 ; 0.92]	0.80 [0.65 ; 0.98]
CHA_2DS_2-VASc score								
0-1	1 657	1 665	1.32 [0.64 ; 2.74]	1.16 [0.51 ; 2.65]	1.02 [0.56 ; 1.83]	1.23 [0.79 ; 1.92]	1.26 [0.88 ; 1.80]	1.29 [0.58 ; 2.88]
2	3 923	3 798	1.04 [0.70 ; 1.57]	0.68 [0.47 ; 0.97]	0.77 [0.60 ; 0.99]	0.87 [0.71 ; 1.06]	0.86 [0.73 ; 1.01]	0.96 [0.64 ; 1.45]
3	6 531	6 562	0.89 [0.66 ; 1.19]	0.82 [0.64 ; 1.04]	0.85 [0.71 ; 1.02]	0.87 [0.76 ; 0.99]	0.88 [0.78 ; 0.98]	0.68 [0.50 ; 0.94]
≥ 4	11 203	11 289	1.11 [0.94 ; 1.32]	0.89 [0.75 ; 1.05]	0.94 [0.83 ; 1.07]	0.83 [0.76 ; 0.90]	0.89 [0.83 ; 0.95]	0.90 [0.72 ; 1.11]
Risk factors								
Congestive heart failure	5 467	5 393	1.19 [0.90 ; 1.57]	0.96 [0.76 ; 1.21]	1.07 [0.89 ; 1.28]	0.84 [0.76 ; 0.93]	0.90 [0.82 ; 0.99]	0.78 [0.57 ; 1.07]
Hypertension	10 694	10 710	1.08 [0.89 ; 1.30]	0.81 [0.68 ; 0.97]	0.87 [0.76 ; 0.99]	0.84 [0.77 ; 0.91]	0.88 [0.82 ; 0.95]	0.81 [0.65 ; 1.00]
Diabetes mellitus	4 997	5 088	1.22 [0.95 ; 1.56]	0.96 [0.75 ; 1.23]	1.01 [0.84 ; 1.21]	0.83 [0.73 ; 0.95]	0.91 [0.81 ; 1.02]	0.83 [0.62 ; 1.10]
Stroke or TIA history	2 619	2 654	1.05 [0.77 ; 1.42]	0.96 [0.70 ; 1.33]	0.93 [0.72 ; 1.19]	0.94 [0.78 ; 1.12]	0.97 [0.84 ; 1.13]	0.94 [0.56 ; 1.60]
Vascular disease history	3 922	3 989	1.18 [0.92 ; 1.52]	0.90 [0.68 ; 1.18]	0.92 [0.76 ; 1.13]	0.87 [0.76 ; 1.00]	0.94 [0.83 ; 1.05]	1.06 [0.82 ; 1.37]
Age 65-74 years	3 601	3 609	1.22 [0.80 ; 1.85]	0.87 [0.60 ; 1.27]	0.91 [0.69 ; 1.19]	1.12 [0.88 ; 1.43]	1.09 [0.91 ; 1.32]	1.08 [0.72 ; 1.63]
Age ≥ 75 years	18 344	18 325	1.05 [0.90 ; 1.22]	0.84 [0.73 ; 0.96]	0.89 [0.81 ; 0.99]	0.83 [0.77 ; 0.89]	0.87 [0.82 ; 0.92]	0.80 [0.67 ; 0.96]
HAS-BLED score								
0-1	5 401	5 074	1.04 [0.71 ; 1.54]	1.11 [0.79 ; 1.56]	1.02 [0.80 ; 1.30]	0.85 [0.72 ; 1.01]	0.91 [0.79 ; 1.06]	0.77 [0.49 ; 1.19]
2-3	15 799	16 199	1.06 [0.90 ; 1.24]	0.87 [0.75 ; 1.01]	0.93 [0.83 ; 1.04]	0.86 [0.79 ; 0.93]	0.90 [0.84 ; 0.96]	0.94 [0.78 ; 1.13]
>3	2 114	2 041	1.10 [0.75 ; 1.60]	0.54 [0.38 ; 0.77]	0.62 [0.48 ; 0.80]	0.81 [0.68 ; 0.97]	0.83 [0.71 ; 0.97]	0.52 [0.31 ; 0.88]
Quintiles of logit hdPS								
Quintile 1	4 617	4 708	1.16 [0.87 ; 1.54]	0.94 [0.72 ; 1.22]	0.95 [0.78 ; 1.16]	0.95 [0.84 ; 1.07]	0.98 [0.88 ; 1.09]	0.98 [0.71 ; 1.35]
Quintile 2	4 620	4 706	1.21 [0.88 ; 1.67]	0.81 [0.61 ; 1.09]	0.98 [0.80 ; 1.21]	0.88 [0.76 ; 1.00]	0.91 [0.81 ; 1.03]	0.96 [0.67 ; 1.38]
Quintile 3	4 611	4 715	1.13 [0.84 ; 1.52]	0.76 [0.57 ; 1.01]	0.79 [0.63 ; 0.98]	0.79 [0.68 ; 0.92]	0.86 [0.76 ; 0.98]	0.85 [0.58 ; 1.26]
Quintile 4	4 653	4 673	1.07 [0.78 ; 1.46]	0.90 [0.67 ; 1.21]	0.89 [0.71 ; 1.12]	0.80 [0.68 ; 0.95]	0.87 [0.76 ; 1.00]	0.68 [0.47 ; 0.99]
Quintile 5	4 813	4 512	0.74 [0.53 ; 1.02]	0.80 [0.60 ; 1.06]	0.84 [0.68 ; 1.04]	0.76 [0.64 ; 0.91]	0.78 [0.68 ; 0.90]	0.81 [0.58 ; 1.14]

10.4.5. Rivaroxaban 15 mg versus dabigatran 110 mg comparison of the 1-year risk of outcomes during the exposure period (on treatment)

For matched patients of the specific population and a 60-day grace period for drug discontinuation definition, the risk of SSE, major bleeding and the composite of the three main outcomes (SSE, major bleeding, and death) was significantly lower with dabigatran 110 mg compared to rivaroxaban 15 mg: 21% [6% to 35%], 22% [7% to 35%], and 8% [1% to 15%], respectively, with no difference for death risk (HR: 1.04 [0.95 to 1.14]) (**Figure 22**; Appendix 1-7, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101).

For individual SSE outcomes, there was also a significant lower risk with dabigatran 110 mg for other SE or surgical procedure for SE (39% [16% to 56%]), but not for ischemic or undefined stroke (HR: 1.12 [0.90 to 1.39]) (**Figure 23)**. The ACS risk, as well as individual ACS outcomes, STEMI, NSTEMI and unstable angina were not different (HR: 0.97 [0.79 to 1.19], 0.90 [0.62 to 1.30], 0.68 [0.39 to 1.19], 1.12 [0.87 to 1.44], respectively) (**Figures 22 and 23)**. For bleeding subgroups, the risk was significantly lower with dabigatran for CRB (28% [17% to 36%]), haemorrhagic stroke (54% [33% to 69%]), urogenital bleeding (34% [5% to 54%]), and other bleeding (40% [21 to 54]), but not for other critical organ or site bleeding (1.40 [0.95 to 2.08]), and GI bleeding (1.02 [0.83 to 1.29]) (**Figures 22 and 23**).

For all outcomes, hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figures 22 and 23**).

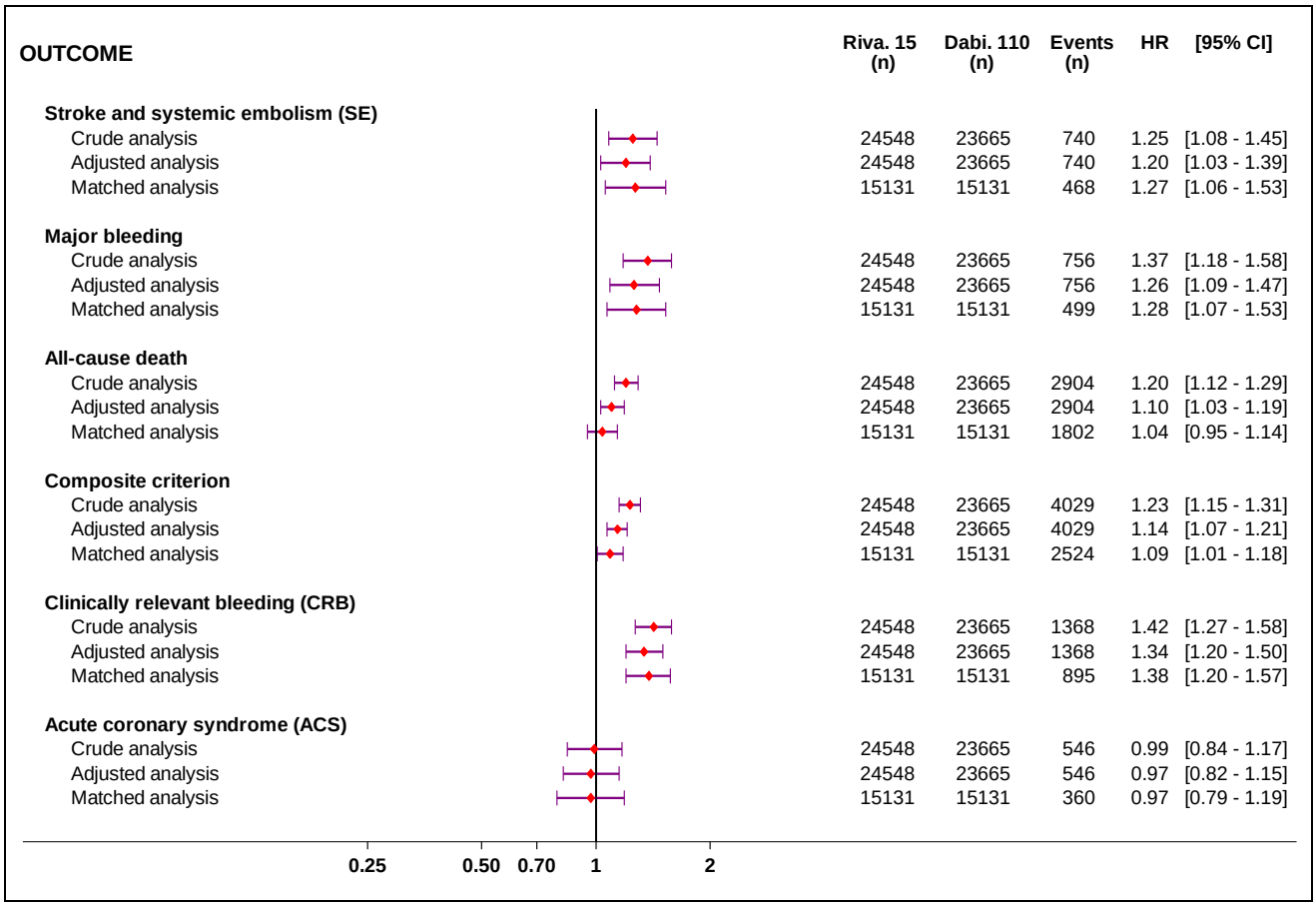
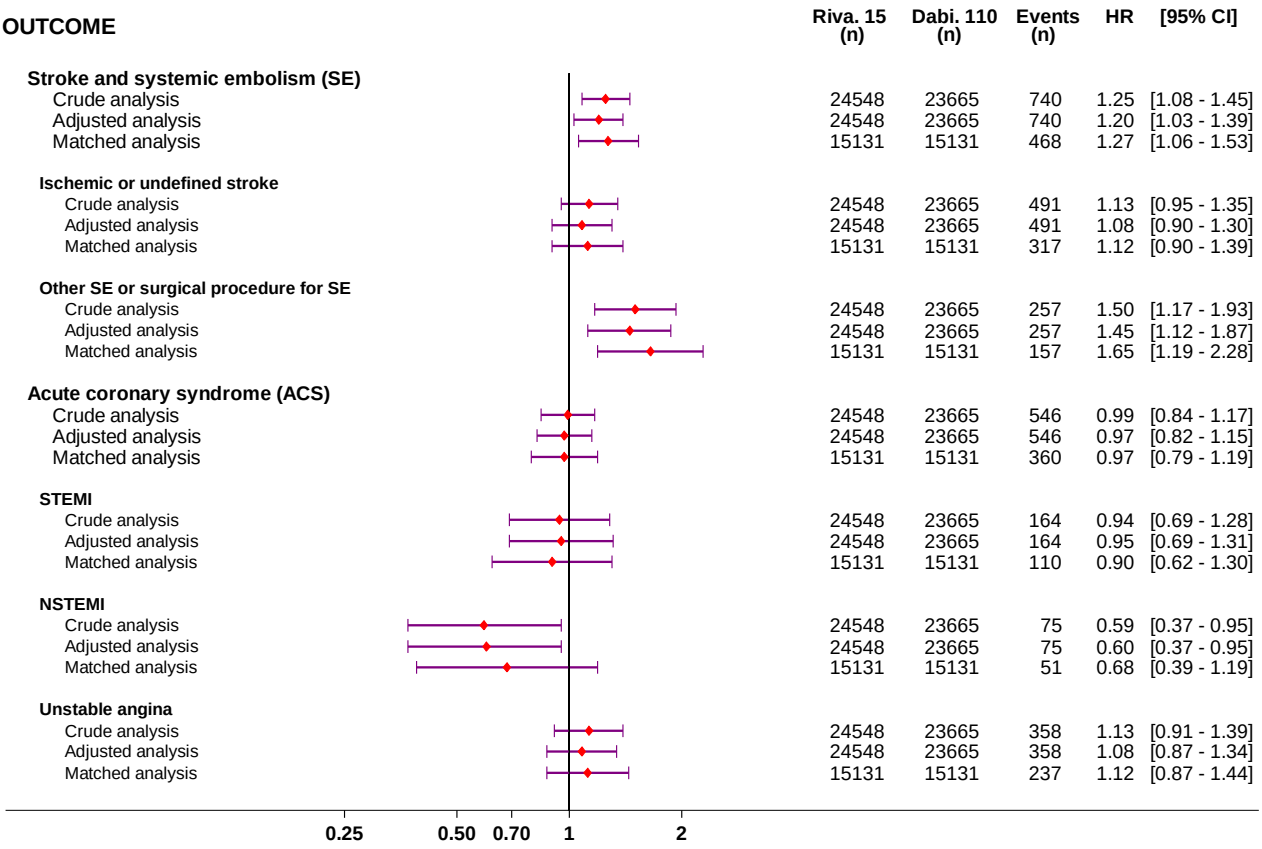


Figure 22. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation (main analysis)



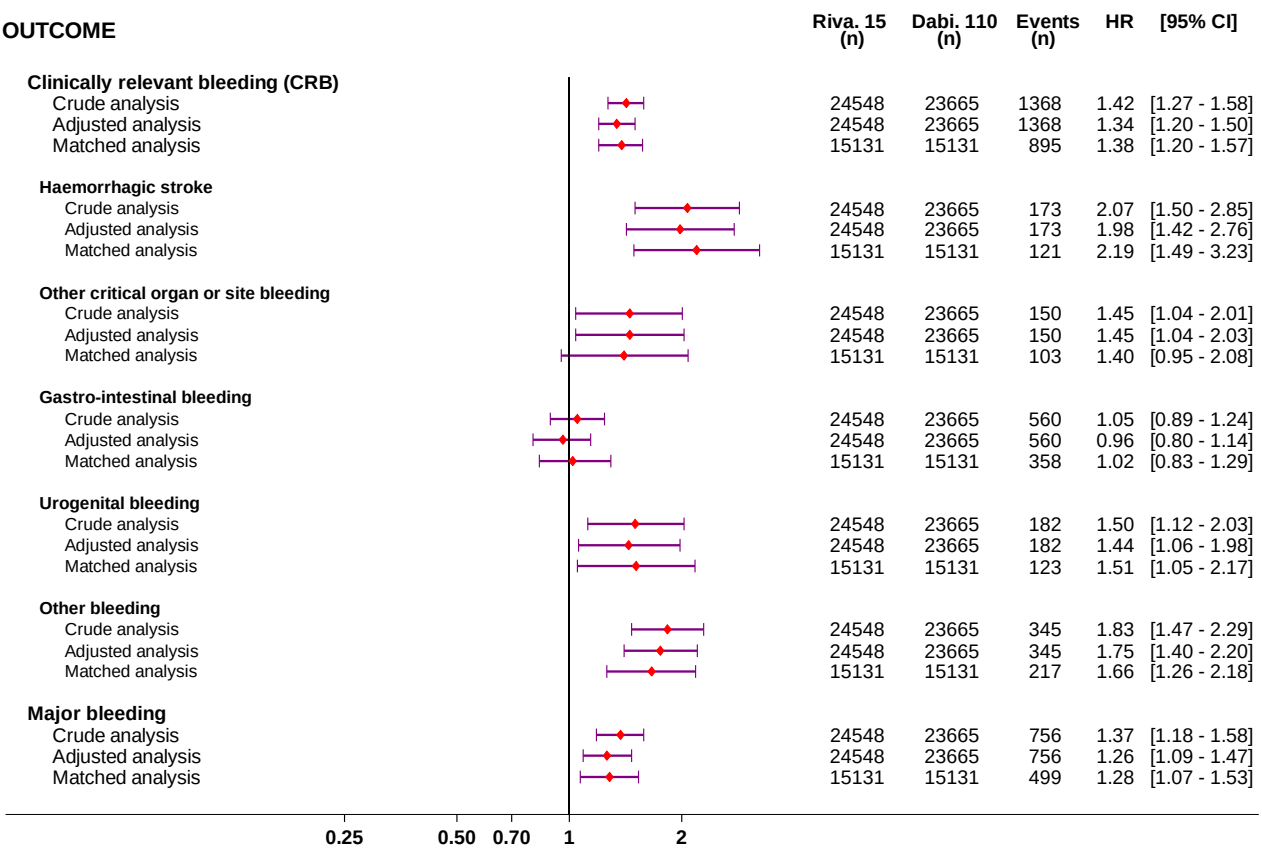


Figure 23. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95% CI of outcome details for the specific population and a 60-day grace period for drug discontinuation (main analysis)

For the sensitivity analyses, results for main and secondary outcomes remained essentially unchanged with a 30-day grace period (**Figure 24**; Appendix 1-16, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), as well as for the sensitive population and a 60-day grace period (**Figure 24**; Appendix 1-12, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49), except for the risk of SSE (at the significant threshold with a 30-day grace period, 1.22 [1.00 to 1.49], and with no difference for the sensitive population and a 60-day grace period, 1.16 [0.99 to 1.36]), and for the risk of the composite (at the significant threshold with a 30-day grace period, 1.09 [1.00 to 1.18]).

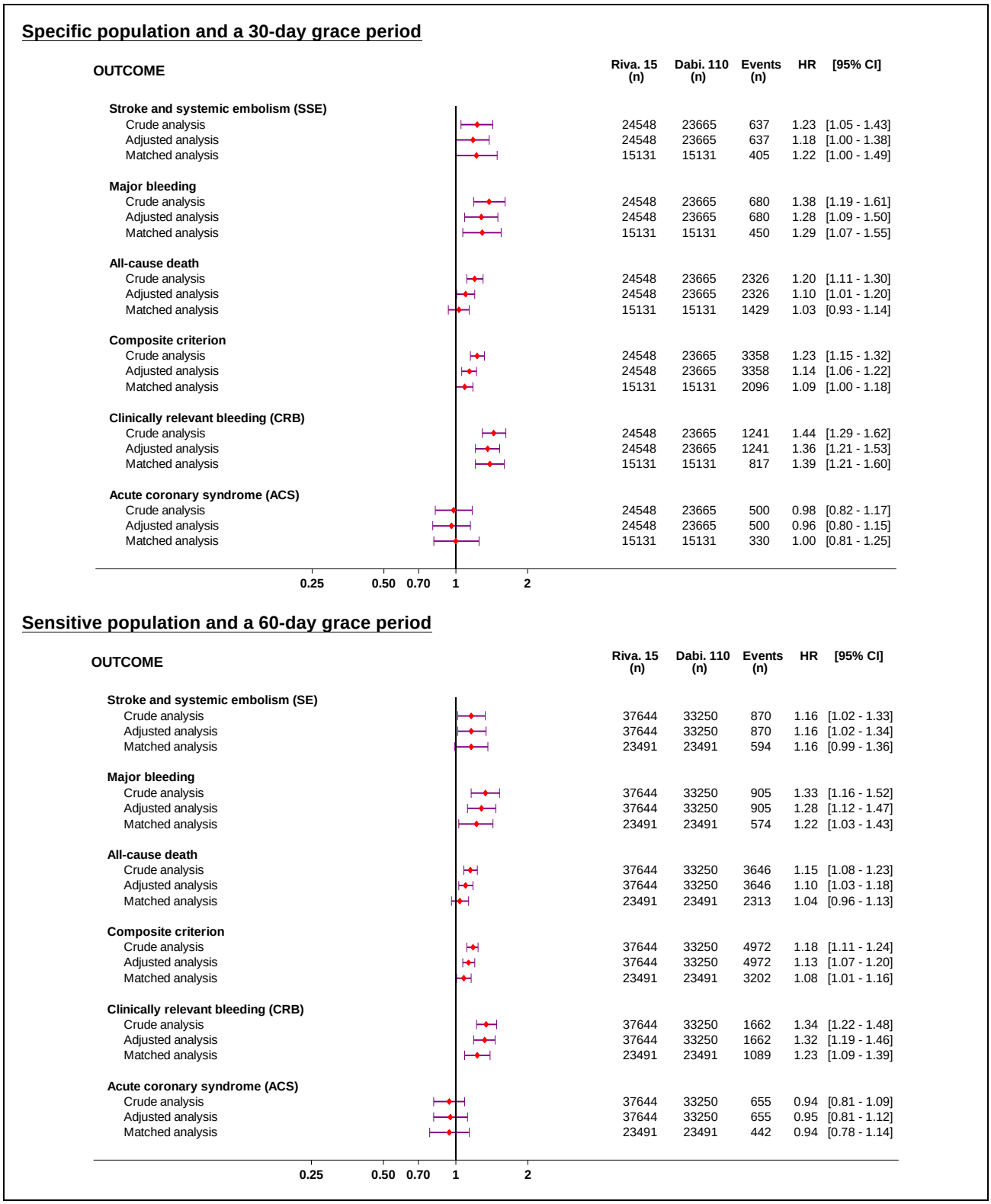


Figure 24. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period (sensitivity analyses)

For the rivaroxaban 15 mg versus dabigatran 110 mg comparison, stratified analyses for the specific population and a 60-day grace period (**Table 51**) showed substantial variations of the HR point estimate according to the different subgroups:

- **For stroke and systemic embolism,**
  - At least 25% non-significantly lower with rivaroxaban for < 65 years old (25%) with very few patients,
  - Between 10% and 24% non-significantly lower with rivaroxaban for HAS-BLED scores 0-1 (13%),
  - Relatively similar with HR between 0.91 and 1.10 for 2014 index date (1.07), 70-74 years old (0.93), CHA_2DS_2-VASc scores 0-1, 2 and 3 (0.96, 0.93 and 1.08, respectively), and the third quintile of logit hdPS (1.0),
  - Between 10% and 24% lower with dabigatran for all matched patients (21%), female (17%), 75-79 years old (15%), stroke or TIA history (19%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (10% and 24%, respectively), HAS-BLED scores > 3 (22%), the first and last quintiles (15% and 12%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - At least 25% lower with dabigatran for 2013 index date (29%), male (25%), 65-69 and ≥ 80 years old (38% and 26%, respectively), CHA_2DS_2-VASc scores ≥ 4 (34%), congestive heart failure (32%), hypertension (32%), diabetes mellitus (30%), vascular disease history (47%), HAS-BLED scores 2-3 (28%), the second and fourth quintiles (37% and 40%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Without clear systematic variation;
- **For major bleeding,**
  - Relatively similar with HR between 0.91 and 1.10 for CHA_2DS_2-VASc score 2 (1.07), diabetes mellitus (1.09), and the two last quintiles of logit hdPS (1.07 and 1.09, respectively),
  - Between 10% and 24% lower with dabigatran for all matched patients (22%), 2013 index date (18%), male and female (23% and 20%, respectively), < 65 and ≥ 80 years old (22% and 13%, respectively), CHA_2DS_2-VASc scores 3 and ≥ 4 (22% and 22%, respectively), congestive heart failure (22%), hypertension (24%), vascular disease history (12%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (19%), HAS-BLED scores 2-3 (19%), the first and third quintiles (24% and 17%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - At least 25% lower with dabigatran for 2014 index date (30%), 65-69, 70-74 and 75-79 years old (30%, 43% and 44%, respectively), CHA_2DS_2-VASc scores 0-1 (63%), stroke or TIA history (52%), age 65-74 years as CHA_2DS_2-VASc risk factor (40%), HAS-BLED scores 0-1 and > 3 (26% and 32%, respectively), the second quintile (53%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Without clear systematic variation;
- **For clinically relevant bleeding,**
  - Relatively similar with HR between 0.91 and 1.10 for the last quintile of logit hdPS (0.99),
  - Between 10% and 24% lower with dabigatran for 2013 index date (24%), female (24%), ≥ 80 years old (18%), CHA_2DS_2-VASc score 3 (22%), congestive heart failure (24%), diabetes mellitus (21%), vascular disease history (20%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (24%), the fourth quintile (22%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - At least 25% lower with dabigatran for all matched patients (28%), 2014 index date (33%), male (30%), < 65, 65-69, 70-74 and 75-79 years old (35%, 47%, 46% and 47%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and ≥ 4 (49%, 36% and 26%, respectively), hypertension (27%), stroke or TIA history (50%), age 65-74 years as CHA_2DS_2-VASc risk factor (46%), HAS-BLED scores 0-1, 2-3 and > 3 (29%, 26% and 32%, respectively), the three first quintiles (39%, 46% and 32%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),

- Without clear systematic variation;

– **For death,**
  - At least 25% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc scores 0-1 (31%),
  - Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.04), 2013 and 2014 index date (1.04 and 1.03, respectively), male and female (1.02 and 1.05, respectively), < 65 and ≥ 80 years old (1.05 and 0.95, respectively), CHA_2DS_2-VASc scores 2 and ≥ 4 (0.92 and 1.03, respectively), diabetes mellitus (1.02), stroke or TIA history (1.03), age ≥ 75 years as CHA_2DS_2-VASc risk factor (1.0), all HAS-BLED scores (0.92, 1.07 and 1.02, respectively), and the four last quintiles of logit hdPS (1.05, 0.98, 1.10 and 0.92, respectively),
  - Between 10% and 24% non-significantly lower with dabigatran for CHA_2DS_2-VASc score 3 (15%), congestive heart failure (12%), hypertension (11%), vascular disease history (15%), and the first quintile (15%),
  - At least 25% lower with dabigatran for 65-69, 70-74 and 75-79 years old (38%, 31% and 32%, respectively), age 65-74 years as CHA_2DS_2-VASc risk factor (33%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - With a gradient for CHA_2DS_2-VASc, from 0.69 to 1.03 for scores 0-1 to scores ≥ 4 HR, and no clear systematic variation for the other factors;

– **For the composite criterion (stroke and systemic embolism, major bleeding and death),**
  - Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.09), 2014 index date (1.04), male and female (1.09 and 1.09, respectively), < 65, and ≥ 80 years old (0.93 and 1.02, respectively), CHA_2DS_2-VASc scores 0-1, 2 and ≥ 4 (0.94, 0.97 and 1.09, respectively), diabetes mellitus (1.05), age ≥ 75 years as CHA_2DS_2-VASc risk factor (1.07), HAS-BLED scores 0-1 (0.97), the third and last quintiles (0.99 and 1.02, respectively),
  - Between 10% and 24% lower with dabigatran for 2013 index date (11%), 70-74 years old (23%), CHA_2DS_2-VASc score 3 (16%), congestive heart failure (14%), hypertension (15%), stroke or TIA history (12%), vascular disease history (19%), HAS-BLED scores 2-3 and > 3 (11% and 11%, respectively), the two first and fourth quintiles (12%, 20% and 10%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - At least 25% significantly lower with dabigatran for 65-69 and 75-79 years old (38% and 30%, respectively), and age 65-74 years as CHA_2DS_2-VASc risk factor (28%),
  - Without clear systematic variation;

– **For ACS,**
  - At least 25% non-significantly lower with rivaroxaban for 2014 index date (28%), HAS-BLED score > 3 (28%), and the two last quintiles of logit hdPS (40% and 26%, respectively),
  - Between 10% and 24% non-significantly lower with rivaroxaban for female (16%), 65-69 and ≥ 80 years old (20% and 19%, respectively), congestive heart failure (15%), hypertension (17%), and age ≥ 75 years as CHA_2DS_2-VASc risk factor (13%),
  - Relatively similar with HR between 0.91 and 1.10 for all matched patients (0.97), male (1.08), 75-79 years old (1.06), CHA_2DS_2-VASc scores 2, 3, and ≥ 4 (1.01, 1.02 and 0.91, respectively), diabetes mellitus (0.92), stroke or TIA history (0.96), HAS-BLED scores 0-1 and 2-3 (0.99 and 0.99, respectively),
  - Between 10% and 24% non-significantly lower with dabigatran for 2013 index date (12%), vascular disease history (24%), the second and third quintiles (13% and 14%, respectively),
  - At least 25% significantly lower with dabigatran for < 65 and 70-74 years old (35% and 57%, respectively), CHA_2DS_2-VASc scores 0-1 (33%), age 65-74 years as CHA_2DS_2-VASc risk factor (33%), the first quintile (28%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - With a gradient for CHA_2DS_2-VASc, from 0.91 to 1.49 for scores ≥ 4 to scores 0-1 HR, and no clear systematic variation for the other factors.

Table 51. Rivaroxaban 15 mg versus dabigatran 110 mg stratified analyses of main and secondary outcomes for matched patients, hazard ratio (HR and 95%CI)

	Rivaroxaban 15 mg n	**Dabigatran 110 mg** n	Stroke and systemic embolism HR [95%CI]	Major bleeding HR [95%CI]	Clinically relevant bleeding HR [95%CI]	Death (all causes) HR [95%CI]	Composite criterion HR [95%CI]	Acute coronary syndrome HR [95%CI]
All matched patients	15 131	15 131	1.27 [1.06 ; 1.53]	1.28 [1.07 ; 1.53]	1.38 [1.20 ; 1.57]	1.04 [0.95 ; 1.14]	1.09 [1.01 ; 1.18]	0.97 [0.79 ; 1.19]
Index date								
2013	10 017	10 017	1.40 [1.11 ; 1.77]	1.22 [0.98 ; 1.51]	1.32 [1.13 ; 1.56]	1.04 [0.93 ; 1.17]	1.12 [1.02 ; 1.24]	1.13 [0.87 ; 1.46]
2014	5 114	5 114	1.07 [0.79 ; 1.46]	1.42 [1.03 ; 1.95]	1.49 [1.18 ; 1.88]	1.03 [0.88 ; 1.21]	1.04 [0.91 ; 1.19]	0.72 [0.51 ; 1.03]
Gender								
Male	7 229	7 229	1.34 [1.04 ; 1.73]	1.30 [1.02 ; 1.66]	1.43 [1.20 ; 1.71]	1.02 [0.90 ; 1.17]	1.09 [0.98 ; 1.22]	1.08 [0.82 ; 1.41]
Female	7 902	7 902	1.21 [0.93 ; 1.58]	1.25 [0.97 ; 1.62]	1.31 [1.07 ; 1.60]	1.05 [0.92 ; 1.20]	1.09 [0.98 ; 1.22]	0.84 [0.61 ; 1.16]
Age (years)								
<65	686	692	0.75 [0.24 ; 2.36]	1.28 [0.35 ; 4.76]	1.54 [0.55 ; 4.32]	1.05 [0.53 ; 2.05]	0.93 [0.53 ; 1.60]	1.55 [0.55 ; 4.35]
65-69	867	859	1.61 [0.64 ; 4.08]	1.42 [0.51 ; 3.98]	1.89 [0.92 ; 3.88]	1.62 [0.86 ; 3.07]	1.61 [1.00 ; 2.59]	0.80 [0.35 ; 1.86]
70-74	1 409	1 401	0.93 [0.49 ; 1.76]	1.76 [0.94 ; 3.31]	1.84 [1.15 ; 2.96]	1.44 [0.97 ; 2.16]	1.30 [0.95 ; 1.78]	2.35 [1.12 ; 4.91]
75-79	2 998	2 909	1.18 [0.78 ; 1.81]	1.77 [1.09 ; 2.88]	1.87 [1.33 ; 2.64]	1.47 [1.12 ; 1.92]	1.42 [1.14 ; 1.76]	1.06 [0.67 ; 1.68]
≥ 80	9 171	9 270	1.36 [1.09 ; 1.71]	1.15 [0.94 ; 1.42]	1.22 [1.04 ; 1.43]	0.95 [0.85 ; 1.05]	1.02 [0.93 ; 1.11]	0.81 [0.62 ; 1.06]
CHA_2DS_2-VASc score								
0-1	961	964	0.96 [0.36 ; 2.55]	2.70 [0.87 ; 8.40]	1.96 [0.89 ; 4.36]	0.69 [0.37 ; 1.28]	0.94 [0.57 ; 1.54]	1.49 [0.53 ; 4.21]
2	2 613	2 673	0.93 [0.57 ; 1.51]	1.07 [0.67 ; 1.71]	1.56 [1.11 ; 2.18]	0.92 [0.71 ; 1.19]	0.97 [0.78 ; 1.20]	1.01 [0.61 ; 1.69]
3	4 408	4 365	1.08 [0.75 ; 1.54]	1.29 [0.92 ; 1.80]	1.28 [0.99 ; 1.63]	1.18 [0.98 ; 1.42]	1.19 [1.02 ; 1.38]	1.02 [0.66 ; 1.58]
≥ 4	7 149	7 129	1.52 [1.19 ; 1.94]	1.28 [1.01 ; 1.63]	1.35 [1.13 ; 1.63]	1.03 [0.91 ; 1.16]	1.09 [0.99 ; 1.21]	0.91 [0.70 ; 1.20]
Risk factors								
Congestive heart failure	3 391	3 267	1.48 [0.99 ; 2.20]	1.28 [0.91 ; 1.80]	1.32 [1.02 ; 1.71]	1.13 [0.97 ; 1.31]	1.16 [1.02 ; 1.33]	0.85 [0.57 ; 1.28]
Hypertension	6 876	6 808	1.48 [1.13 ; 1.95]	1.32 [1.02 ; 1.71]	1.37 [1.14 ; 1.66]	1.12 [0.99 ; 1.27]	1.17 [1.05 ; 1.31]	0.83 [0.62 ; 1.10]
Diabete mellitus	3 204	3 147	1.43 [1.04 ; 1.98]	1.09 [0.78 ; 1.53]	1.26 [0.97 ; 1.62]	1.02 [0.84 ; 1.23]	1.05 [0.90 ; 1.23]	0.92 [0.64 ; 1.32]
Stroke or TIA history	1 679	1 746	1.23 [0.81 ; 1.87]	2.10 [1.26 ; 3.50]	2.01 [1.35 ; 2.98]	1.03 [0.80 ; 1.32]	1.14 [0.93 ; 1.40]	0.96 [0.49 ; 1.91]
Vascular disease history	2 355	2 252	1.90 [1.29 ; 2.79]	1.14 [0.77 ; 1.69]	1.25 [0.93 ; 1.68]	1.17 [0.95 ; 1.44]	1.24 [1.05 ; 1.48]	1.31 [0.92 ; 1.86]
Age 65-74 years	2 276	2 260	1.11 [0.66 ; 1.88]	1.66 [0.97 ; 2.84]	1.85 [1.25 ; 2.76]	1.49 [1.06 ; 2.09]	1.39 [1.07 ; 1.81]	1.49 [0.87 ; 2.55]]
Age ≥ 75 years	12 169	12 179	1.32 [1.08 ; 1.61]	1.23 [1.02 ; 1.49]	1.32 [1.14 ; 1.52]	1.00 [0.91 ; 1.11]	1.07 [0.98 ; 1.16]	0.87 [0.69 ; 1.10]
HAS-BLED score								
0-1	3 571	3 633	0.87 [0.56 ; 1.35]	1.35 [0.89 ; 2.05]	1.41 [1.03 ; 1.93]	0.92 [0.74 ; 1.14]	0.97 [0.81 ; 1.17]	0.99 [0.55 ; 1.79]
2-3	10 335	10 323	1.39 [1.12 ; 1.73]	1.24 [1.01 ; 1.52]	1.36 [1.16 ; 1.58]	1.07 [0.96 ; 1.20]	1.12 [1.02 ; 1.23]	0.99 [0.79 ; 1.25]
>3	1 225	1 175	1.28 [0.74 ; 2.21]	1.47 [0.79 ; 2.76]	1.46 [0.94 ; 2.26]	1.02 [0.77 ; 1.34]	1.12 [0.88 ; 1.42]	0.72 [0.36 ; 1.45]
Quintiles of logit hdPS								
Quintile 1	3 025	3 027	1.18 [0.75 ; 1.86]	1.32 [0.83 ; 2.08]	1.63 [1.17 ; 2.27]	1.18 [0.94 ; 1.47]	1.13 [0.94 ; 1.37]	1.39 [0.88 ; 2.20]
Quintile 2	2 976	3 077	1.58 [0.99 ; 2.52]	2.14 [1.35 ; 3.38]	1.86 [1.36 ; 2.55]	1.05 [0.85 ; 1.30]	1.25 [1.04 ; 1.50]	1.15 [0.71 ; 1.85]
Quintile 3	3 035	3 017	1.00 [0.70 ; 1.43]	1.21 [0.80 ; 1.83]	1.47 [1.07 ; 2.02]	0.98 [0.79 ; 1.22]	0.99 [0.83 ; 1.19]	1.16 [0.73 ; 1.85]
Quintile 4	3 051	3 002	1.67 [1.13 ; 2.47]	1.07 [0.74 ; 1.55]	1.28 [0.96 ; 1.71]	1.10 [0.90 ; 1.36]	1.11 [0.93 ; 1.32]	0.60 [0.37 ; 0.99]
Quintile 5	3 044	3 008	1.13 [0.75 ; 1.71]	1.09 [0.78 ; 1.53]	0.99 [0.76 ; 1.28]	0.92 [0.77 ; 1.11]	1.02 [0.87 ; 1.19]	0.74 [0.47 ; 1.15]

10.5. Other analyses: Healthcare resources use and costs during the drug exposure on the 1-year follow-up period for the specific NVAF matched populations and a 60-day grace period

10.5.1. Healthcare resources use during the drug exposure on the 1-year follow-up period

10.5.1.1. Specific AF healthcare resources use

Nearly all patients in the rivaroxaban 20 mg group (90%) and in the VKA group (94%) had at least one specific medical visit (linked to prescription of AF drugs or specific lab tests) during the drug exposure for rivaroxaban, dabigatran, and VKA on the 1-year follow-up period for matched populations. Specific lab tests were also widely used, and concerned 82% of patients in the rivaroxaban 20 mg group and 97% of those in the VKA group. About 3 patients out of 10 (29% and 30%, respectively) had at least one specific hospitalisation (primary diagnosis of AF, clinically relevant bleeding, SSE, or ACS), and the stays in a rehabilitation department (SRR) within 7 days after hospital discharge for outcome specific hospitalisation concerned very few patients (< 1% in the two groups) (**Table 52**; Appendix 1-17, Table 1).

For rivaroxaban 20 mg and dabigatran 150 mg groups, results for the specific AF healthcare resources use were similar for specific medical visits (89% in the two groups), specific lab tests (80% in the two groups), and stays in SRR (< 1% in the two groups). Specific hospitalisations were slightly less frequent for the rivaroxaban 20 mg group than the dabigatran 150 mg group (33% vs 41%) (**Table 53**; Appendix 1-17, Table 87).

For the reduced dose groups, rivaroxaban 15 mg and VKA, results were similar to those for rivaroxaban 20 mg and VKA groups for specific medical visits (89% and 94%, respectively), specific lab tests (83% and 97%, respectively), and stays in SRR (< 1% in the two groups). However, specific hospitalisations were less frequent in rivaroxaban 15 mg and VKA groups than rivaroxaban 20 mg and VKA groups (19% and 23%, respectively) (**Table 54**; Appendix 1-17, Table 44).

For rivaroxaban 15 mg and dabigatran 110 mg groups, results were similar to those for rivaroxaban 20 mg and dabigatran 150 mg groups for specific medical visits (89% in the two groups), specific lab tests (84% and 82%, respectively), and stays in SRR (< 1% in the two groups). However, specific hospitalisations were less frequent in rivaroxaban 15 mg and dabigatran 110 mg groups than rivaroxaban 20 mg and dabigatran 150 mg groups (19% and 22%, respectively) (**Table 55**; Appendix 1-17, Table 130).

Table 52. Specific AF healthcare resources use during the drug exposure for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 31171		VKA n = 31171	
Type of specific areas of expenditures (several answers possible), n (%)				
AF drugs[1]	31171	(100.0)	31171	(100.0)
DOAC	*31171*	*(100.0)*	*1162*	*(3.7)*
VKA	*293*	*(0.9)*	*31171*	*(100.0)*
Other AF drugs	*25438*	*(81.6)*	*25849*	*(82.9)*
Specific medical consultations and visits[2]	27967	(89.7)	29319	(94.1)
Specific lab tests[3]	25654	(82.3)	30313	(97.2)
Specific hospitalisations[4]	9054	(29.0)	9391	(30.1)
AF specific hospitalisation	*7892*	*(25.3)*	*7881*	*(25.3)*
Other specific hospitalisation	*1418*	*(4.5)*	*1789*	*(5.7)*
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[5]	94	(0.3)	147	(0.5)

[1] *Reimbursements for DOAC/VKA, amiodarone/drodenarone, beta-blockers alone if no amiodarone/drodenarone reimbursements, and antiarrhythmics (propafenone, flecainide, cibenzoline)*
[2] *Medical consultations and visits linked to prescription of AF drugs or specific lab tests including related transport*
[3] *INR, hemostasis, coagulation, creatinine, urea, ALAT and ASAT tests including related transport and related nursing acts plus majoration and travel allowances*
[4] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[5] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 53. Specific AF healthcare resources use during the drug exposure for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323	
Type of specific areas of expenditures (several answers possible), n (%)				
AF drugs[1]	15323	(100.0)	15323	(100.0)
DOAC	*15323*	*(100.0)*	*15323*	*(100.0)*
VKA	*129*	*(0.8)*	*111*	*(0.7)*
Other AF drugs	*12663*	*(82.6)*	*13072*	*(85.3)*
Specific medical consultations and visits[2]	13641	(89.0)	13663	(89.2)
Specific lab tests[3]	12326	(80.4)	12278	(80.1)
Specific hospitalisations[4]	5099	(33.3)	6274	(40.9)
AF specific hospitalisation	*4682*	*(30.6)*	*5983*	*(39.0)*
Other specific hospitalisation	*546*	*(3.6)*	*392*	*(2.6)*
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[5]	37	(0.2)	28	(0.2)

[1] *Reimbursements for DOAC/VKA, amiodarone/drodenarone, beta-blockers alone if no amiodarone/drodenarone reimbursements, and antiarrhythmics (propafenone, flecainide, cibenzoline)*
[2] *Medical consultations and visits linked to prescription of AF drugs or specific lab tests including related transport*
[3] *INR, hemostasis, coagulation, creatinine, urea, ALAT and ASAT tests including related transport and related nursing acts plus majoration and travel allowances*
[4] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[5] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 54. Specific AF healthcare resources use during the drug exposure for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 23314		VKA n = 23314	
Type of specific areas of expenditures (several answers possible), n (%)				
AF drugs[1]	23314	(100.0)	23314	(100.0)
DOAC	*23314*	*(100.0)*	*904*	*(3.9)*
VKA	*298*	*(1.3)*	*23314*	*(100.0)*
Other AF drugs	*18392*	*(78.9)*	*18907*	*(81.1)*
Specific medical consultations and visits[2]	20832	(89.4)	21951	(94.2)
Specific lab tests[3]	19462	(83.5)	22664	(97.2)
Specific hospitalisations[4]	4473	(19.2)	5294	(22.7)
AF specific hospitalisation	*3174*	*(13.6)*	*3808*	*(16.3)*
Other specific hospitalisation	*1409*	*(6.0)*	*1667*	*(7.2)*
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[5]	99	(0.4)	156	(0.7)

[1] *Reimbursements for DOAC/VKA, amiodarone/drodenarone, beta-blockers alone if no amiodarone/drodenarone reimbursements, and antiarrhythmics (propafenone, flecainide, cibenzoline)*
[2] *Medical consultations and visits linked to prescription of AF drugs or specific lab tests including related transport*
[3] *INR, hemostasis, coagulation, creatinine, urea, ALAT and ASAT tests including related transport and related nursing acts plus majoration and travel allowances*
[4] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[5] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 55. Specific AF healthcare resources use during the drug exposure for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131	
Type of specific areas of expenditures (several answers possible), n (%)				
AF drugs[1]	15131	(100.0)	15131	(100.0)
DOAC	*15131*	*(100.0)*	*15131*	*(100.0)*
VKA	*214*	*(1.4)*	*159*	*(1.1)*
Other AF drugs	*11921*	*(78.8)*	*12226*	*(80.8)*
Specific medical consultations and visits[2]	13548	(89.5)	13473	(89.0)
Specific lab tests[3]	12638	(83.5)	12475	(82.4)
Specific hospitalisations[4]	2831	(18.7)	3290	(21.7)
AF specific hospitalisation	*1972*	*(13.0)*	*2626*	*(17.4)*
Other specific hospitalisation	*934*	*(6.2)*	*732*	*(4.8)*
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[5]	70	(0.5)	61	(0.4)

[1] *Reimbursements for DOAC/VKA, amiodarone/drodenarone, beta-blockers alone if no amiodarone/drodenarone reimbursements, and antiarrhythmics (propafenone, flecainide, cibenzoline)*
[2] *Medical consultations and visits linked to prescription of AF drugs or specific lab tests including related transport*
[3] *INR, hemostasis, coagulation, creatinine, urea, ALAT and ASAT tests including related transport and related nursing acts plus majoration and travel allowances*
[4] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[5] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

10.5.1.2. Total healthcare resources use

For rivaroxaban 20 mg and VKA groups:

- At least 85% of patients had medical visits and technical acts during the drug exposure period (98% in the rivaroxaban 20 mg group and 99% in the VKA group), non-cardiovascular and non-antidiabetic drug dispensing (95% and 97%, respectively), and lab tests (87% and 98%, respectively);
- Between 50% and 85% had expenditures of nursing acts (65% and 85%, respectively), products and services (56% and 61%, respectively), and public hospital external consultations and acts (54% and 60%, respectively);

- Between 20% and 50% expenditures of other medical healthcare resources (42% and 43%, respectively), transport (38% and 45%, respectively), other non-cardiovascular hospitalisations (27% and 31%, respectively), and physiotherapy acts (25% and 27%, respectively);
- Less than 20% of patients had other cardiovascular hospitalisations (15% and 18%, respectively), assistances, pensions and disability allowances (6% and 7%, respectively), sick leaves and daily allowances (5% and 6%, respectively) (**Table 56**; Appendix 1-17, Table 1).

For the dabigatran 150 mg group, the general healthcare resources use was almost the same as for rivaroxaban 20 mg, except for expenditures of other non-cardiovascular hospitalisations and assistances, pensions and disability allowances (-13% and -14%, respectively) (**Table 57**; Appendix 1-17, Table 87).

For reduced dose groups, rivaroxaban 15 mg and VKA groups, results compared to rivaroxaban 20 mg and VKA groups were:

- Almost the same for medical visits and technical acts, non-cardiovascular and non-antidiabetic drugs, lab tests, and nursing acts;
- Higher for transport (+29% in the rivaroxaban 15 mg group and +24% in the VKA group), physiotherapy acts (+24% and +26%, respectively), other cardiovascular hospitalisations (+20% and +17%, respectively), other non-cardiovascular hospitalisations (+19% and +16%, respectively), and products and services (+14% and +15%, respectively);
- Lower for public hospital external consultations and acts (-15% and -12%, respectively); other medical healthcare resources (-14% and -7%, respectively), assistances, pensions and disability allowances (-17% and -29%, respectively), sick leaves and daily allowances (-80% and -80%, respectively) (**Table 58**; Appendix 1-17, Table 44).

For rivaroxaban 15 mg and dabigatran 110 mg groups, similar results were found for the two groups (**Table 59**; Appendix 1-17, Table 130).

Table 56. Total healthcare resources use during the drug exposure for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 31171		VKA n = 31171	
Type of areas of expenditures (several answers possible), n (%)				
Medical areas of expenditures				
Cardiovascular/antidiabetic drugs	31171	(100.0)	31171	(100.0)
Medical consultations, visits and technical acts	30530	(97.9)	30759	(98.7)
Non-cardiovascular/non-antidiabetic drugs	29595	(94.9)	30197	(96.9)
Lab tests	26973	(86.5)	30462	(97.7)
Nursing acts	20226	(64.9)	26432	(84.8)
Products and services	17360	(55.7)	18961	(60.8)
Public hospital external consultations and acts (MCO)	16868	(54.1)	18654	(59.8)
Other medical healthcare resources	13124	(42.1)	13299	(42.7)
Transport	11800	(37.9)	14039	(45.0)
Specific hospitalisations[1]	9054	(29.0)	9391	(30.1)
Other non-cardiovascular hospitalisations	8532	(27.4)	9600	(30.8)
Physiotherapy acts	7702	(24.7)	8323	(26.7)
Other cardiovascular hospitalisations	4602	(14.8)	5680	(18.2)
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[2]	94	(0.3)	147	(0.5)
Allowances				
Assistances, pensions and disability allowances	1964	(6.3)	2080	(6.7)
Sick leaves and daily allowances	1559	(5.0)	1710	(5.5)

[1] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*

[2] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 57. Total healthcare resources use during the drug exposure for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323	
Type of areas of expenditures (several answers possible), n (%)				
Medical areas of expenditures				
Cardiovascular/antidiabetic drugs	15323	(100.0)	15323	(100.0)
Medical consultations, visits and technical acts	14998	(97.9)	14988	(97.8)
Non-cardiovascular/non-antidiabetic drugs	14210	(92.7)	14150	(92.3)
Lab tests	13060	(85.2)	13006	(84.9)
Nursing acts	8985	(58.6)	9151	(59.7)
Products and services	7441	(48.6)	7075	(46.2)
Public hospital external consultations and acts (MCO)	7997	(52.2)	8298	(54.2)
Other medical healthcare resources	6666	(43.5)	6431	(42.0)
Transport	4503	(29.4)	4378	(28.6)
Specific hospitalisations[1]	5099	(33.3)	6274	(40.9)
Other non-cardiovascular hospitalisations	3605	(23.5)	3251	(21.2)
Physiotherapy acts	3103	(20.3)	2931	(19.1)
Other cardiovascular hospitalisations	2037	(13.3)	1943	(12.7)
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[2]	37	(0.2)	28	(0.2)
Allowances				
Assistances, pensions and disability allowances	1013	(6.6)	945	(6.2)
Sick leaves and daily allowances	1349	(8.8)	1373	(9.0)

[1] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[2] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 58. Total healthcare resources use during the drug exposure for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 23314		VKA n = 23314	
Type of areas of expenditures (several answers possible), n (%)				
Medical areas of expenditures				
Cardiovascular/antidiabetic drugs	23314	(100.0)	23314	(100.0)
Medical consultations, visits and technical acts	22801	(97.8)	23030	(98.8)
Non-cardiovascular/non-antidiabetic drugs	22402	(96.1)	22939	(98.4)
Lab tests	20302	(87.1)	22764	(97.6)
Nursing acts	16370	(70.2)	20039	(86.0)
Products and services	14816	(63.5)	16238	(69.6)
Public hospital external consultations and acts (MCO)	10657	(45.7)	12462	(53.5)
Other medical healthcare resources	8328	(35.7)	9247	(39.7)
Transport	11445	(49.1)	13057	(56.0)
Specific hospitalisations[1]	4473	(19.2)	5294	(22.7)
Other non-cardiovascular hospitalisations	7362	(31.6)	8353	(35.8)
Physiotherapy acts	7227	(31.0)	8035	(34.5)
Other cardiovascular hospitalisations	4153	(17.8)	4933	(21.2)
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[2]	99	(0.4)	156	(0.7)
Allowances				
Assistances, pensions and disability allowances	1212	(5.2)	1246	(5.3)
Sick leaves and daily allowances	239	(1.0)	276	(1.2)

[1] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[2] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

Table 59. Total healthcare resources use during the drug exposure for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131	
Type of areas of expenditures (several answers possible), n (%)				
Medical areas of expenditures				
Cardiovascular/antidiabetic drugs	15131	(100.0)	15131	(100.0)
Medical consultations, visits and technical acts	14803	(97.8)	14806	(97.9)
Non-cardiovascular/non-antidiabetic drugs	14505	(95.9)	14488	(95.8)
Lab tests	13171	(87.0)	13037	(86.2)
Nursing acts	10570	(69.9)	10566	(69.8)
Products and services	9482	(62.7)	9262	(61.2)
Public hospital external consultations and acts (MCO)	6892	(45.5)	6868	(45.4)
Other medical healthcare resources	5495	(36.3)	5289	(35.0)
Transport	7285	(48.1)	7101	(46.9)
Specific hospitalisations[1]	2831	(18.7)	3290	(21.7)
Other non-cardiovascular hospitalisations	4719	(31.2)	4500	(29.7)
Physiotherapy acts	4601	(30.4)	4396	(29.1)
Other cardiovascular hospitalisations	2620	(17.3)	2542	(16.8)
Stays in rehabilitation department (SSR) linked to outcome specific hospitalisation[2]	70	(0.5)	61	(0.4)
Allowances				
Assistances, pensions and disability allowances	743	(4.9)	742	(4.9)
Sick leaves and daily allowances	109	(0.7)	116	(0.8)

[1] *Hospital-discharge summary with a primary diagnosis of AF, clinically relevant bleeding (with primary, linked or associated diagnosis for haemorrhagic stroke), SSE (or surgical procedure for systemic arterial embolism), and acute coronary syndrome including related transport*
[2] *Stay in SSR within 7 days after hospital discharge for outcome specific hospitalisation*

10.5.2. Healthcare resource costs during the drug exposure on the 1-year follow-up period

10.5.2.1. Specific AF healthcare resource costs

For matched patients, the mean total AF medical specific cost per patient during the drug exposure period, and according to the national health perspective, was €1,835 for the rivaroxaban 20 mg group, and €1,706 in the VKA group (**Figure 25; Table 60**; Appendix 1-17, Table 2). The mean cost per patient of each specific area of expenditure was lower for the rivaroxaban 20 mg group than the VKA group, except for AF drugs (**Figure 25; Table 60**; Appendix 1-17, Tables 4 to 8):

- Firstly, specific hospitalisations for both groups, with a mean cost per patient of €988 for rivaroxaban 20 mg and €1,107 for VKA (54% and 65% of the mean total specific cost of each group, respectively), plus SSR stays linked to outcome specific hospitalisations with a mean of €40 and €52, respectively (2% and 3% of the mean total specific cost, respectively),
- AF drugs with a mean of €638 and €89, respectively (35% and 5% of the mean total specific cost, respectively),
- Specific lab tests with a mean of €39 and €293, respectively (2% and 17% of the mean total specific cost, respectively),
- Specific medical visits with a mean of €130 and €165, respectively (7% and 10% of the mean total specific cost, respectively).

With the sensitivity analysis using the three other definitions for stays in SSR, the mean cost of stays in SSR per patient remained low and varied from €47 in taking into account stays in SSR with a specific nosological group within two weeks after an outcome specific hospitalisation to €67 including all stays in SSR within two weeks after an outcome specific hospitalisation for the rivaroxaban 20 mg group, and from €63 to €84 in the VKA group, respectively (Appendix 1-17, Tables 38, 40 and 42).

For the dabigatran 150 mg group, the mean total AF medical specific cost per patient during the drug exposure period and the mean cost of each specific area of expenditure were almost the same as for rivaroxaban 20 mg (**Figure 26; Table 61**; Appendix 1-17, Tables 88, 90, 91, 92, 93 and 94).

For reduced dose groups, rivaroxaban 15 mg and VKA groups, the mean total AF medical specific cost per patient during the drug exposure period was slightly lower, €1,631 in the rivaroxaban 15 mg group, and €1,623 in the VKA group (**Figure 27; Table 62**; Appendix 1-17, Table 45). The specific AF healthcare resource cost structure in each group was similar to that of standard dose groups, and the mean cost of each specific area of expenditure remained lower for the rivaroxaban 15 mg group than the VKA group, except for AF drugs (**Figure 27; Table 62**; Appendix 1-17, Tables 47 to 51).

For the dabigatran 110 mg group, the mean total AF medical specific cost per patient during the drug exposure period and the mean cost of each specific area of expenditure were slightly lower than rivaroxaban 15 mg, except for stays in SSR (**Figure 28; Table 63**; Appendix 1-17, Tables 131, 133, 134, 135, 136 and 137).

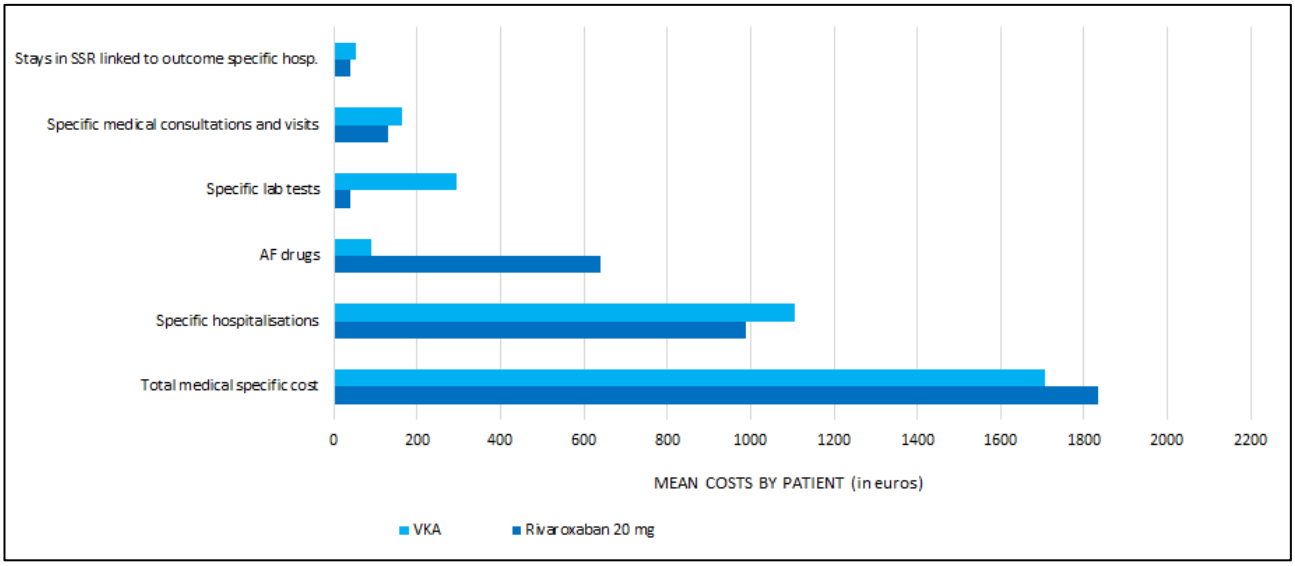


Figure 25. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and VKA matched patients

Table 60. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 31171		VKA n = 31171	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical specific AF cost, in € per patient	**1835.2 (3568.8)**	**[558.7; 1591.6]**	**1705.7 (3735.3)**	**[338.8; 1382.3]**
Specific hospitalisations	988.3 (2998.8)	[0.0; 517.0]	1107.2 (3285.1)	[0.0; 573.1]
AF specific hospitalisation	*708.4 (2200.4)*	*[0.0; 354.0]*	*705.6 (2190.7)*	*[0.0; 385.1]*
Other specific hospitalisation	*291.0 (2081.7)*	*[0.0; 0.0]*	*415.6 (2508.2)*	*[0.0; 0.0]*
AF drugs	638.3 (374.1)	[246.4; 964.3]	89.3 (64.5)	[37.7; 129.9]
DOAC	*589.4 (345.2)*	*[229.9; 898.4]*	*3.4 (20.1)*	*[0.0; 0.0]*
VKA	*0.1 (0.6)*	*[0.0; 0.0]*	*35.6 (27.4)*	*[15.4; 46.8]*
Other AF drugs	*48.9 (50.0)*	*[6.7; 78.7]*	*50.3 (47.9)*	*[9.6; 80.2]*
Specific medical consultations and visits	129.8 (129.6)	[44.0; 174.0]	164.5 (165.8)	[66.0; 216.2]
Stays in SSR linked to outcome specific hospitalisation	40.1 (1464.1)	[0.0; 0.0]	51.7 (1278.2)	[0.0; 0.0]
Specific lab tests	38.7 (91.1)	[5.2; 34.8]	292.9 (352.2)	[112.2; 371.2]

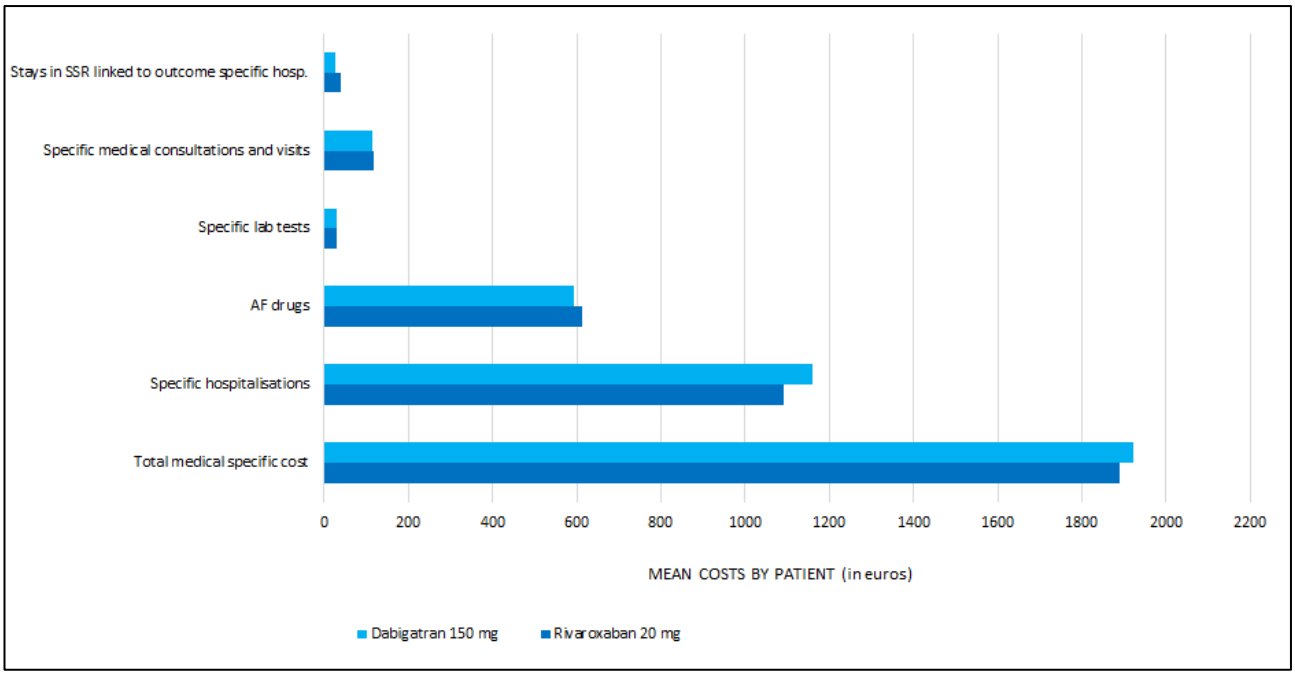


Figure 26. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and dabigatran 150 mg matched patients

Table 61. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical specific AF cost, in € per patient	**1889.9 (3697.5)**	**[531.3; 1666.9]**	**1923.3 (3190.7)**	**[503.5; 1882.1]**
Specific hospitalisations	1091.3 (3034.2)	[0.0; 647.6]	1161.1 (2899.9)	[0.0; 925.2]
AF specific hospitalisation	*893.1 (2469.4)*	*[0.0; 518.6]*	*992.7 (2454.1)*	*[0.0; 721.9]*
Other specific hospitalisation	*210.8 (1799.7)*	*[0.0; 0.0]*	*182.0 (1584.7)*	*[0.0; 0.0]*
AF drugs	612.5 (370.8)	[223.1; 940.4]	593.0 (377.4)	[205.4; 939.6]
DOAC	*562.8 (340.6)*	*[209.5; 873.5]*	*543.6 (346.0)*	*[197.0; 878.5]*
VKA	*0.0 (0.6)*	*[0.0; 0.0]*	*0.0 (0.6)*	*[0.0; 0.0]*
Other AF drugs	*49.7 (52.1)*	*[7.2; 78.8]*	*49.3 (50.7)*	*[8.7; 77.1]*
Specific medical consultations and visits	116.8 (115.7)	[38.5; 158.0]	114.2 (114.3)	[37.1; 155.0]
Stays in SSR linked to outcome specific hospitalisation	39.2 (1672.6)	[0.0; 0.0]	26.3 (965.4)	[0.0; 0.0]
Specific lab tests	30.0 (68.6)	[4.1; 27.9]	28.7 (66.4)	[4.1; 27.8]

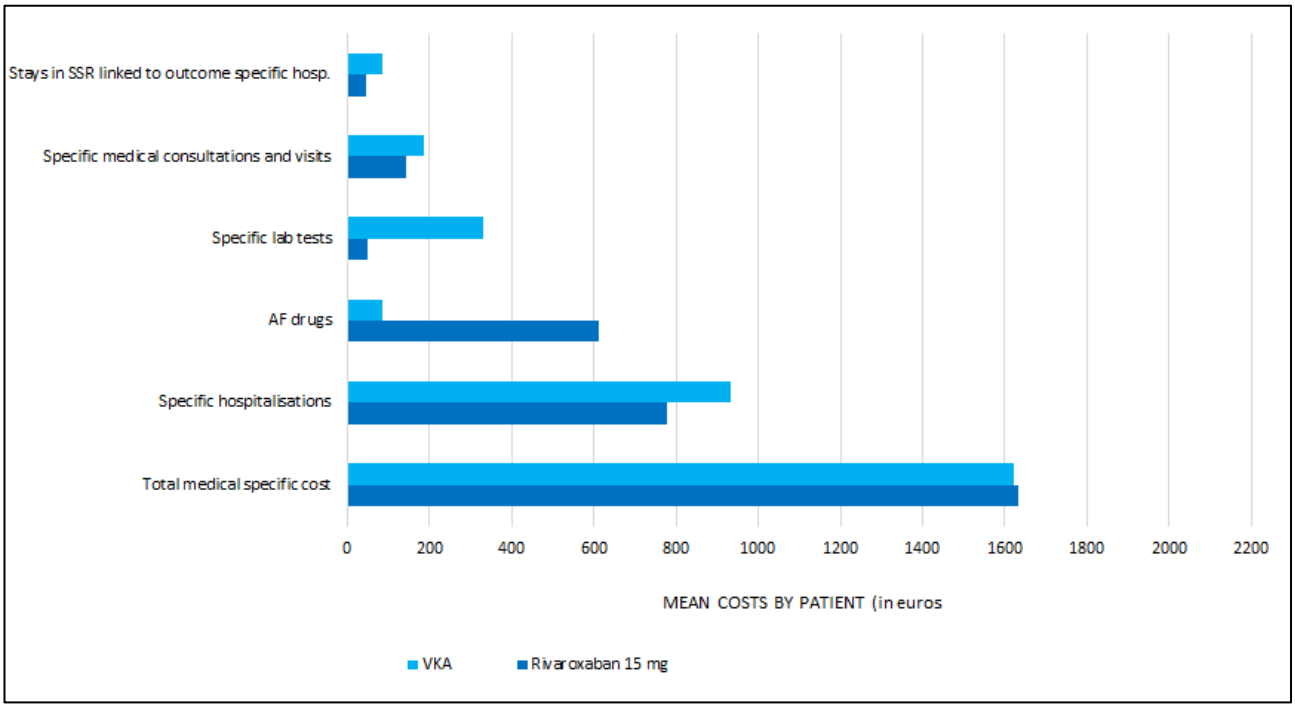


Figure 27. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and VKA matched patients

Table 62. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 23314		VKA n = 23314	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical specific AF cost, in € per patient	**1631.2 (3216.6)**	**[407.9; 1397.3]**	**1623.3 (3982.8)**	**[352.0; 1202.9]**
Specific hospitalisations	778.5 (2704.8)	[0.0; 0.0]	934.2 (3063.2)	[0.0; 0.0]
AF specific hospitalisation	*405.6 (1710.1)*	*[0.0; 0.0]*	*455.4 (1815.5)*	*[0.0; 0.0]*
Other specific hospitalisation	*380.3 (2133.0)*	*[0.0; 0.0]*	*488.7 (2510.4)*	*[0.0; 0.0]*
AF drugs	612.2 (385.1)	[209.7; 961.5]	85.9 (60.8)	[36.7; 125.0]
DOAC	*568.4 (358.8)*	*[188.2; 903.2]*	*3.6 (20.9)*	*[0.0; 0.0]*
VKA	*0.1 (0.7)*	*[0.0; 0.0]*	*33.7 (25.4)*	*[15.2; 44.7]*
Other AF drugs	*43.8 (46.3)*	*[6.3; 72.5]*	*48.7 (46.2)*	*[9.6; 78.6]*
Specific medical consultations and visits	143.6 (143.4)	[44.2; 195.4]	187.7 (175.2)	[77.1; 247.1]
Specific lab tests	50.2 (106.0)	[5.9; 48.3]	330.4 (343.2)	[129.7; 422.1]
Stays in SSR linked to outcome specific hospitalisation	46.6 (1386.5)	[0.0; 0.0]	85.1 (2148.0)	[0.0; 0.0]

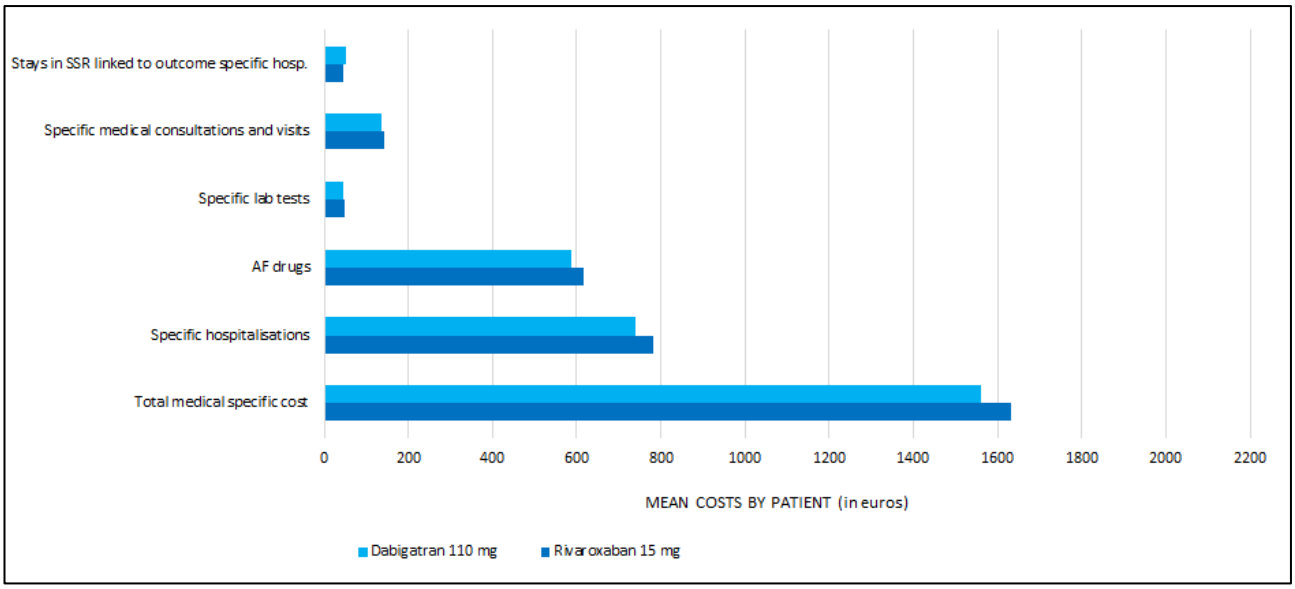


Figure 28. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and dabigatran 110 mg matched patients

Table 63. Specific costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical specific AF cost, in € per patient	**1631.9 (3249.6)**	**[405.7; 1380.7]**	**1561.3 (3092.6)**	**[357.1; 1412.1]**
Specific hospitalisations	782.0 (2922.3)	[0.0; 0.0]	740.9 (2575.6)	[0.0; 0.0]
AF specific hospitalisation	*377.6 (1589.8)*	*[0.0; 0.0]*	*442.0 (1667.5)*	*[0.0; 0.0]*
Other specific hospitalisation	*411.5 (2484.0)*	*[0.0; 0.0]*	*306.7 (1981.3)*	*[0.0; 0.0]*
AF drugs	614.8 (385.1)	[213.1; 962.6]	586.8 (385.2)	[180.5; 952.0]
DOAC	*570.3 (358.5)*	*[188.2; 901.9]*	*542.3 (356.8)*	*[153.9; 894.2]*
VKA	*0.1 (0.7)*	*[0.0; 0.0]*	*0.1 (0.6)*	*[0.0; 0.0]*
Other AF drugs	*44.4 (47.1)*	*[6.3; 73.5]*	*44.5 (46.6)*	*[6.3; 73.2]*
Specific medical consultations and visits	142.2 (139.8)	[44.2; 193.1]	136.7 (143.4)	[44.0; 186.0]
Specific lab tests	48.3 (99.5)	[5.9; 46.6]	43.9 (89.8)	[5.7; 42.6]
Stays in SSR linked to outcome specific hospitalisation	44.6 (991.8)	[0.0; 0.0]	53.1 (1248.4)	[0.0; 0.0]

10.5.2.2. Total healthcare resource costs

For matched patients, the mean total medical cost per patient during the drug exposure period, and according to the national health perspective, was €6,356 for the rivaroxaban 20 mg group, and €7,793 for the VKA group (**Figure 29; Table 64**; Appendix 1-17, Table 16). The mean cost per patient of each area of expenditure was lower for the rivaroxaban 20 mg group than the VKA group, except for cardiovascular and antidiabetic drugs (**Figure 29; Table 64**; Appendix 1-17, Tables 17 to 29 and 31):

- Firstly, other non-cardiovascular hospitalisations for both groups, with a mean cost per patient of €1,267 for rivaroxaban 20 mg and €1,616 for VKA (20% and 21% of the mean total medical cost of each group, respectively),
- Other cardiovascular hospitalisations with a mean of €867 and €1,498, respectively (14% and 19% of the mean total medical cost, respectively),
- Specific hospitalisations with a mean of €988 and €1,107, respectively (16% and 14% of the mean total medical cost, respectively), plus SSR stays linked to outcome specific

hospitalisations with a mean of €40 and €52, respectively (2% and 3% of the mean total specific cost, respectively),

- Cardiovascular and antidiabetic drugs with a mean of €914 and €433, respectively (14% and 6% of the mean total medical cost, respectively),
- Medical visits and technical acts with a mean of €756 and €819, respectively (12% and 11% of the mean total medical cost, respectively),
- Nursing acts with a mean of €318 and €539, respectively (5% and 7% of the mean total medical cost, respectively),
- Non-cardiovascular and non-antidiabetic drugs with a mean of €342 and €439, respectively (5% and 6% of the mean total medical cost, respectively),
- Lab tests with a mean of €145 and €360, respectively (2% and 5% of the mean total medical cost, respectively),
- Products and services with a mean of €244 and €322, respectively (4% and 4% of the mean total medical cost, respectively),
- Transport with a mean of €175 and €264, respectively (3% and 3% of the mean total medical cost, respectively),
- Public hospital external consultations and acts with a mean of €129 and €152 (2% and 2% of the mean total medical cost, respectively),
- Physiotherapy acts with a mean of €119 and €140, respectively (2% and 2% of the mean total medical cost, respectively),
- And other medical healthcare resources with a mean of €70 and €74 (1% and 1% of the mean total medical cost, respectively).

The mean total allowances cost per patient was €350 (58% of the mean total allowances cost for assistances, pensions and disability allowances, and 42% for sick leaves and daily allowances) and €398 (52% of the mean total allowances cost for assistances, pensions and disability allowances, and 48% for sick leaves and daily allowances), respectively (**Figure 29; Table 64**; Appendix 1-17, Tables 33 to 35).

For the rivaroxaban 20 mg group, the mean total medical cost per patient during the drug exposure period was slightly higher than for dabigatran 150 mg (€5,546 *vs* €5,206), and the healthcare resource cost structure was almost the same, with (**Figure 30; Table 65**; Appendix 1-17, Tables 102 to 115, and 117):

- Lower cost only for specific hospitalisations, and products and services,
- Higher cost for all other medical areas of expenditure.

The mean total allowances cost per patient was also quite the same (€442 *vs* €432) (**Figure 30; Table 65**; Appendix 1-17, Tables 119 to 121).

For reduced dose groups, rivaroxaban 15 mg and VKA groups, the mean total medical cost per patient during the drug exposure period was slightly higher, €7,112 in the rivaroxaban 15 mg group, and €8,681 in the VKA group (**Figure 31; Table 66**; Appendix 1-17, Table 59). The healthcare resource cost structure in each group was almost the same to that of standard dose groups, and the mean cost of each area of expenditure remained lower for the rivaroxaban 15 mg group than the VKA group, except for cardiovascular and antidiabetic drugs (**Figure 31; Table 66**; Appendix 1-17, Tables 60 to 72 and 74). The mean total allowances cost per patient was €159 (79% of the mean total allowances cost for assistances, pensions and disability allowances, and 21% for sick leaves and daily allowances) and €177 (75% of the mean total allowances cost for assistances, pensions and disability allowances, and 25% for sick leaves and daily allowances), respectively (**Figure 31; Table 66**; Appendix 1-17, Tables 76 to 78).

For the rivaroxaban 15 mg group, the mean total medical cost per patient during the drug exposure period remained slightly higher than for dabigatran 110 mg (€6,898 *vs* €6,501), and the healthcare resource cost structure was almost the same, with (**Figure 32; Table 67**; Appendix 1-17, Tables 145 to 158, and 160):

- Lower cost only for transport, and stays in SSR linked to outcome specific hospitalisations,
- Higher cost for all other medical areas of expenditure.

The mean total allowances cost per patient was also the same (€132 *vs* €133) (**Figure 32; Table 67**; Appendix 1-17, Tables 162 to 164).

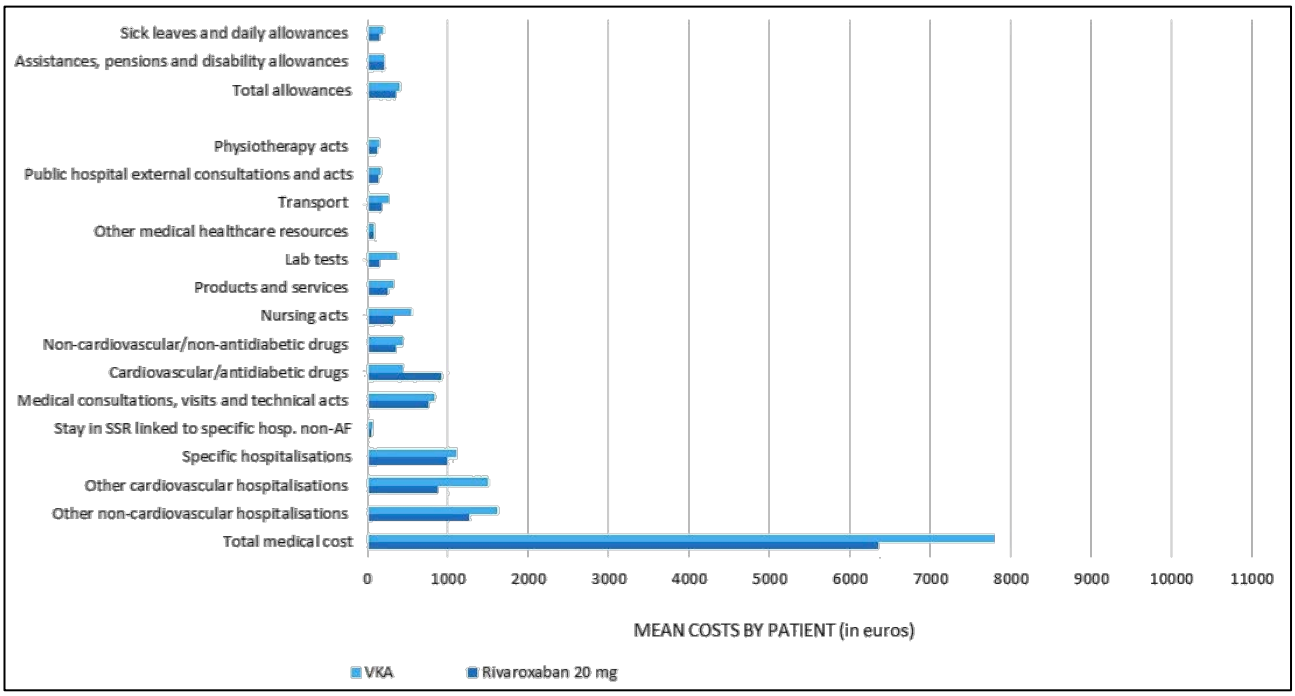


Figure 29. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and VKA matched patients

Table 64. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 31171		VKA n = 31171	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical cost, in € per patient	**6355.9 (8431.8)**	**[1697.0; 7894.1]**	**7793.0 (12279.4)**	**[1687.5; 9799.6]**
Other non-cardiovascular hospitalisations	1266.9 (3977.4)	[0.0; 554.7]	1615.8 (4959.7)	[0.0; 867.9]
Specific hospitalisations	988.3 (2998.8)	[0.0; 517.0]	1107.2 (3285.1)	[0.0; 573.1]
Cardiovascular/antidiabetic drugs	914.3 (644.3)	[344.1; 1291.3]	433.1 (437.8)	[145.9; 565.7]
Other cardiovascular hospitalisations	867.2 (3812.0)	[0.0; 0.0]	1497.8 (8455.5)	[0.0; 0.0]
Medical consultations, visits and technical acts	755.7 (1039.5)	[202.4; 912.2]	819.3 (1107.5)	[243.1; 968.4]
Non-cardiovascular/non-antidiabetic drugs	341.9 (1257.0)	[19.4; 288.9]	439.4 (1715.8)	[31.5; 341.2]
Nursing acts	318.0 (1528.9)	[0.0; 42.2]	539.3 (1715.8)	[17.8; 288.8]
Products and services	243.5 (830.1)	[0.0; 112.0]	321.9 (1000.4)	[0.0; 175.0]
Transport	175.0 (701.6)	[0.0; 94.8]	264.1 (973.0)	[0.0; 172.5]
Lab tests	144.9 (255.7)	[28.7; 176.3]	360.3 (352.9)	[157.6; 462.2]
Public hospital external consultations and acts	128.7 (241.2)	[0.0; 162.9]	152.3 (263.0)	[0.0; 200.8]
Physiotherapy acts	118.6 (430.9)	[0.0; 0.0]	140.1 (466.8)	[0.0; 35.5]
Other medical healthcare resources	70.2 (288.1)	[0.0; 28.9]	74.1 (318.2	[0.0; 28.7]
Stays in SSR linked to outcome specific hospitalisation	40.1 (1464.1)	[0.0; 0.0]	51.7 (1278.2)	[0.0; 0.0]
Total allowances cost, in € per patient	**349.6 (1756.8)**	**[0.0; 0.0]**	**398.0 (1825.5)**	**[0.0; 0.0]**
Assistances, pensions and disability allowances	203.0 (1339.0)	[0.0; 0.0]	205.5 (1277.3)	[0.0; 0.0]
Sick leaves and daily allowances	146.6 (1084.2)	[0.0; 0.0]	192.5 (1265.8)	[0.0; 0.0]

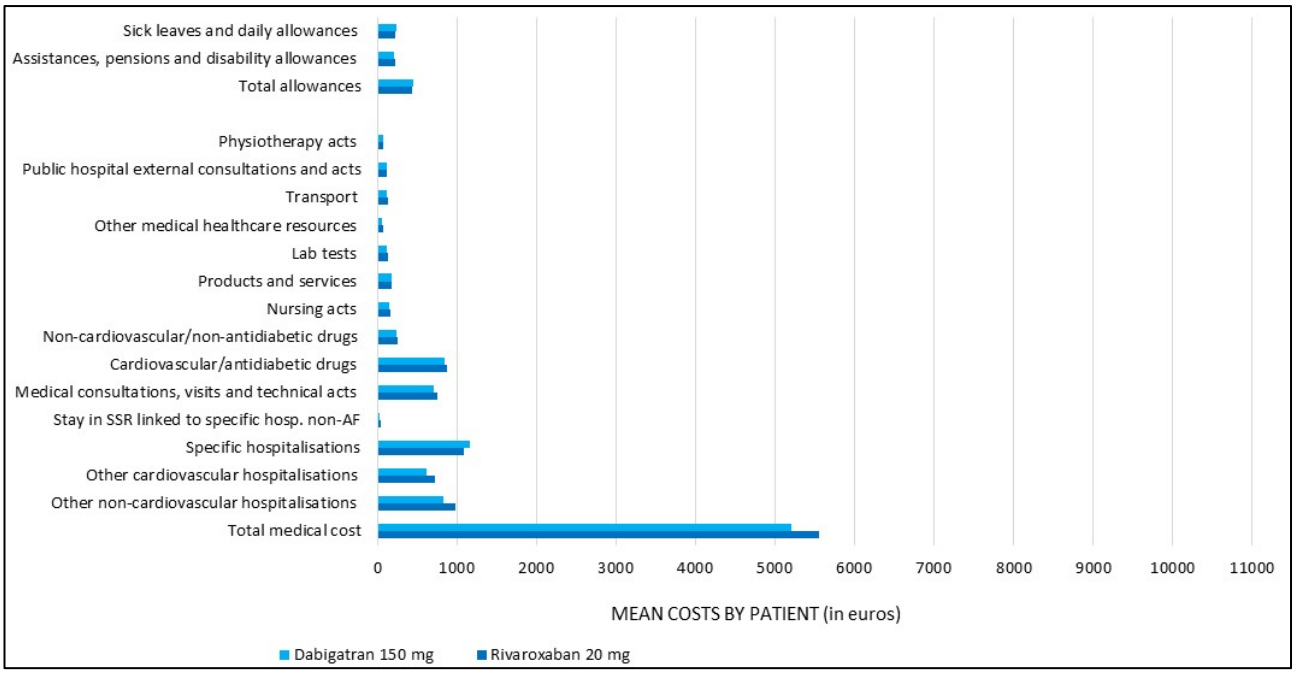


Figure 30. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and dabigatran 150 mg matched patients

Table 65. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 15323		Dabigatran 150 mg n = 15323	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical cost, in € per patient	**5546.0 (7855.4)**	**[1442.9; 6671.9]**	**5206.3 (6879.3)**	**[1419.9; 6234.7]**
Specific hospitalisations	1091.3 (3034.2)	[0.0; 647.6]	1161.1 (2899.9)	[0.0; 925.2]
Other non-cardiovascular hospitalisations	972.8 (3570.0)	[0.0; 0.0]	821.6 (3131.4)	[0.0; 0.0]
Cardiovascular/antidiabetic drugs	877.7 (644.1)	[297.5; 1257.0]	845.8 (649.5)	[266.1; 1238.9]
Medical consultations, visits and technical acts	753.5 (1027.3)	[191.3; 898.2]	708.0 (954.9)	[178.4; 855.2]
Other cardiovascular hospitalisations	727.9 (3763.5)	[0.0; 0.0]	611.1 (2920.8)	[0.0; 0.0]
Non-cardiovascular/non-antidiabetic drugs	256.8 (1053.9)	[7.6; 207.4]	244.1 (999.4)	[6.8; 197.9]
Products and services	174.7 (690.3)	[0.0; 67.2]	179.8 (711.0)	[0.0; 61.4]
Nursing acts	156.1 (981.3)	[0.0; 23.9]	140.5 (946.1)	[0.0; 23.7]
Lab tests	128.9 (215.1)	[24.2; 160.2]	122.4 (181.5)	[23.0; 157.3]
Transport	123.7 (593.0)	[0.0; 38.4]	117.7 (545.7)	[0.0; 34.2]
Public hospital external consultations and acts	119.8 (230.7)	[0.0; 149.4]	116.9 (218.5)	[0.0; 152.0]
Physiotherapy acts	74.1 (304.0)	[0.0; 0.0]	66.7 (288.6)	[0.0; 0.0]
Other medical healthcare resources	65.9 (251.9)	[0.0; 31.1]	62.2 (250.2)	[0.0; 28.7]
Stays in SSR linked to outcome specific hospitalisation	39.2 (1672.6)	[0.0; 0.0]	26.3 (965.4)	[0.0; 0.0]
Total allowances cost, in € per patient	**432.0 (1920.6)**	**[0.0; 0.0]**	**442.2 (2003.2)**	**[0.0; 0.0]**
Assistances, pensions and disability allowances	216.3 (1365.2)	[0.0; 0.0]	201.9 (1292.0)	[0.0; 0.0]
Sick leaves and daily allowances	215.7 (1289.7)	[0.0; 0.0]	240.3 (1495.4)	[0.0; 0.0]

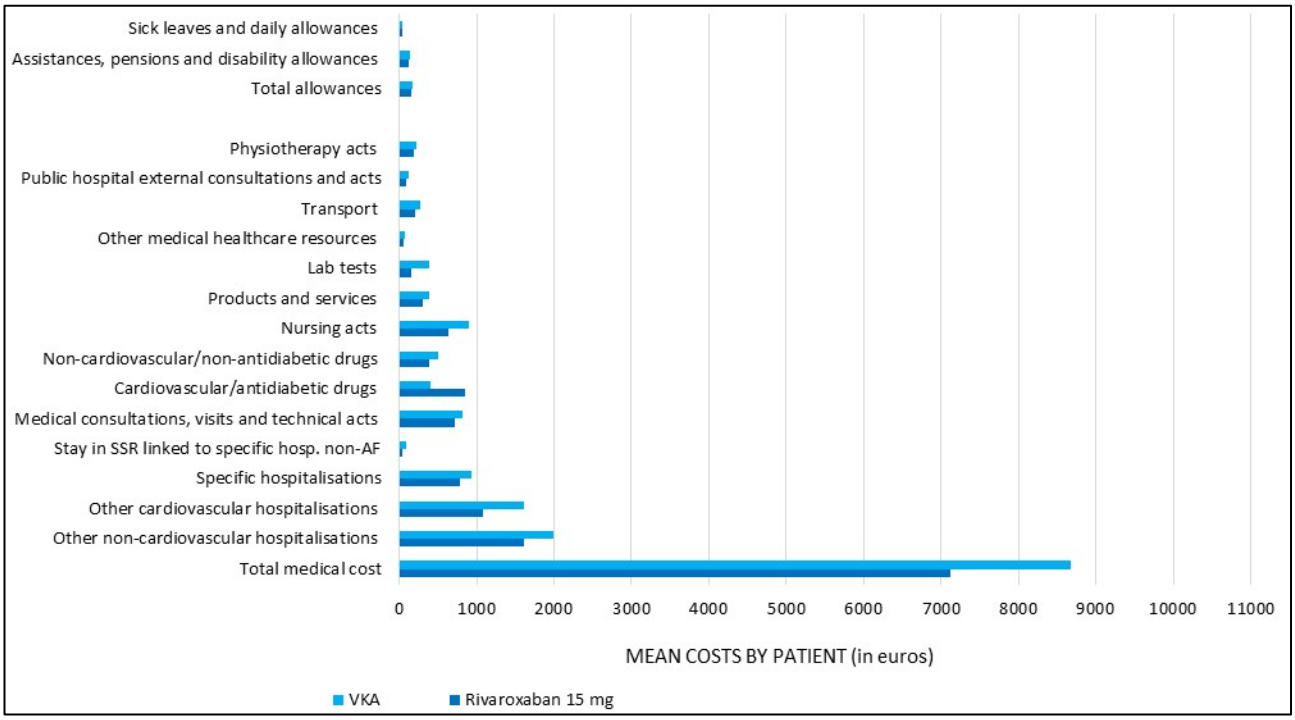


Figure 31. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and VKA matched patients

Table 66. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 23314		VKA n = 23314	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical cost, in € per patient	**7111.8 (8672.8)**	**[1824.3; 9347.9]**	**8681.3 (10433.3)**	**[2017.0; 11487.4]**
Other non-cardiovascular hospitalisations	1608.7 (4307.2)	[0.0; 1213.3]	1986.3 (4834.1)	[0.0; 2127.6]
Other cardiovascular hospitalisations	1086.0 (3732.3)	[0.0; 0.0]	1611.1 (5188.6)	[0.0; 0.0]
Cardiovascular/antidiabetic drugs	854.0 (611.0)	[286.4; 1243.8]	400.2 (386.0)	[143.6; 526.8]
Specific hospitalisations	778.5 (2704.8)	[0.0; 0.0]	934.2 (3063.2)	[0.0; 0.0]
Medical consultations, visits and technical acts	718.7 (998.1)	[196.0; 880.3]	824.3 (1056.5)	[268.9; 988.8]
Nursing acts	629.3 (2172.3)	[0.0; 101.0]	905.7 (2362.1)	[30.5; 454.9]
Non-cardiovascular/non-antidiabetic drugs	393.6 (1409.2)	[32.1; 358.5]	502.0 (1883.5)	[54.6; 423.9]
Products and services	303.2 (866.2)	[0.0; 180.8]	385.5 (1066.3)	[0.0; 271.5]
Transport	199.7 (691.2)	[0.0; 171.4]	266.6 (789.5)	[0.0; 251.1]
Physiotherapy acts	190.7 (575.6)	[0.0; 86.0]	222.5 (606.1)	[0.0; 140.1]
Lab tests	163.1 (283.0)	[31.2; 197.2]	386.0 (364.7)	[168.2; 495.3]
Public hospital external consultations and acts	97.4 (206.2)	[0.0; 116.9]	123.9 (235.3)	[0.0; 158.1]
Other medical healthcare resources	58.9 (270.3)	[0.0; 20.2]	69.6 (354.4)	[0.0; 23.4]
Stays in SSR linked to outcome specific hospitalisation	46.6 (1386.5)	[0.0; 0.0]	85.1 (2148.0)	[0.0; 0.0]
Total allowances cost, in € per patient	**158.5 (1123.6)**	**[0.0; 0.0]**	**177.3 (1237.3)**	**[0.0; 0.0]**
Assistances, pensions and disability allowances	124.6 (966.2)	[0.0; 0.0]	133.8 (1031.8)	[0.0; 0.0]
Sick leaves and daily allowances	33.9 (535.2)	[0.0; 0.0]	43.5 (645.0)	[0.0; 0.0]

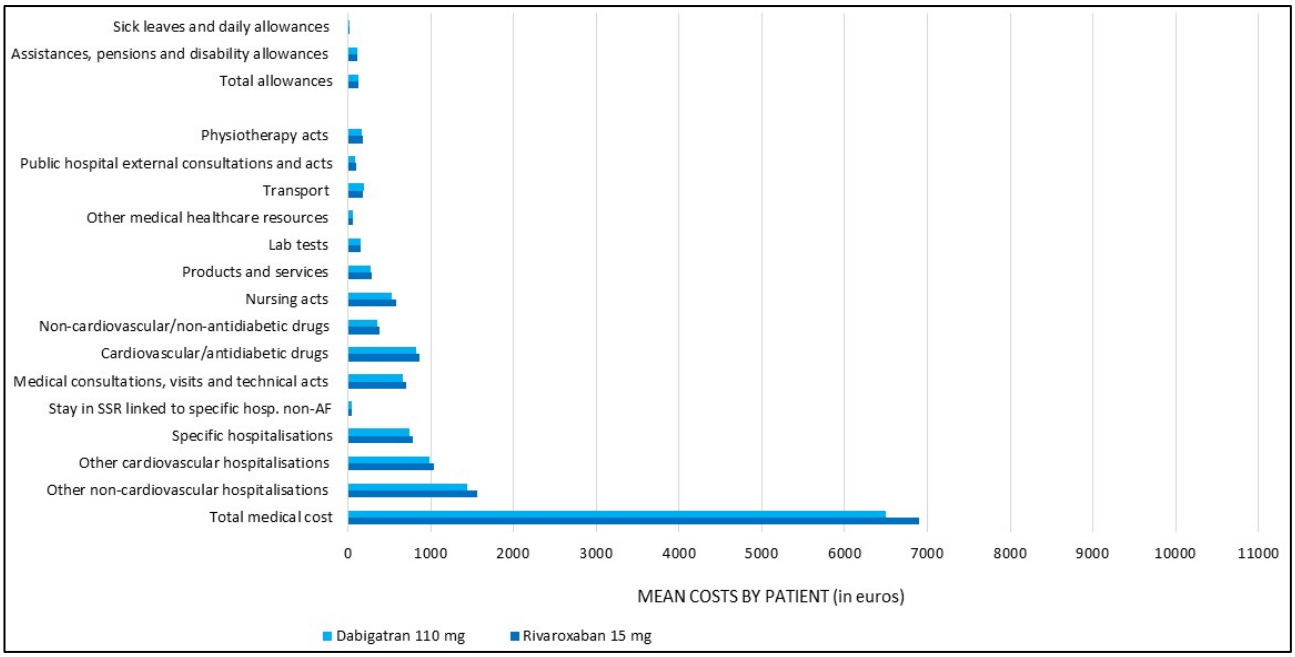


Figure 32. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and dabigatran 110 mg matched patients

Table 67. Total costs per patient during the drug exposure according to the national health insurance perspective for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 15131		Dabigatran 110 mg n = 15131	
	Mean (± SD)	**[p25%; p75%]**	**Mean (± SD)**	**[p25%; p75%]**
Total medical cost, in € per patient	**6897.5 (8361.6)**	**[1771.5; 9016.2]**	**6501.2 (8003.1)**	**[1669.9; 8495.1]**
Other non-cardiovascular hospitalisations	1555.7 (4094.4)	[0.0; 1173.2]	1435.4 (3841.3)	[0.0; 855.0]
Other cardiovascular hospitalisations	1043.8 (3581.6)	[0.0; 0.0]	991.4 (3698.0)	[0.0; 0.0]
Cardiovascular/antidiabetic drugs	858.6 (609.6)	[292.8; 1249.8]	818.6 (610.6)	[258.1; 1226.8]
Specific hospitalisations	782.0 (2922.3)	[0.0; 0.0]	740.9 (2575.6)	[0.0; 0.0]
Medical consultations, visits and technical acts	708.4 (947.7)	[195.3; 869.6]	669.0 (877.7)	[177.4; 836.9]
Nursing acts	577.4 (2090.8)	[0.0; 90.0]	526.1 (1890.7)	[0.0; 79.3]
Non-cardiovascular/non-antidiabetic drugs	380.0 (1315.0)	[28.3; 349.9]	359.1 (1252.2)	[26.7; 326.0]
Products and services	282.6 (819.4)	[0.0; 160.3]	273.6 (811.8)	[0.0; 149.3]
Transport	185.4 (576.5)	[0.0; 162.2]	189.0 (692.2)	[0.0; 152.4]
Physiotherapy acts	182.8 (567.5)	[0.0; 80.2]	166.6 (525.2)	[0.0; 60.8]
Lab tests	160.5 (264.0)	[31.1; 194.4]	147.7 (257.6)	[27.3; 179.7]
Public hospital external consultations and acts	95.6 (202.4)	[0.0; 115.6]	91.0 (193.2)	[0.0; 108.7]
Other medical healthcare resources	57.2 (253.9)	[0.0; 20.2]	55.5 (250.5)	[0.0; 19.5]
Stays in SSR linked to outcome specific hospitalisation	44.6 (991.8)	[0.0; 0.0]	53.1 (1248.4)	[0.0; 0.0]
Total allowances cost, in € per patient	**132.9 (1052.8)**	**[0.0; 0.0]**	**132.1 (917.9)**	**[0.0; 0.0]**
Assistances, pensions and disability allowances	110.4 (929.9)	[0.0; 0.0]	112.8 (825.4)	[0.0; 0.0]
Sick leaves and daily allowances	22.5 (451.6)	[0.0; 0.0]	19.3 (380.8)	[0.0; 0.0]

10.6. Adverse events/adverse reactions

The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products from EMA (EMA/873138/2011 Rev 2, 28 July 2017) specifies: For Non-interventional post-authorisation studies with a design based on secondary use of data (VI.C.1.2.1.2): *"The design of such studies is characterised by secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification".*

This study was a database analysis using secondary individual anonymous information and all clinical events studied (SSE, major bleeding, CRB, death, and ACS) were reported in aggregate in this final study report, according to the EMA Guideline on good pharmacovigilance practices (Module VI).

11. DISCUSSION

11.1.Key results

Among the 734 599 patients identified in the nationwide SNDS database with a first dispensing of DOAC (dabigatran or rivaroxaban) or VKA over two years (2013-2014) and without history of prior DOAC (dabigatran, rivaroxaban or apixaban) or VKA dispensing in the 3 years, 220 011 were included in the specific study population: 69 736 (32%) in the rivaroxaban group (19.3% with the 20 mg standard dose, 11.2% with the 15 mg reduced dose, and 1.2% with the 10 mg dose), 41 609 (19%) in the dabigatran group (7.7% with the 150 mg standard dose, 10.8% with the 110 mg reduced dose, and 0.5% with the 75 mg dose), and 108 666 (49%) in the VKA group. The sensitive population included 302 031 patients: 101 009 (33%) in the rivaroxaban group (19.6% with the 20 mg standard dose, 12.5% with the 15 mg reduced dose, and 1.3% with the 10 mg dose), 56 523 (19%) in the dabigatran group (7.2% with the 150 mg standard dose, 11.0% with the 110 mg reduced dose, and 0.5% with the 75 mg dose), and 144 499 (48%) in the VKA group. Patients of the specific population had an AF diagnosis from LTD or hospitalisation or procedure for AF before index date, without rheumatic valve disease or valve replacement. The sensitive population included the specific population, plus patients having a high probability to have an AF, based on an AF disease score.

For each comparison, patients were individually matched 1:1 on the date of the first drug (DOAC or VKA) dispensing (± 14 days), gender, age at index date (± 1 year), and logit of hdPS (± caliper): 31 171 patients per group for rivaroxaban 20 mg versus VKA in the specific population and 43 162 per group in the sensitive population (73% of rivaroxaban patients), 15 323 per group for rivaroxaban 20 mg versus dabigatran 150 mg in the specific population and 20 257 per group in the sensitive population (91% and 94% of dabigatran patients), 23 314 per group for rivaroxaban 15 mg versus VKA in the specific population and 35 585 per group in the sensitive population (95% of rivaroxaban patients), and 15 131 per group for rivaroxaban 15 mg versus dabigatran 110 mg in the specific population and 23 491 per group in the sensitive population (64% and 71% of dabigatran patients).

The key results were really close for the specific population for the two grace periods (60 and 30 days) for drug discontinuation definition, as well as for the senstive population and a 60-day grace period. Consequently, the following key results were presented for the main analysis, specific population and a 60-day grace period.

Patient characteristics

The description of patients at index date showed large differences between groups (standardised differences > 20% for a lot of variables). In particular, patients in the rivaroxaban 20 mg group were younger, with fewer comorbidities, hospitalisations before index date, stroke and bleeding risk factors compared to those in the VKA group, and more similar to those in the dabigatran 150 mg group with a mean of 3.4 years more and some risk factors linked to age more frequent for patients in the rivaroxaban group. For the reduced dose, patients in the rivaroxaban 15 mg group had similar age, but also fewer comorbidities, hospitalisations before index date, stroke and bleeding risk factors compared to those in the VKA group, and similar to those in the dabigatran 110 mg group with a mean of 1.2 years more and some risk factors linked to age slightly more frequent for patients in the rivaroxaban group. These differences were well demonstrated through hdPS distributions, with however a large overlap, allowing a 1:1 matching for a high rate of patients of the smaller group. After matching, all standardised differences became weak or equal to zero, with a good overlapping of hdPS distributions.

The most common first prescriber of rivaroxaban 20 mg and 15 mg was a cardiologist for 39% of patients for both doses, followed by hospital physicians (30% and 25%, respectively), and GP (20% and 24%, respectively). It was similar for dabigatran 150 mg and 110 mg: cardiologists (38% and 32%, respectively), hospital physicians (34% and 32%, respectively), and GP (17% and 23%, respectively), while VKA were mainly prescribed by hospital physicians (40%), followed by GP (26%), and a few by cardiologists (17%).

In this real-life study, the reduced dose of DOAC was frequently used and concerned 35% of patients for the rivaroxaban group and 57% of those for the dabigatran group. The higher use of the reduced dabigatan dose is explained by the difference in indications/recommendations of use in special populations: dabigatran 110mg is recommended for older patients (≥ 80 years), or 75-80 years old when thromboembolism risk is low and bleeding risk is high, patients with moderate renal impairment or high risk of bleeding, whereas rivaroxaban 15mg is just recommended for patients with moderate renal impairment and can be used with caution in patients with severe renal impairment. It seems that physicians were particularly worried for the bleeding risk, especially for oldest patients.

For all patients of rivaroxaban 20 mg, dabigatran 150 mg and VKA groups respectively, the mean age was 68.6 (± 11.1), 65.2 (± 10.1) and 78.4 (± 11.0) years, with 64%, 69% and 52% of men, 66%, 58% and 91% of CHA_2DS_2-VASc ≥ 2, 4%, 3% and 17% of HAS-BLED > 3. For reduced DOAC doses, rivaroxaban 15 mg and dabigatran 110 mg, patients were more alike the VKA group, with a mean age of 79.8 (± 9.3) and 78.6 (± 9.4) years, 47% and 49% of men, 92% and 91% of CHA_2DS_2-VASc ≥ 2, 9% and 8% of HAS-BLED > 3, respectively.

After matching, the mean age was 71.2 (± 10.0) years with 62% of men, 76% of CHA_2DS_2-VASc ≥ 2, and 5% of HAS-BLED > 3 in both groups, for rivaroxaban 20 mg and VKA groups, 66.0 (± 9.3) years with 70% of men, 58% of CHA_2DS_2-VASc ≥ 2, and 3% of HAS-BLED > 3 in both groups for rivaroxaban 20 mg and dabigatran 150 mg groups, 80.1 (± 8.7) years with 48% of men, 93% of CHA_2DS_2-VASc ≥ 2, 9% of HAS-BLED > 3 in both groups for rivaroxaban 15 mg and VKA groups, 80.2 (± 7.8) years with 48% of men, 94% of CHA_2DS_2-VASc ≥ 2, 8% of HAS-BLED > 3 in both groups, respectively for rivaroxaban 15 mg and dabigatran 110 mg groups.

Incidence

The 1-year cumulative incidence of discontinuation or switch was 43.1% (95%CI [42.6% to 43.5%]) with rivaroxaban 20 mg (about 2/3 of discontinuations and 1/3 of switches), 49.7% [48.9% to 50.4%] with dabigatran 150 mg (58% discontinuations and 42% switches), and 40.4% [40.1% to 40.7%] with VKA (3/4 of discontinuations and 1/4 of switches). It was 44.6% [44.0% to 45.3%] with rivaroxaban 15 mg (57% discontinuations and 43% switches) and 49.4% [48.8% to 50.1%] with dabigatran 110 mg (50% discontinuations and 50% switches).

The number of person-years (PY) during the first drug exposure was 29 391, 11 101, and 77 480 PY, respectively for all rivaroxaban 20 mg, dabigatran 150 mg, and VKA patients, and 16 124 and 15 079 PY, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients. For

matched patients, there were 21 921 and 22 786 PY, respectively for rivaroxaban 20 mg and VKA groups, 10 613 and 10 160 PY, respectively for rivaroxaban 20 mg and dabigatran 150 mg groups, 15 383 and 17 254 PY, respectively for rivaroxaban 15 mg and VKA groups, and 10 045 and 9 596 PY, respectively for rivaroxaban 15 mg and dabigatran 110 mg groups. For all treatment groups, the Medication Possession Ratio was greater than 80% for more than 90% for all and matched patients.

For all patients of rivaroxaban 20 mg, dabigatran 150 mg and VKA groups, respectively, the incidence rate of first event per 100 PY was 1.5 [1.4 to 1.6], 1.4 [1.2 to 1.6] and 3.1 [3.0 to 3.2] for SSE, 1.4 [1.3 to 1.5], 0.6 [0.5 to 0.7], and 3.8 [3.7 to 3.9] for major bleedings, 3.4 [3.2 to 3.6], 1.9 [1.6 to 2.2] and 15.6 [15.3 to 15.9] for death, 5.8 [5.5 to 6.1], 3.7 [3.3 to 4.1] and 20.6 [20.3 to 20.9] for the composite criterion (first event from SSE, major bleeding, and death). For reduced DOAC doses, rivaroxaban 15 mg and dabigatran 110 mg, respectively, it was 2.6 [2.4 to 2.8] and 2.1 [1.9 to 2.3] for SSE, 2.8 [2.5 to 3.1] and 2.0 [1.8 to 2.2] for major bleeding, 10.1 [9.6 to 10.6] and 8.5 [8.1 to 8.9] for death, 14.3 [13.8 to 14.8] and 11.7 [11.2 to 12.2] for the composite.

Standard dose risk comparison

The risk of all main outcomes, SSE, major bleeding (ISTH definition, Schulman 2005) and death, as well as the composite of these three events was significantly lower with rivaroxaban 20 mg compared to VKA for matched patients: 21% [10% to 31%], 33% [23% to 41%], 33% [27% to 39%], and 30% [26% to 35%], respectively. The risk was also significantly lower with rivaroxaban 20 mg for individual SSE outcomes, 20% [5% to 33%] for ischemic or undefined stroke, and 24% [5% to 39%] for other SE or surgical procedure for SE. That was also the case for most important bleeding subgroups: CRB, haemorrhagic stroke, other critical organ or site bleeding, and other bleeding (17% [9% to 24%], 33% [14% to 48%], 50% [33% to 62%], 32% [19% to 43%], respectively), without significant increase of GI bleeding (HR: 1.11 [0.95 to 1.31]). For ACS, the risk was significantly lower with the rivaroxaban, including STEMI and NSTEMI (20% [7% to 31%], 38% [15% to 55%] and 43% [15% to 62%], respectively). Results were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles.

Stratified analyses were performed for main and secondary outcomes, according to index date, gender, age classes, CHA_2DS_2-VASc score and its individual risk factors (congestive heart failure, hypertension, diabetes mellitus, stroke or TIA history, vascular disease history, age 65-74 years, age ≥ 75 years), HAS-BLED score and hdPS quintiles. The lower risk with rivaroxaban 20 mg compared to VKA was confirmed for most subgroups, with substantial HR point estimate variations from: 0.60 (last quintile) to 1.04 (CHA_2DS_2-VASc scores 0-1) for SSE, 0.40 (last quintile) to 1.04 (vascular disease history) for major bleeding, 0.54 (75-79 years old) to 0.82 (stroke or TIA history) for death, 0.56 (75-79 years old) to 0.85 (vascular disease history) for the composite criterion, with a HAS-BLED HR gradient from 0-1 to > 3 scores for all main outcomes, SSE (0.76 to 0.92), major bleeding (0.66 to 0.72), death (0.61 to 0.74), composite criterion (0.66 to 0.76), and a quintile HR gradient from the last to the first quintile of logit hdPS for major bleeding (0.40 to 0.83), CRB (0.64 to 0.99), and composite criterion (0.59 to 0.78), and no clear systematic variation for the other factors and outcomes.

For the rivaroxaban 20 mg and dabigatran 150 mg comparison, the risk of SSE was lower, but not significantly with rivaroxaban for matched patients (HR: 0.90 [0.71 to 1.13]), while the risk of major bleeding, death, and the composite of the three main outcomes (SSE, major bleeding and death) was significantly lower with dabigatran: 43% [22% to 58%], 22% [6% to 35%] and 17% [5% to 28%], respectively. The risk was also significantly lower with dabigatran for CRB, haemorrhagic stroke, and GI bleeding (44% [32% to 54%], 57% [24% to 76%], 30% [4% to 48%], respectively), but not for other critical organ or site bleeding (HR: 0.96 [0.53 to 1.74]). For ACS, the risk was significantly lower with dabigatran (26% [5% to 43%]). Results were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles. Stratified analyses for main and secondary outcomes showed non-systematic substantial variations according to sub-groups, mostly in favour of rivaroxaban for SSE, from a HR of 0.54 (vascular disease history) to 1.22 (HAS-BLED scores > 3), in favour of dabigatran for major bleeding, from 1.11 (2014 index date) to 4.12 (second quintile of logit hdPS), mainly in favour of dabigatran for death, from 0.83

(HAS-BLED scores > 3) to 2.02 (second quartile), and for composite criterion, from 0.88 (vascular disease history) to 1.52 (third quintile).

Reduced dose risk comparison

For the reduced dose comparison, there was no statistical difference between risk with rivaroxaban 15 mg and VKA for matched patients for SSE (HR: 1.05 [0.92 to 1.21]) and a significant lower risk for the two other outcomes of the main objective, major bleeding and death, as well as for the composite of these three events: 16% [4% to 26%], 15% [10% to 21%], and 11% [6% to 16%], respectively. The lack of SSE risk difference persisted for individual outcomes, ischemic or undefined stroke, and other SE or surgical procedure for SE. The risk was also significantly lower for haemorrhagic stroke and CRB (26% [5% to 42%] and 11% [2% to 19%], respectively), and at the significant threshold for other critical organ or site bleeding (HR: 0.76 [0.58 to 1.00]), without significant increase for GI bleeding (HR: 1.13 [0.96 to 1.33]). The risk of ACS was at the significant threshold (HR: 0.85 [0.73 to 1.00]). Results were similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles. Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.74 (last quintile) to 1.32 (CHA_2DS_2-VASc scores 0-1) with a gradient from the first to the last quintile (0.74 to 1.16), and not one significant HR. For the three other outcomes, the risk was in favour of rivaroxaban for almost all subgroups, with a HR from 0.54 (HAS-BLED scores > 3) to 1.16 (CHA_2DS_2-VASc scores 0-1) for major bleeding, with a HAS-BLED gradient, from 0.54 to 1.11 for scores > 3 to 0-1, 0.76 (last quintile) to 1.23 (CHA_2DS_2-VASc scores 0-1) for death, with a CHA_2DS_2-VASc gradient from 0.83 to 1.23 for scores ≥ 4 to 0-1, and 0.78 (last quintile) to 1.26 (CHA_2DS_2-VASc scores 0-1) for composite criterion, without clear systematic variation for the other factors and outcomes.

For the rivaroxaban 15 mg and dabigatran 110 mg comparison, the risk of SSE, major bleeding and the composite of the three main outcomes (SSE, major bleeding and death) was significantly lower with dabigatran 110 mg compared to rivaroxaban 15 mg: 21% [6% to 35%], 22% [7% to 35%], and 8% [1% to 15%], respectively, with no difference for death risk (HR: 1.04 [0.95 to 1.14]). For individual SSE outcomes, there was also a significant lower risk with dabigatran for other SE or surgical procedure for SE (39% [16% to 56%]), but not for ischemic or undefined stroke (HR: 1.12 [0.90 to 1.39]). The risk was significantly lower with dabigatran for CRB (28% [17% to 36%]), haemorrhagic stroke (54% [33% to 69%]), urogenital bleeding (34% [5% to 54%]), and other bleeding (40% [21 to 54]), but not for other critical organ or site bleeding (1.40 [0.95 to 2.08]), and GI bleeding (1.02 [0.83 to 1.29]). The ACS risk, as well as individual ACS outcomes, STEMI, NSTEMI and unstable angina were not different (HR: 0.97 [0.79 to 1.19], 0.90 [0.62 to 1.30], 0.68 [0.39 to 1.19], 1.12 [0.87 to 1.44], respectively). Results were mostly similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles. Stratified analyses for main and secondary outcomes showed non-systematic substantial variations across sub-groups, mainly in favour of dabigatran, from a HR of 0.75 (< 65 years old) to 1.90 (vascular disease history) for SSE, 1.07 (CHA_2DS_2-VASc score 2 and fourth quintile) to 2.14 (second quintile) for major bleeding, 0.69 (CHA_2DS_2-VASc scores 0-1) to 1.62 (65-69 years old) for death, 0.93 (< 65 years old) to 1.61 (65-69 years old) for composite criterion.

For the 4 comparisons, rivaroxaban 20 mg versus VKA, rivaroxaban 20 mg versus dabigatran 150 mg, rivaroxaban 15 mg versus VKA, rivaroxaban 15 mg versus dabigatran 110 mg, hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses for the specific population with a 30-day grace period for drug discontinuation definition, and for the sensitive population with a 60-day grace period for drug discontinuation definition.

Healthcare resources use and costs

For rivaroxaban 20 mg, matched patients during the drug exposure period and national health perspective, the total AF medical specific cost per patient was 7% higher compared to VKA due exclusively to the high cost of DOAC drugs. However, the total medical cost was about 18% lower compared to VKA due mainly to the lower cost for other cardiovascular hospitalisations (€867 and €1,498, respectively) and for other non-cardiovascular hospitalisations (€1,267 and €1,616, respectively). Compared to the dabigatran 150 mg group, the total specific cost was similar (mean AF medical specific cost of €1,890 and €1,923, respectively), but 7% higher for the total medical

cost, with from €100 to €150 lower cost for other non-cardiovascular hospitalisations (€973 and €822, respectively), and for other cardiovascular hospitalisations (€728 and €611, respectively).

For the reduced rivaroxaban dose (15 mg), the total AF medical specific cost was really close to the VKA group (€1,631 and €1,623, respectively), while the total medical cost was 18% lower (€7,112 and €8,681, respectively). Compared to the dabigatran 110 mg, the total medical specific cost and the total medical cost were slightly higher (€1,632 and €1,561 for the total medical specific cost, and €6,898 and €6,501 for the total medical cost, respectively).

11.2.Limitations

The SNDS is a national healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It is therefore fully representative of the French population. It provided a unique opportunity to identify new users of DOAC or VKA for NVAF in 2013 and 2014, with exhaustive information about reimbursed outpatient healthcare resources including reimbursed drugs, as well as all public and private hospitalisations. The main limit is that it was built for administrative and reimbursement purposes with a lack of clinical information that could impact the patient prognosis.

Selection bias

Since all subjects identified were extracted from a national database covering almost all the French population, there is no study selection bias, nor attrition bias, except for a few emigrations.

Information bias

AF indication: Patients were initially identified through anticoagulant dispensing, which may be prescribed for several medical conditions, and then for AF indication. The main analysis was performed using a specific AF definition, in order to minimize the risk of false positives, but which could be considered too restrictive (LTD for AF or a hospitalisation with an AF diagnosis before the index date). To address this point, a sensitive AF definition was used. The sensitive population included the specific NVAF population, plus patients with probable AF using an AF disease score. Patient characteristics and anticoagulant treatment pattern of the sensitive population were similar to those of the specific population, as well as outcome and hazard ratios for all comparisons, strengthening the results of the study. Furthermore, there is no reason that the specific and sensitive AF definitions would give different results between DOAC and VKA, excluding an information bias.

Drug exposure: VKA and DOAC exposure was assessed using exhaustive non-hospital reimbursed drug claims. The data entry of this information is done by pharmacies using barcodes for drugs and personal smart card from patients, automatically transmitted to the patient's health system scheme for direct reimbursement to the pharmacy, allowing minimal risk of data entry error. Drugs prescribed during hospital stays are not recorded, but it should concern only few subjects for very short periods of time, and the impact over a 1-year follow-up should be negligible. Drug exposure was defined as the time between index date and the end of follow-up or treatment discontinuation for those concerned. Treatment discontinuation was defined with a 60-day grace period to take into account the drug supply in real life, short discontinuations or poor drug adherence. The sensitivity analysis using a shorter grace period (30 days) provided similar hazard ratios that strengthen the robustness of study results for the on treatment analysis.

Outcomes: Since deaths are recorded in the database using the national death registry, there is no information bias for this outcome. To take into account death as a competing risk of other clinical outcomes (SSE, major bleeding, ACS, CRB), the Fine and Gray model was used (Fine 1999). Clinical outcomes were defined using the ICD-10 primary discharge diagnosis, which is the health problem that motivated the hospital admission. The coding is done by the hospital physician of the patient to determine the cost of the hospitalisation, with a hospital process of coherence and quality information verification. Nevertheless, miscoding cannot be excluded but should be really sparse for the clearly defined events studied (SSE, major bleeding, ACS, CRB). Furthermore, the PMSI coding is fully independent from the study and there is no reason that a potential outcome miscoding would be different between DOAC and VKA, excluding an information bias.

Confounding bias

In this study, there is a clear indication bias between each dose of DOAC and VKA, with large differences in patients and disease characteristics, including stroke and bleeding risk factors. To control of this bias, a hdPS, including the main known risk factors (gender, age, AF risk factor score, bleeding risk factor score) in addition to 500 other variables, was defined. The propensity score (PS) is a statistical technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment. The, PS and more recently hdPS (Schneeweiss 2009, Rassen 2012), were developed to summarise a large set of variables that characterize each subject for status and unmeasured confounders not recorded in a database (i.e. drugs, medical status, hospitalisation, other co-morbidities directly, or indirectly linked with unmeasured confounders). Adjusting for large numbers of covariates ascertained from subject healthcare claims data may improve control of confounding, as these variables may collectively be proxies for unobserved factors.

The hdPS included age, gender, specialty of DOAC/VKA prescriber, stroke risk factors, bleeding risk factors, hospitalisation other than cardioversion or catheter-based ablation, chronic obstructive pulmonary disease, diabetes and coronary diseases, hospital and non-hospital costs on year and one month before index date, as well as 500 selected from 4 dimensions: i) LTD, ii) 3-year hospitalisation diagnosis history, iii) 1-year medical and paramedical visits and lab tests history, and iv) 1-year drug (ATC code 7 digits) dispensation history. It was very effective to balance each group comparison for 1:1 matching, as well as adjustment, minimizing the risk of residual confounding.

11.3.Interpretation

This post approval study, performed about 6 months after dabigatran and rivaroxaban became available in France, is a real-world cohort of about 220 000 first users of anticoagulant for NVAF with a specific AF definition in 2013 and 2014 in France, half (49.4%) starting a VKA, 31.7% rivaroxaban, 19.3% with the 20 mg standard dose, 11.2% with the 15 mg reduced dose and 1.2% with the 10 mg dose, and 18.9% dabigatran, 7.7% with the 150 mg standard dose, 10.8% with the 110 mg reduced dose and 0.5% with the 75 mg dose. From them, patients were individually 1:1 matched for each comparison, 31 171 patients per group for rivaroxaban 20 mg versus VKA, 23 314 for rivaroxaban 15 mg versus VKA, 15 323 for rivaroxaban 20 mg versus dabigatran 150 mg, and 15 131 for rivaroxaban 15 mg versus dabigatran 110 mg. This represents a high rate of matching for the smaller group of each comparison: 73.3% for rivaroxaban 20 mg versus VKA, 94.8% for rivaroxaban 15 mg versus VKA, 90.8% for rivaroxaban 20 mg versus dabigatran 150 mg and 63.8% for rivaroxaban 15 mg versus dabigatran 110 mg.

Compared to the ROCKET-AF randomized control trial, our study included 4.4 times more patients for the comparison rivaroxaban 20 mg versus VKA (**Table 68**; Patel 2011). The rivaroxaban 20 mg SSE risk reduction was the same (21%), with a tighter 95%CI in our study in relation with a larger population ([10% to 31%] and [4% to 34%], respectively). For major bleeding and CRB, the risk was clearly lower for rivaroxaban 20 mg compared to VKA in our study (33% [27% to 39%] and 17% [9% to 24%], respectively). In contrast in the ROCKET-AF trial, the risk was similar between rivaroxaban 20 mg and VKA for major bleeding and CRB (1.04 [0.90-1.20] and 1.03 [0.96-1.11], respectively), and associated with a 45% significant increase of GI bleedings in the rivaroxaban group. The risk of death was also lower in our study than the non-significant difference in the ROCKET-AF trial (HR: 0.85 [0.70-1.02]), which could have been significant with more patients and statistical power. Lastly, for rivaroxaban 20 mg and VKA comparison, the 20% ACS risk reduction in our study was close to that of myocardial infarction in the ROCKET-AF trial (19%). This risk reduction was significant in our study ([0.69-0.93]) but not in the ROCKET-AF trial ([0.63-1.06]); maybe because of the different size populations and statistical power. Better benefit-risk of DOAC in real-life might be due to poorer drug surveillance than in a strict randomized control trial, especially for INR surveillance and VKA dose adjustment, as well as several potential VKA interactions (Singer 2013). It could also be explained by the VKA used in France, mainly fluindione (74.5% of VKA prescriptions) followed by warfarin (22.5%) and acenocoumarol (3.0%), whereas warfarin was the comparator in the ROCKET-AF trial and the most used in most other countries.

Eight database studies of new rivaroxaban and VKA users and similar outcomes were identified (**Table 68**), three from US (Laliberté 2014, Coleman 2016, Yao 2016), three from North Europe (Larsen 2016, Gorst-Rasmussen 2016, Staerk 2017), one from Taiwan (Chan 2016) and one from France using also the SNDS database (Maura 2015).

Rivaroxaban 20 mg versus VKA, mainly warfarin, was assessed in five of these studies (the 4 European and one US studies), plus two US studies with mixed doses but mainly 20 mg. The risk of ischemic stroke, or ischemic SSE, or ischemic stroke, transient ischemic attack and SE was of the same order as in our study for 4 studies (Sweden, one Denmark and two US studies with HR point estimate between 0.71 to 0.83), but only one significant (Sweden study, Larsen 2016), and three that did not reach the significant threshold, probably in relation with smaller population than in our study, or shorter follow-up with fewer events as in the Coleman US study (Coleman 2016). For the three other studies (France, one Denmark and one US studies), this risk of ischemic SSE, or ischemic stroke was not significantly different (HR point estimate between 0.89 and 1.01). None of these studies showed a significant difference for major bleeding or CRB (HR point estimate between 0.81 to 1.08, four studies), nor for GI bleeding (HR point estimate between 1.21 and 1.27, two studies), and nor for death (HR point estimate between 0.92 and 0.96, two studies).

Rivaroxaban 20 mg versus dabigatran 150 mg was assessed in one Denmark study, with 1 629 and 5 320 patients, respectively, and no difference for ischemic stroke, transient ischemic attack and SE (0.84 HR point estimate), and significant higher risk of CRB and death with rivaroxaban (HR: 1.73 [1.24-2.42] and 1.40 [1.03-1.91], respectively). This comparison was also assessed by a network meta-analysis of 5 randomized controlled trails: 4 DOAC (apixaban, dabigatran, edoxaban, rivaroxaban) versus warfarin and clopidogrel ± ASA versus VKA, with an odds ratio estimation of 1.33 [1.01-1.76] for stroke or SE and 1.10 [0.90-1.35] for major bleeding (Cameron 2014).

Rivaroxaban 15 mg versus VKA was assessed only in one Denmark study with very few patients, plus two studies (Taiwan and France) with mixed doses, mainly 15 mg. The risk of SSE was significantly lower for rivaroxaban in the Taiwan study (49% [26% to 66%]), not significantly lower in one Denmark study (0.72 HR point estimate) and about the same as in our study in the French study (1.01 HR point estimate). The risk of CRB was assessed in the Taiwan and the French studies, without significant risk difference (0.72 and 0.97 HR point estimate in the Taiwan and the French studies, respectively). The risk of GI bleeding was assessed only in the Taiwan study with no significant risk difference (1.43 HR point estimate), while risk of death was significantly lower with rivaroxaban (53% [33% to 67%]).

Rivaroxaban 15 mg versus dabigatran 110 mg was also assessed in one Denmark study, with no significant risk difference for transient ischemic attack and SE, CRB and death (0.78, 1.29 and 1.47 HR point estimate, respectively), but with only 776 rivaroxaban patients and weak statistical power.

All non-US studies were done in nationwide databases, but with really fewer rivaroxaban subjects for each dose than in our study. The three US studies used private insurance databases, which are large but not representative of the US population and with at least about two, three and 10 times fewer rivaroxaban subjects than in our study. In our study, the use of hdPS matching method allowed to balance groups for potential confounders. The hdPS was used only in one Denmark study but with hdPS decile stratification, and above all relatively few 20 mg and 10 mg rivaroxaban patients, which limit the usefulness to put a large number of variables in the hdPS. Four studies (the three US and the French one) used PS matching, which allows balancing variables included in the PS between the two groups, but with a higher risk of residual confounding than hdPS. The Taiwan and Sweden studies used PS weighting which seems less effective than matching. Lastly, the second Denmark study used risk factor adjustment that seems limited to well adjust treatment assignment with a large indication bias between rivaroxaban and VKA.

Furthermore, our study shows substantial non-systematic variations across subgroups stratified analysis that could impact the global result according to the distribution of these subgroups in the population analyses, as for example between 2013 and 2014 index date, in relation with the fall of dabigatran first prescription and use in 2014.

Finally, the BROTHER study is, to date, the largest study to assess the benefit-risk in NVAF standard and reduced doses of rivaroxaban (20 and 15 mg) versus VKA, as well as versus standard and reduced doses of dabigatran (150 and 110 mg). The study was performed within a nationwide database, with high specificity of NVAF diagnosis, as well as, outcomes diagnosis, using 1:1 hdPS matching to well balance groups for a large set of variables, that work also together as a proxy for potential confounders not available in the database, limiting the risk of residual confounding. The study shows a better benefit-risk with rivaroxaban 20 mg compared to VKA, with a significant lower risk of SSE, major bleeding and death, the three main outcomes, for all patients and most subgroups analyses, as well as for most of secondary outcomes, especially haemorrhagic stroke, CRB and ACS, and without significant GI bleeding increase risk. The benefit-risk was also in favour of the rivaroxaban 15 mg compared to VKA with a similar SSE risk, and significant lower risk of major bleeding and death for all patients and most subgroups analyses, as well as several secondary outcomes, especially haemorrhagic stroke, CRB, a risk of ACS at the significant threshold and still without significant GI bleeding increase risk.

For the comparison between the two DOAC, the study shows a better benefit and lower risk with dabigatran. For standard dose, there was no difference of SSE risk, but higher risk, with rivaroxaban 20 mg than dabigatran 150 mg, of major bleeding and death, as well as several secondary outcomes, in particular haemorrhagic stroke, CRB, GI bleeding and ACS, but with substantial variations across subgroups analysed. For reduced dose, the risk of SSE and major bleeding was higher with rivaroxaban 15 mg than dabigatran 110 mg, as well as several secondary outcomes, such as haemorrhagic stroke, CRB and ACS, but not for death and GI bleeding, still with substantial variations across subgroups analysed.

The total medical cost was in favour of rivaroxaban 20 mg and 15 mg compared to VKA, and in favour of dabigatran 150 mg and 110 mg compared to rivaroxaban. These results were related to the frequency of hospitalisations, and mainly hospitalisations of other cardiovascular and other non-cardiovascular, which were more frequent in VKA and rivaroxaban (20 mg and 15 mg) groups.

Table 68. Results of pre-registration randomized trial and observational studies of new rivaroxaban/VKA users, HR [95%CI]

Main author (Country year)	N	SSE	Major bleeding	CRB	GI bleeding	MI	Death (all-cause)
		HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
Patel 2011 (ROCKET-AF)					ND		
- Riva. 20 mg vs warfarin	7 131 / 7 133	0.79 [0.66-0.96](j)	1.04 [0.90-1.20]	1.03 [0.96-1.11]	3.2% / 2.2% (1.45)	0.81 [0.63-1.06]	0.85 [0.70-1.02]
Cameron 2014							
- R 20 mg vs warfarin		0.88 [0.74-1.04]	1.03 [0.89-1.19]				
- R 20 mg vs D 150 mg		1.33 [1.01-1.76]	1.10 [0.90-1.35]				
Chan 2016 (Taiwan)							
- R 15 mg(a) vs warfarin	3 916 / 5 251(d)	0.51 [0.35-0.74]		0.77 [0.53-1.13]	1.43 [0.88-2.33]	0.63 [0.21-1.89]	0.47 [0.33-0.67]
- R 15 mg(a) vs D(b) 110mg	3 916 / 5 921(d)						
Coleman 2016 (USA)							
- R 20 mg vs warfarin	11 411 / 11 411(e)	0.71 [0.47-1.07](k)					
Laliberté 2014 (USA)							
- R(c) vs warfarin	3 654 / 14 616(f)	0.77 [0.55-1.09]	1.08 [0.71-1.64]		1.27 [0.99-1.63]		
Gorst-Rasmussen 2016 (Denmark)							
- R 20 mg vs warfarin	1 629 / 11 045(g)	0.78 [0.59-1.03](l)		1.06 [0.83-1.37](n)			0.96 [0.79-1.17]
- R 15 mg vs warfarin	776 / 11 045(g)	0.72 [0.48-1.09](l)		0.93 [0.65-1.33](n)			1.46 [1.22-1.76]
- R 20 mg vs D 150 mg	1 629 / 5 320(g)	0.84 [0.59-1.20](l)		1.73 [1.24-2.42](n)			1.40 [1.03-1.91]
- R 15 mg vs D 110 mg	776 / 3 588(g)	0.78 [0.51-1.19](l)		1.29 [0.87-1.90](n)			1.47 [1.21-1.79]
Larsen 2016 (Sweden)							
- R 20mg vs warfarin	7 192 / 35 436(d)	0.83 [0.69-0.99]	1.06 [0.91-1.23](m)	0.99 [0.86-1.14](o)			0.92 [0.82-1.03]
Maura 2015 (France)							
- R 20 mg vs VKA	2 861 / 5 722(h)	0.89 [0.33-2.35]		0.81[0.44-1.49](p)			
- R 10-15 mg vs VKA	1 790 / 3 580(h)	1.01 [0.41-2.51]		0.97[0.53-1.76](p)			
Staerk 2017 (Denmark)							
- R 20 mg vs VKA	5 693 / 18 094(i)	0.89 [0.67-1.19](k)					
Yao 2016 (USA)							
- R(c) vs warfarin	16 175 / 16 175(e)	1.01 [0.75-1.19](k)		1.04 [0.90-1.20](p)	1.21 [1.02-1.43]		

(a) R 15 mg (77.8%), 10 mg (10.6%) & 20mg (12.6%); (b) D 110 mg (89.5%) & 150 mg (10.5%); (c) Mainly 20mg; (d) Propensity score weighting; (e) 1:1 propensity score matching; (f) 1:4 propensity score matching; (g) Stratified by hdPS decile; (h) 1:2 propensity score matching; (i) Risk factor adjustment; (j) ITT during treatment; (k) Ischemic stroke; (l) Stroke, systemic embolism and TIA; (m) intracranial bleeding, bleeding with anaemia, haemothorax, haematuria, epistaxis, and bleeding in the eye; (n) GI, intracranial and major bleeding; (o) GI, intracranial and other sites bleeding; (p) Hospitalisation for bleeding;

11.4. Generalizability

Results of this study can be generalisable to the French population because patients were identified from a whole population database, without any sampling. The patients that were included were therefore fully representative of the inclusion population, i.e. patients with NVAF diagnosis from LTD or hospitalisation or procedure for AF, as well as those with probable AF based on an AF disease score. These results are set within a specific healthcare system in which the most used VKA was fluindione, and might or not apply to other countries.

12. OTHER INFORMATION

Not applicable

13. CONCLUSION

From the conditions of use in 2013 and 2014 in France, rivaroxaban and VKA were prescribed preferentially to rather different patients, while differences between the two DOAC were less marked. When effects are compared within similar patients in hdPS matched groups, as well as for all patients from adjusted analyses and most subgroups from stratified analyses, this nationwide cohort study shows a significantly overall better benefit-risk of rivaroxaban versus VKA, for both doses, including for SSE, death, major bleeding and haemorrhagic stroke, without increased risk of gastrointestinal bleeding with the 20 mg, and with the 15 mg, for death, major bleeding, including haemorrhagic stroke, but not for SSE, and also without increase of GI bleeding.

For the two DOAC comparisons, this study shows a better benefit and lower risk with dabigatran for either dose (20 mg and 15 mg vs 150 and 110 mg, respectively). The risk was not different between rivaroxaban 20 mg and dabigatran 150 mg for SSE, but lower with dabigatran for death, major bleeding, including haemorrhagic stroke and GI bleeding. For reduced dose, the risk was lower with dabigatran 110 mg than rivaroxaban 15 mg for SSE and major bleeding, including haemorrhagic stroke, but not for death or GI bleeding; with however, substantial variations across stratification subgroups analysed.

For healthcare resources use and costs during the drug exposure period, rivaroxaban was cost-saving for both doses (20 mg and 15 mg) for NVAF compared to VKA with a 18% lower total medical cost for the national health perspective. For the two DOAC comparisons, this study shows a better benefit and lower risk with dabigatran for either dose (150 mg and 110 mg) with a 6-7% lower total medical cost.

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Appendix 1. List of stand-alone documents

Number	Document reference number	Date	Title
1-1			Table of correspondence between the model of report by the HAS and the EMA guidance
1-2	Version 1.0	18 December 2015	Protocol
1-3	Version 3.0	26 October 2018	Statistical Analysis Plan
1-4	Version 2.0	11 October 2018	Results Rivaroxaban 20 mg vs VKA Specific NVAF population, grace period of 60 days, one-year of follow-up
1-5	Version 2.0	11 October 2018	Results Rivaroxaban 20 mg vs dabigatran 150 mg Specific NVAF population, grace period of 60 days, one-year of follow-up
1-6	Version 2.0	11 October 2018	Results Rivaroxaban 15 mg vs VKA Specific NVAF population, grace period of 60 days, one-year of follow-up
1-7	Version 2.0	11 October 2018	Results Rivaroxaban 15 mg vs dabigatran 110 mg Specific NVAF population, grace period of 60 days, one-year of follow-up
1-8	Version 2.0	11 October 2018	Additional results Specific NVAF population, grace period of 60 days, one-year of follow-up
1-9	Version 1.0	11 October 2018	Results Rivaroxaban 20 mg vs VKA Sensitive NVAF population, grace period of 60 days, one-year of follow-up
1-10	Version 1.0	11 October 2018	Results Rivaroxaban 20 mg vs dabigatran 150 mg Sensitive NVAF population, grace period of 60 days, one-year of follow-up
1-11	Version 1.0	11 October 2018	Results Rivaroxaban 15 mg vs VKA Sensitive NVAF population, grace period of 60 days, one-year of follow-up
1-12	Version 1.0	11 October 2018	Results Rivaroxaban 15 mg vs dabigatran 110 mg Sensitive NVAF population, grace period of 60 days, one-year of follow-up
1-13	Version 1.0	11 October 2018	Results Rivaroxaban 20 mg vs VKA Specific NVAF population, grace period of 30 days, one-year of follow-up
1-14	Version 1.0	11 October 2018	Results Rivaroxaban 20 mg vs dabigatran 150 mg Specific NVAF population, grace period of 30 days, one-year of follow-up
1-15	Version 1.0	11 October 2018	Results Rivaroxaban 15 mg vs VKA Specific NVAF population, grace period of 30 days, one-year of follow-up
1-16	Version 1.0	11 October 2018	Results Rivaroxaban 15 mg vs dabigatran 110 mg

			Specific NVAF population, grace period of 30 days, one-year of follow-up
1-17	Version 2.0	26 October 2018	Healthcare resources and costs Specific NVAF population (matched patients), grace period of 60 days, one-year of follow-up
1-18			Signature pages

Appendix 2. Additional information

Not applicable.