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

Two-year clinical outcomes

Version 1.0, 16 November 2018

Sponsor: Bayer AG

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PASS information

Title	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.
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	16 November 2018
EU PAS register number	EUPAS14567
Active substance	B01AF01 ATC code: Rivaroxaban B01AE07 ATC code: Dabigatran etexilate B01AA ATC code: Vitamin K antagonists (VKA)
Medicinal product	Xarelto® Pradaxa® Vitamin K antagonists (VKA)
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	Bayer AG
Joint PASS	No
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.
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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.

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. Secondary outcomes were clinically relevant bleeding (CRB), acute coronary syndrome (ACS) and a composite criterion of SSE, major bleeding or death.

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. Consequently, only the 2013 patients have a two-year follow-up and were included in this 2-year analysis.

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
This report concerns the 2-year follow-up for the new DOAC or VKA users in 2013. Among the 387 788 patients identified in the nationwide SNDS database with a first dispensing of rivaroxaban, dabigatran or VKA in 2013, without history of prior DOAC or VKA dispensing in the 3 years, 118 048 patients were included in the specific NVAF population: 34 803 (30%) in the rivaroxaban group (17% with the 20 mg standard dose, 11% with the 15 mg reduced dose, and 1% with the 10 mg dose), 29 993 (25%) in the dabigatran group (10% with the 150 mg standard dose, 15% with the 110 mg reduced dose, and 1% with the 75 mg dose), and 53 252 (45%) 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 163 349 patients: 51 304 (31%) in the rivaroxaban group (18% with the standard dose, 12% with the reduced dose, and 1% with the 10 mg dose), 40 933 (25%) in the dabigatran group (9% with the standard dose, 15% with the reduced dose, and 1% with the 75 mg dose), and 71 112 (44%) in the VKA group.

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): 15 680 patients per group for rivaroxaban 20 mg versus VKA in the specific population and 21 963 per group in the sensitive population (77% and 75% of rivaroxaban patients, respectively), 10 342 per group for rivaroxaban 20 mg versus dabigatran 150 mg in the specific population and 13 893 per group in the sensitive population (89% and 92% of dabigatran patients, respectively), 12 018 per group for rivaroxaban 15 mg versus VKA in the specific population and 18 333 per group in the sensitive population (94% and 93% of rivaroxaban patients, respectively), and 9 952 per group for rivaroxaban 15 mg versus dabigatran 110 mg in the specific population and 15 773 per group in the sensitive population (57% and 64% 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.

Clinical outcomes studied during the anticoagulant (rivaroxaban, dabigatran, VKA) exposure on the 2-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 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

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 3.7 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 1.5 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 (41% and 39%, respectively), followed by hospital physicians (29% and 25%, respectively), and GP (21% and 25%, respectively). It was similar for dabigatran 150 mg and 110 mg: cardiologists (40% and 33%, respectively), hospital physicians (33% and 32%, respectively), and GP (16% and 22%, respectively), while VKA were mainly prescribed by hospital physicians (40%), followed by GP (27%), and a few by cardiologists (17%).

In this real-life study, the reduced dose of DOAC was frequently used and concerned 37% of patients for the rivaroxaban group and 59% 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 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 69.2 (± 11.1), 65.4 (± 10.1) and 78.0 (± 11.1) years, with 63%, 69% and 52% of men, 68%, 58% and 90% of CHA_2DS_2-VASc ≥ 2, 4%, 3% and 16% 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 80.2 (± 9.2) and 78.7 (± 9.4) years, 47% and 49% of men, 93% and 92% of CHA_2DS_2-VASc ≥ 2, 9% of HAS-BLED > 3 for both, respectively.

After matching, the mean age was 71.3 (± 10.1) 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, 66.3 and 66.2 (± 9.3) years with 69% of men, 59% of CHA_2DS_2-VASc ≥ 2, and 3% of HAS-BLED > 3 in both groups for rivaroxaban 20 mg and dabigatran 150 mg groups, 80.4 (± 8.6) years with 47% of men, 93% of CHA_2DS_2-VASc ≥ 2, 10% of HAS-BLED > 3 in both groups for rivaroxaban 15 mg and VKA groups, 80.5 and 80.4 (± 7.9) years with 47% 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 number of person-years (PY) during the first drug exposure was 23 768, 12 698, and 59 588 PY, respectively for all rivaroxaban 20 mg, dabigatran 150 mg, and VKA patients, and 13 712 and 17 830 PY, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients. For matched patients, there were 18 524 and 18 489 PY, respectively for rivaroxaban 20 mg and VKA groups, 12 104 and 11 395 PY, respectively for rivaroxaban 20 mg and dabigatran 150 mg groups, 12 989 and 14 076 PY, respectively for rivaroxaban 15 mg and VKA groups, and 10 935 and 9 995 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 85% for all and matched patients.

Overall incidence of outcomes for all 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 1.3 [1.2 to 1.4], 1.1 [0.9 to 1.3] and 2.6 [2.5 to 2.7] for SSE, 1.2 [1.1 to 1.3], 0.5 [0.4 to 0.6], and 3.1 [3.1 to 3.2] for major bleedings, 3.0 [2.8 to 3.2], 1.7 [1.5 to 1.9] and 13.0 [12.7 to 13.3] for death, 5.1 [4.8 to 5.4], 3.1 [2.8 to 3.4] and 17.0 [16.7 to 17.3] 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 2.3 [2.0 to 2.6] and 1.7 [1.5 to 1.9] for SSE, 2.3 [2.3 to 2.6] and 1.6 [1.4 to 1.8] for major bleeding, 8.5 [8.0 to 9.0] and 7.0 [6.6 to 7.4] for death, 11.8 [11.3 to 12.3] and 9.5 [9.1 to 9.9] for the composite.

Two-year cumulative incidence and risk comparison (main analysis for matched patients of the specific population with a 60-day grace period for the drug discontinuation)

Rivaroxaban 20 mg versus VKA

The 2-year cumulative incidence was significantly lower with rivaroxaban 20 mg than VKA for two main outcomes: 2.4% [2.1 to 2.7] vs. 3.5% [3.2 to 3.9] (HR: 0.69 [0.59 to 0.81]) for major bleeding, 6.5% [6.0 to 7.0] vs. 9.7% [9.1 to 10.3] (HR: 0.67 [0.61 to 0.74]) for death, while the risk was similar between the two groups for SSE (2.6% [2.3 to 2.9] vs. 2.7% [2.4 to 3.0] (HR: 0.99 [0.84 to 1.16]). It was also significantly lower with rivaroxaban for the three secondary outcomes: 5.5% [5.0 to 5.9] vs. 6.4% [5.9 to 6.9] (HR: 0.86 [0.77 to 0.97]) for CRB, 1.6% [1.4 to 1.9] vs. 2.2% [1.9 to 2.5] (HR: 0.75 [0.62 to 0.91]) for ACS, and 10.2% [9.6 to 10.8] vs. 14.0% [13.3 to14.7] (HR: 0.73 [0.68 to 0.79]) for the composite criterion.

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban for other critical organ or site bleeding (HR: 0.38 [0.26 to 0.56]) and other bleeding (0.75 [0.60 to 0.93]), but not statistically different for haemorrhagic stroke, GI bleeding, and urogenital bleeding (0.84 [0.63 to 1.12], 1.02 [0.84 to 1.22], 1.12 [0.86 to 1.46], respectively). For other individual events of major outcomes, the risk was significantly lower with rivaroxaban for STEMI (0.51 [0.34 to 0.76]), but not for ischemic or undefined stroke (0.97 [0.79 to 1.19]), other SE or surgical procedure for SE (1.02 [0.78 to 1.34]), NSTEMI (0.64 [0.39 to 1.05]), and unstable angina (0.87 [0.69 to 1.09]).

Stratified analyses were performed for main and secondary outcomes, according to 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: 0.67 (fourth quintile) to 1.24 (diabetes mellitus) for SSE, 0.44 (65-69 years old) to 0.94 (vascular disease history) for major bleeding, 0.47 (last quintile) to 0.82 (HAS BLED scores > 3) for death, 0.61 (65-69 years old) to 0.89 (70-74 years old) for the composite criterion, with a HAS-BLED HR gradient for all main outcomes from > 3 to 0-1 scores for SSE (0.86 to 1.15), from 0-1 to > 3 scores for major bleeding (0.59 to 0.89), death (0.59 to 0.82), composite criterion (0.70 to 0.83), a CHA_2DS_2-VASc HR gradient from 0-1 to ≥ 4 scores for major bleeding (0.55 to 0.86), and a quintile HR gradient from the last to the first quintile of logit hdPS for major bleeding (0.54 to 0.86), and no clear systematic variation for the other factors and outcomes.

The HR point estimate after one year of follow-up for the 2013 matched patients was quite the same for two of the three main outcomes (major bleeding and death) with some variations of the 95%CI, and a little better HR with rivaroxaban but also not significant for SSE (0.90 [0.74 to 1.08]). It was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with some variations of the 95%CI, including a non-significant 95%CI for CRB. It was quite the same for the 2013-2014 matched patients at one-year presented in the previous report, with twice more patients: similar HR for two of the three main outcomes (major bleeding and death) with narrower 95%CI due to larger population, but a significant lower risk for SSE with rivaroxaban compared to VKA (HR: 0.79 [0.69 to 0.90] for 2013 and 2014 matched patients, and 0.68 [0.56 to 0.83] for the only 2014 matched patients). Result was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with narrower 95%CI due to larger population.

Rivaroxaban 20 mg versus dabigatran 150 mg

The 2-year cumulative incidence was significantly higher with rivaroxaban 20 mg than dabigatran 150 mg for two main outcomes: major bleeding (1.7% [1.4 to 2.1] vs. 0.8% [0.6 to 1.1], HR: 2.13 [1.53 to 2.95]), death (3.9% [3.5 to 4.4] vs. 3.0% [2.6 to 3.5], HR: 1.30 [1.08 to 1.57]), and almost the same for SSE (2.0% [1.7 to 2.4] vs. 2.0% [1.6 to 2.3], HR: 1.03 [0.81 to 1.31]). It was also significantly higher with rivaroxaban for CRB (4.5% [4.0 to 5.0] vs. 2.3% [1.9 to 2.7], HR: 2.0 [1.64 to 2.44]), the composite criterion (7.0% [6.4 to 7.6] vs. 5.6% [5.0 to 6.2], HR: 1.26 [1.10 to 1.45]), and almost the same for ACS (1.5% [1.2 to 1.8] vs. 1.4% [1.2 to 1.8], HR: 1.07 [0.81 to 1.42]).

The 2-year risk of other individual events was significantly higher with rivaroxaban 20 mg for haemorrhagic stroke (HR: 4.46 [2.18 to 9.15]), GI bleeding (1.73 [1.26 to 2.35]), urogenital bleeding (2.24 [1.46 to 3.44]), other bleeding (1.91 [1.25 to 2.92]), but not for other critical organ or site bleeding (1.13 [0.59 to 2.15]), ischemic or undefined stroke (1.16 [0.86 to 1.57]), other SE or surgical procedure for SE (0.85 [0.57 to 1.26]), STEMI (0.57 [0.32 to 1.01]), NSTEMI (2.01 [0.94 to 4.27]), and unstable angina (1.17 [0.83 to 1.65]).

Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.66 (second quintile) to 2.12 (fourth quintile), with a HAS-BLED gradient from 0.88 to 1.33 for scores 0-1 to > 3, and only one significant HR. For the three other outcomes, the risk was in favour of dabigatran for almost all subgroups, with a HR from 1.59 (HAS-BLED scores > 3) to 3.73 (< 65 years old) for major bleeding, with a HAS-BLED gradient, from 1.59 to 2.21 for scores > 3 to 0-1, 1.11 (first and fourth quintiles) to 2.02 (HAS-BLED scores > 3) for death, with a HAS-BLED gradient, from 1.19 to 2.02 for scores 0-1 to > 3, and 0.95 (second quintile) to 1.90 (70-74 years old) for composite criterion, with a HAS-BLED gradient, from 1.18 to 1.59 for scores 0-1 to > 3, without clear systematic variation for the other factors and outcomes.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main outcomes (SSE, major bleeding, death) and two of the three secondary outcomes (CRB and composite criterion) with some variations of the 95%CI, while the risk of ACS was significantly lower with dabigatran (HR: 1.57 [1.15 to 2.14]). For the 2013-2014 matched patients at one-year, HR was similar with some variations of the 95%CI for death, a little better with rivaroxaban but also not significant for SSE, and with a lower difference for major bleeding but always in favour of dabigatran. It was similar with some variations of the 95%CI for CRB, and the

composite criterion, and also with a lower difference for ACS with dabigatran (HR: 1.35 [1.05 to 1.75]).

Rivaroxaban 15 mg versus VKA

The 2-year cumulative incidence was significantly lower with rivaroxaban 15 mg than VKA for two main outcomes: major bleeding (3.7% [3.3 to 4.1] vs. 4.6% [4.2 to 5.1], HR: 0.80 [0.69 to 0.93]), death (14.1% [13.3 to 14.9] vs. 18.3% [17.5 to 19.2], HR: 0.79 [0.73 to 0.85]), and not statistically different between the two groups for SSE (3.7% [3.3 to 4.1] vs. 3.2% [2.9 to 3.6], HR: 1.14 [0.97 to 1.34]). It was also significantly lower with rivaroxaban for CRB (6.7% [6.2 to 7.3] vs. 7.6% [7.1 to 8.2], HR: 0.88 [0.79 to 0.99]) and the composite criterion (18.9% [18.0 to 19.8] vs. 23.2% [22.3 to 24.1], HR: 0.83 [0.77 to 0.88]), and almost the same for ACS (2.4% [2.0 to 2.7] vs. 2.3% [2.0 to 2.7], HR: 1.03 [0.85 to 1.26]).

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban 15 mg for other critical organ or site bleeding (HR: 0.69 [0.50 to 0.94]) and other bleeding (0.74 [0.60 to 0.93]), but not for haemorrhagic stroke, GI bleeding and urogenital bleeding (0.83 [0.64 to 1.07], 1.02 [0.84 to 1.25] and 1.03 [0.77 to 1.39], respectively). For other individual events of major outcomes, the risk was not different between groups: ischemic or undefined stroke (1.13 [0.92 to 1.38]), other SE or surgical procedure for SE (1.15 [0.88 to 1.49]), STEMI (0.98 [0.69 to 1.37]), NSTEMI (1.09 [0.63 to 1.86]) and unstable angina (1.16 [0.91 to 1.48]).

Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.83 (70-74 years old) to 2.39 (65-69 years old), and one significant HR. For the three other outcomes, the risk was in favour of rivaroxaban for almost all subgroups, with a HR from 0.53 (second quintile) to 1.14 (HAS-BLED scores 0-1) for major bleeding, with a HAS-BLED gradient, from 0.56 to 1.14 for scores > 3 to 0-1, 0.67 (last quintile) to 1.49 (CHA_2DS_2-VASc scores 0-1) for death, with a quintile gradient from 0.67 to 0.85 for the last to the first quintile, and 0.76 (last quintile) to 1.17 (CHA_2DS_2-VASc scores 0-1) for composite criterion, with a weak HAS-BLED gradient, from 0.80 to 0.89 for scores > 3 to 0-1.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for SSE, death as well as for major bleeding but with a non-significant 95%CI (HR: 0.90 [0.75 to 1.07]. It was also the same for the composite criterion, as well as for CRB but with a non-significant 95%CI (0.92 [0.81 to 1.05]), and somewhat different but yet not significant for ACS (0.92 [0.74 to 1.15]). For the 2013-2014 matched patients at one-year, HR and 95%CI were in the same range for two of the three main outcomes (major bleeding and death), and a point estimate close to 1 for SSE. HR and 95%CI were also in the same range for CRB and the composite criterion, and a difference at the significant threshold for ACS in favour of rivaroxaban (HR: 0.85 [0.73 to 1.00]).

Rivaroxaban 15 mg versus dabigatran 110 mg

The 2-year cumulative incidence was significantly higher with rivaroxaban 15 mg than dabigatran 110 mg for two main outcomes: SSE (3.5% [3.0; 3.9] vs. 2.7% [2.3; 3.1], HR: 1.34 [1.10-1.64]), and major bleeding (3.6% [3.2; 4.1] vs. 2.7% [2.3; 3.1], HR: 1.31 [1.08 to 1.59]), and not statistically different between the two groups for death (12.9% [12.1; 13.8] vs. 12.3% [11.4; 13.2], HR: 1.06 [0.96 to 1.17]). It was also significantly higher with rivaroxaban for CRB (6.6% [6.0; 7.2] vs. 4.9% [4.3; 5.4], HR: 1.34 [1.16 to 1.54]) and the composite criterion (17.5% [16.6; 18.5] vs. 15.7% [14.8; 16.7], HR: 1.14 [1.04 to 1.24]), and not statistically different for ACS (2.3% [1.9; 2.6] vs. 2.2% [1.9; 2.6], HR: 1.05 [0.84 to 1.32]).

For other individual events, the risk at 2-year was significantly higher with rivaroxaban 15 mg for other SE or surgical procedure for SE (HR: 1.95 [1.35 to 2.82]), haemorrhagic stroke (2.55 [1.67 to 3.91]), other critical organ or site bleeding (1.75 [1.12 to 2.73]), urogenital bleeding (1.52 [1.03 to 2.23]), other bleeding (1.81 [1.31 to 2.50]), but not for ischemic or undefined stroke (1.12 [0.88 to 1.43]), STEMI (1.24 [0.81 to 1.91]), NSTEMI (0.61 [0.35 to 1.06]), unstable angina (1.18 [0.89 to 1.56]), and GI bleeding (0.85 [0.69 to 1.06]).

Stratified analyses for main and secondary outcomes showed non-systematic substantial variations across sub-groups, mainly in favour of dabigatran, from a HR of 0.73 (< 65 years old) to 8.50 (CHA_2DS_2-VASc scores 0-1) for SSE, 0.53 (CHA_2DS_2-VASc scores 0-1) to 2.85 (75-79 years

old) for major bleeding, 0.62 (< 65 years old) to 2.51 (65-69 years old) for death, 0.70 (< 65 years old) to 2.63 (65-69 years old) for the composite criterion.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion) with 95%CI just below the significant threshold for major bleeding (HR: 1.22 [0.98 to 1.51]). For the 2013-2014 matched patients at one-year, HR and 95% CI were in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion).

Sensitivity analyses

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 complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes for both matched and all patients adjusted analyses.

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, 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 is that the database was built for administrative and reimbursement purposes with a lack of clinical information that could impact the patients' 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 are 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 are 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 shows non-systematic substantial variations across subgroups stratified analysis that could impact the global result according the distribution of theses subgroup in the population analyses.

From the conditions of use in 2013 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, this nationwide cohort study shows a significantly overall better benefit-risk of rivaroxaban versus VKA, for both doses (20 mg and 15 mg), including for major bleeding, death, and composite, but not for SSE, and without increased risk of gastrointestinal bleeding. These results were strengthens with really similar HR when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses according to a more sensitive population definition, a 30-day grace period for drug discontinuation definition, and a complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS. Results were also almost the same for most subgroups from stratified analyses (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); with however some substantial variations of the HR point estimate. It means that the global result of the whole population treated relied of the characteristics of this population; and

could be an explanation for HR variations at one year between 2013 and 2013 + 2014 matched patients, especially a somewhat better SSE HR with rivaroxaban 20 mg for the 2014 matched patients (0.68 [0.56 to 0.83] than for the 2013 matched patients (0.90 [0.74 to 1.08]). Indeed, the trend of DOAC initiation from 2013 to 2014 shown an increase of rivaroxaban, a drop of dabigatran and start of apixaban prescriptions in 2014.

For the two DOAC comparisons, the study shows 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, major bleeding, including haemorrhagic stroke, but not for death, and without increased risk of gastrointestinal bleeding. HR results were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses according to a more sensitive population definition, a 30-day grace period for drug discontinuation definition, and a complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, that strengthens the conclusion of the study. Results were also almost the same for most subgroups from stratified analyses (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), with also some substantial variations of the HR point estimate.

Conclusion

This nationwide cohort study shows that from the conditions of use in 2013 in France, rivaroxaban and VKA were prescribed preferentially to rather different patients, while differences between the two DOAC were smaller. Patients receiving reduce doses were older with more stroke and bleeding risk factors than those receiving standard doses.

Compared to VKA, the rivaroxaban 20 mg had a lower risk of major bleeding, CRB, ACS and death, but not for SSE, with an overall better benefit-risk for the composite criterion (SSE, major bleeding, and death). The overall benefit-risk was also better with rivaroxaban 15 mg than VKA, but a little less marked than for 20 mg, with a lower risk of major bleeding, CRB, and death, and no difference for SSE and ACS. For the two DOAC comparisons, the risk was higher with rivaroxaban 20 mg than dabigatran 150 mg for major bleeding, CRB, and death, and not different for SSE and ACS. For reduced dose, the risk was higher with rivaroxaban 15 mg than dabigatran 110 mg for SSE, major bleeding, CRB, but not for ACS and death. For the four comparisons, some substantial variations were observed across stratification subgroups.

Marketing Authorisation Holder(s)

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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.

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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) – November 2017-November 2018 (two-year clinical outcomes)	
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) – November 2018 (two-year clinical outcomes)	

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**). According to the study design, only the 2013 patients (*i.e.* first reimbursed dispensing of DOAC or VKA in 2013) have a two-year follow-up and were included in the 2-year analysis.

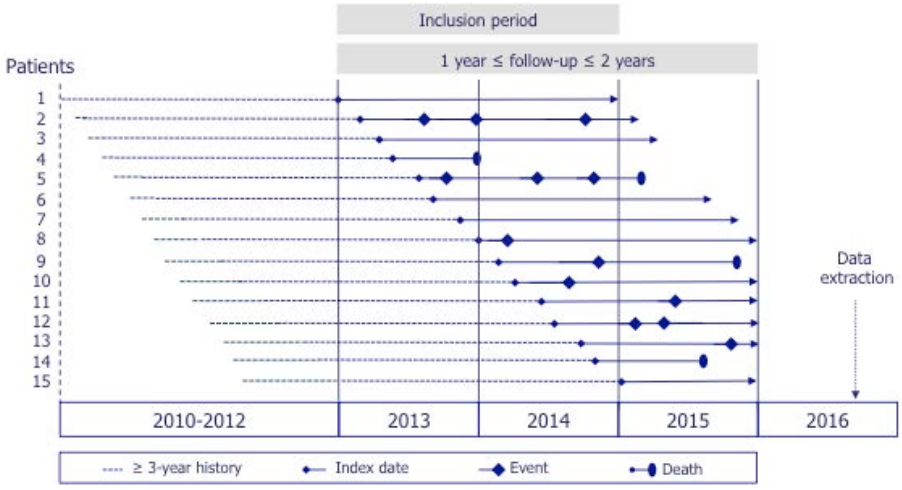


Figure 1. Study design

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:

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

- **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).

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. For the 2-year analysis, the index date concerned only patients with a first reimbursed dispensing of rivaroxaban, dabigatran, or VKA in 2013.

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, stroke and SE (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, stroke and SE (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 stroke and SE, 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 (see the study report “One-year of follow-up”).

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 (and 2-year) follow-up and during drug exposure: dispensing frequency, DDD, MPR, discontinuation, switch,
- Description of healthcare resources use during the drug exposure on the 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 (and 2-year) incidence of outcomes (clinical events) during the drug exposure,
- Comparison of the 1-year (and 2-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).

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 (and 2-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: only for analysis during the 1-year follow-up), 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) (see the study report “One-year of follow-up”).

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 1-16. 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:

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

For the main analysis (specific NVAF population and a grace period of 60 days), two other sensitivity analyses were performed:

- The first considering undefined strokes as haemorrhagic strokes;
- The second with adjustment on the Charlson comorbidity index score for three outcomes (SSE, major bleeding, death).

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. All results (Appendices 1-4 to 1-16) are included in this study report.

10. RESULTS

All results in this report concern the 2-year follow-up period and 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 of comparison for outcomes (SSE, major bleeding, and death) with adjustment on the Charlson comorbidity index score are presented for the main analysis in Appendices 1-4 to 1-7.

Results for stratified analyses for 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.

10.1. Populations (new anticoagulant users in 2013)

Over one year in 2013, 387 788 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, 118 048 patients were included in the specific study population: 34 803 (29.5%) in the rivaroxaban group (17.3% with the 20 mg standard dose, 10.8% with the 15 mg reduced dose, and 1.3% with the 10 mg dose), 29 993 (25.4%) in the dabigatran group (9.9% with the 150 mg standard dose, 14.9% with the 110 mg reduced dose, and 0.6% with the 75 mg dose), and 53 252 (45.1%) in the VKA group (**Figure 2**; Appendices 1-4 to 1-7, Figure 1, Table 1*).* The specific population represented 72.3% of the sensitive population with few variations between treatment groups: 67.8% for rivaroxaban, 73.3% for dabigatran, and 74.9% for VKA, respectively.

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:

- 15 680 patients per group for the comparison rivaroxaban 20 mg versus VKA (76.6% and 29.4% of rivaroxaban 20 mg and VKA patients, respectively) in the specific population, and 21 963 patients per group in the sensitive population (75.1% and 30.9% of rivaroxaban 20 mg and VKA patients, respectively);
- 10 342 patients per group for the comparison rivaroxaban 20 mg versus dabigatran 150 mg (50.5% and 88.5% of rivaroxaban 20 mg and dabigatran 150 mg patients, respectively) in the specific population, and 13 893 patients per group in the sensitive population (47.5% and 91.8% of rivaroxaban 20 mg and dabigatran 150 mg patients, respectively);
- 12 018 patients per group for the comparison rivaroxaban 15 mg versus VKA (93.9% and 22.6% of rivaroxaban 15 mg and VKA patients, respectively) in the specific population, and 18 333 patients per group in the sensitive population (92.9% and 25.8% of rivaroxaban 15 mg and VKA patients, respectively);
- 9 952 patients per group for the comparison rivaroxaban 15 mg versus dabigatran 110 mg (77.8% and 56.7% of rivaroxaban 15 mg and dabigatran 110 mg patients, respectively) in the specific population, and 15 773 patients per group in the sensitive population (79.9% and 63.8% of rivaroxaban 15 mg and dabigatran 110 mg patients, respectively).

	All populations N	
Selection criteria - First reimbursed dispensing of dabigatran, rivaroxaban or VKA - Between 1st January 2013 and 31 December 2013 - Without a 3-year history of DOAC or VKA dispensing	**387 788**	
Exclusion criteria	**269 740**	
- Missing or incorrect data (age, death date)	766	
- Less than 18 years at index date	899	
- At least two treatment groups at index date	156	
- Death at index date	43	
- Less than 3 years history in the SNDS before index date	13 121	
- Alive at index date and without complete follow-up (1-year after index date)	2 291	
- Other probable indications	89 668	
- SSR after orthopaedic surgery	582	
- Rheumatic valve disease history before index date	5 275	
- Valve replacement before index date	7 027	
- Uncertain identification (several twins or beneficiaries)	2 500	
- No atrial fibrillation (neither diagnostic nor probabilistic)	102 111	
- Patient without atrial fibrillation diagnosis but probabilistic information (for the sensitive population definition)	45 301	
	Specific population N	**Sensitive population n**
Study Population	**118 048**	**163 349**
- With NVAF diagnosis information without other probable indication criteria	X	
- With NVAF diagnosis or probabilistic information without other probable indication criteria		X
- rivaroxaban	34 803	51 304
• *rivaroxaban 20 mg*	*20 465*	*29 263*
• *rivaroxaban 15 mg*	*12 800*	*19 739*
• *rivaroxaban 10 mg*	*1 538*	*2 302*
- dabigatran	29 993	40 933
• *dabigatran 150 mg*	*11 685*	*15 131*
• *dabigatran 110 mg*	*17 557*	*24 721*
• *dabigatran 75 mg*	*751*	*1 081*
- VKA	53 252	71 112
All patients after hdPS trimming* for group comparisons		
- rivaroxaban 20 mg versus VKA	20 452 vs 53 249	29 249 vs 71 108
- rivaroxaban 20 mg versus dabigatran 150 mg	20 461 vs 11 663	29 245 vs 15 087
- rivaroxaban 15 mg versus VKA	12 723 vs 53 218	19 681 vs 71 087
- rivaroxaban 15 mg versus dabigatran 110 mg	12 743 vs 17 533	19 716 vs 24 675
1:1 matched populations		
- rivaroxaban 20 mg versus VKA	15 680 vs 15 680	21 963 vs 21 963
- rivaroxaban 20 mg versus dabigatran 150 mg	10 342 vs 10 342	13 893 vs 13 893
- rivaroxaban 15 mg versus VKA	12 018 vs 12 018	18 333 vs 18 333
- rivaroxaban 15 mg versus dabigatran 110 mg	9 952 vs 9 952	15 773 vs 15 773

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

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

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 3 patients for the VKA group (0.006%) and rivaroxaban standard dose comparison, and a maximum of 77 patients for the rivaroxaban 15 mg group (0.6%) and VKA comparison in the specific population;
- a minimum of 4 patients for the VKA group (0.006%) and rivaroxaban standard dose comparison, and a maximum of 58 patients for the rivaroxaban 15 mg group (0.3%) 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, 59% for all patients with rivaroxaban, whereas for dabigatran, the most used was the reduced dose (110 mg), 59% for all patients with dabigatran (**Table 1**; 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.

Table 1. All patients distribution according to initial dose of rivaroxaban and dabigatran

	Rivaroxaban exposure (%)		Dabigatran exposure (%)	
	Dose (mg)	All patients n = 34 803	Dose (mg)	All patients n = 29 993
Standard dose	20	58.8	150	39.0
Reduced dose	15	36.8	110	58.5
Rivaroxaban 10 mg or dabigatran 75 mg	10	4.4	75	2.5

Prescriber speciality

The main prescribers of rivaroxaban 20 mg at index date for the specific population were cardiologists (41%), followed by hospital physicians (29%), and general practitioners (21%). Similar results were found for rivaroxaban 15 mg: cardiologists (39%), hospital physicians and general practitioners (25%) (**Table 2**; Appendices 1-4 to 1-7, Table 25).

For dabigatran 150 mg, the main prescribers were cardiologists (40%), followed by hospital physicians (33%), and general practitioners (16%), while the main prescribers of dabigatran 110 mg were cardiologists (33%) and hospital physicians (32%), followed by general practitioners (22%) (**Table 2**; Appendices 1-6 and 1-7, Table 25).

While VKA were more prescribed at index date by hospital physicians (40%), followed by general practitioners (27%). Cardiologists represented only 17% of the prescribers, more than two times less than in rivaroxaban groups (**Table 2**; Appendices 1-4 and 1-5, Table 25).

Table 2. Prescriber speciality of the first DOAC or VKA dispensing for the specific population

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 20452	**VKA n = 53249**	**Rivaroxaban 20 mg n = 15680**	**VKA n = 15680**
Cardiologist	8286 (40.5)	9044 (17.0)	5144 (32.8)	4753 (30.3)
Hospital physician (undetermined specialty)	5872 (28.7)	21251 (39.9)	4919 (31.4)	5121 (32.7)
General practitioner	4190 (20.5)	14299 (26.9)	3790 (24.2)	3957 (25.2)
Other medical specialty	2104 (10.3)	8655 (16.3)	1827 (11.7)	1849 (11.8)

	Rivaroxaban 20 mg n = 20461	**Dabigatran 150 mg n = 11663**	**Rivaroxaban 20 mg n = 10342**	**Dabigatran 150 mg n = 10342**
Cardiologist	8295 (40.5)	4617 (39.6)	4269 (41.3)	4244 (41.0)
Hospital physician (undetermined specialty)	5874 (28.7)	3847 (33.0)	3133 (30.3)	3219 (31.1)
General practitioner	4188 (20.5)	1907 (16.4)	1814 (17.5)	1770 (17.1)
Other medical specialty	2104 (10.3)	1292 (11.1)	1126 (10.9)	1109 (10.7)

	Rivaroxaban 15 mg n = 12723	**VKA n = 53218**	**Rivaroxaban 15 mg n = 12018**	**VKA n = 12018**
Cardiologist	4979 (39.1)	9013 (16.9)	4366 (36.3)	4208 (35.0)
Hospital physician (undetermined specialty)	3205 (25.2)	21251 (39.9)	3170 (26.4)	3207 (26.7)
General practitioner	3171 (24.9)	14299 (26.9)	3131 (26.1)	3263 (27.2)
Other medical specialty	1368 (10.8)	8655 (16.3)	1351 (11.2)	1340 (11.1)

	Rivaroxaban 15 mg n = 12743	**Dabigatran 110 mg n = 17533**	**Rivaroxaban 15 mg n = 9952**	**Dabigatran 110 mg n = 9952**
Cardiologist	5023 (39.4)	5696 (32.5)	3711 (37.3)	3773 (37.9)
Hospital physician (undetermined specialty)	3200 (25.1)	5583 (31.8)	2622 (26.3)	2642 (26.5)
General practitioner	3153 (24.7)	3916 (22.3)	2485 (25.0)	2410 (24.2)
Other medical specialty	1367 (10.7)	2338 (13.3)	1134 (11.4)	1127 (11.3)

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).

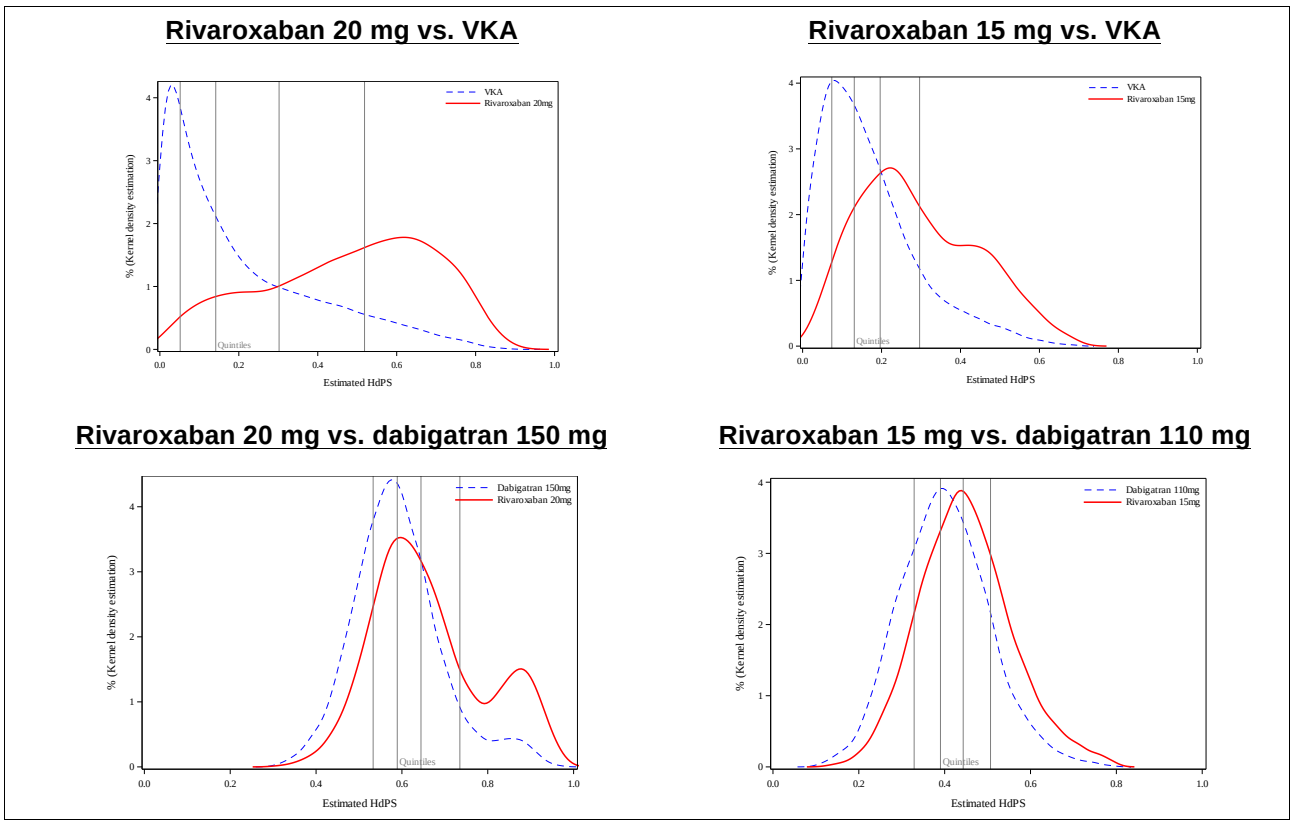


Figure 3. HdPS distribution for all patients of the specific population according to treatment groups after trimming

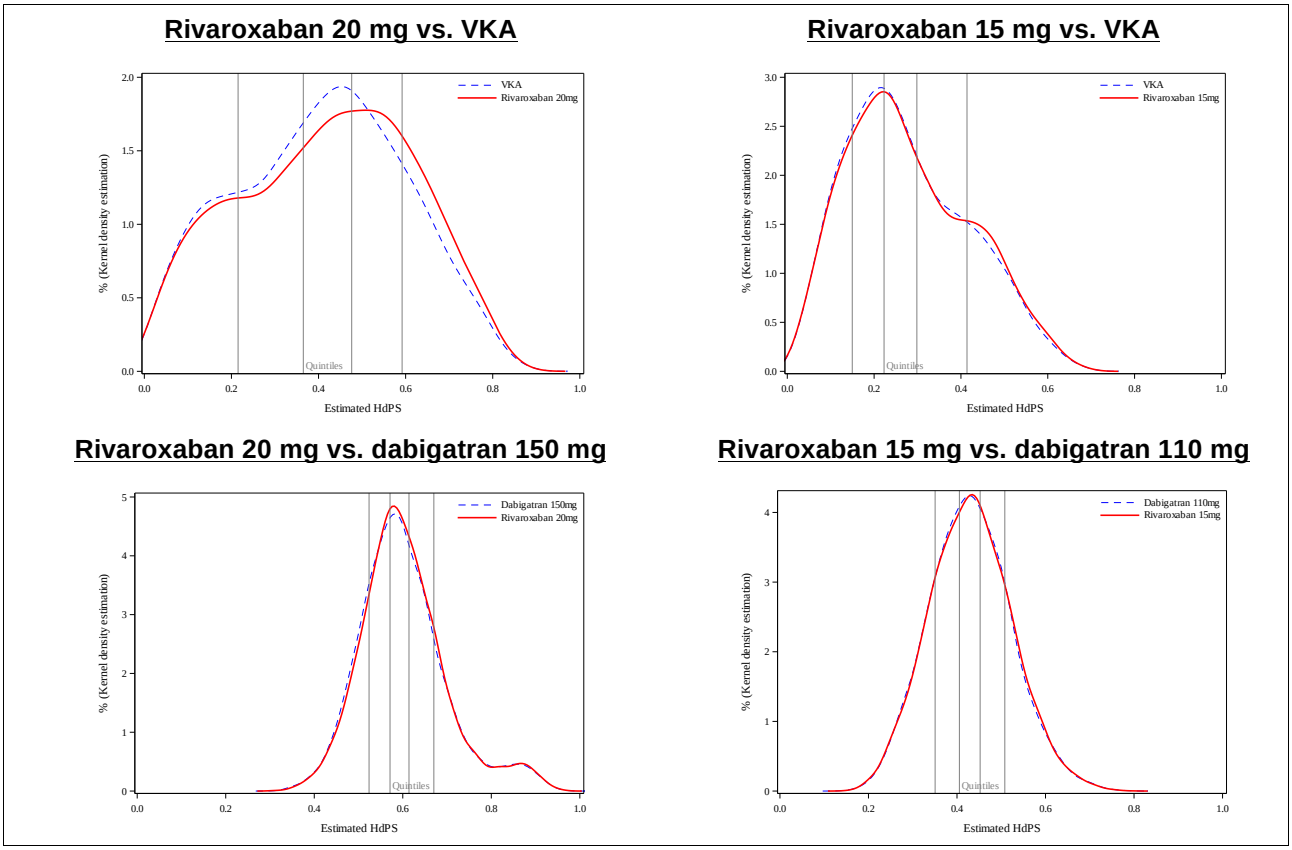


Figure 4. HdPS distribution for matched patients of the specific population according to treatment groups

10.2.3. Baseline demographic characteristics

For patients of the rivaroxaban 20 mg group for the specific population had a mean age of 69.2 (± 11.1) years, with 17% aged 80 years or more, and 63% of men, those of dabigatran 150 mg were younger (65.4 ± 10.1 years), with few aged 80 years or more (< 5%), and about 69% of men, while VKA patients were older (78.0 ± 11.1 years) with more than half of patients aged 80 years or more, and about 52% of men (**Tables 3 and 4**; 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, crude standardized differences between groups decreased drastically or even disappeared after adjustment and matching, with a mean age of 71.3 (± 10.1) years and 62% of men in both matched groups for the comparison with VKA, and about 66 (± 9.3) years and 69% of men in both groups for the comparison with dabigatran. Similar results were found for the sensitive population.

Table 3. 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 = 20452	VKA n = 53249	Rivaroxaban 20 mg n = 15680	VKA n = 15680	Crude	Adjusted	Matched
Gender, n (%)					-23.6	-0.1	0.0
Male	12942 (63.3)	27532 (51.7)	9711 (61.9)	9711 (61.9)	.	.	
Female	7510 (36.7)	25717 (48.3)	5969 (38.1)	5969 (38.1)			
Age at index date (in years)					-80.1	-4.0	-0.2
Size (missing data)	20452 (0)	53249 (0)	15680 (0)	15680 (0)			
Mean (± SD)	69.2 (11.1)	78.0 (11.1)	71.3 (10.1)	71.3 (10.1)			
Median	70.0	80.0	72.0	72.0			
[p25% - p75%]	[63.0;77.0]	[71.0;86.0]	[65.0;79.0]	[65.0;79.0]			
[Min - Max]	[18.0;101.0]	[18.0;107.0]	[22.0;101.0]	[22.0;100.0]			
Age at index date (in categories), n (%)							
< 65 years	6071 (29.7)	6731 (12.6)	3705 (23.6)	3746 (23.9)			
[65-80[	10922 (53.4)	18192 (34.2)	8566 (54.6)	8602 (54.9)			
≥ 80	3459 (16.9)	28326 (53.2)	3409 (21.7)	3332 (21.3)			

Table 4. 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 = 20461	Dabigatran 150 mg n = 11663	Rivaroxaban 20 mg n = 10342	Dabigatran 150 mg n = 10342	Crude	Adjusted	Matched
Gender, n (%)					11.8	-0.4	0.0
Male	12951 (63.3)	8034 (68.9)	7178 (69.4)	7178 (69.4)			
Female	7510 (36.7)	3629 (31.1)	3164 (30.6)	3164 (30.6)			
Age at index date (in years)					35.6	2.8	0.3
Size (missing data)	20461 (0)	11663 (0)	10342 (0)	10342 (0)			
Mean (± SD)	69.1 (11.1)	65.4 (10.1)	66.3 (9.3)	66.2 (9.3)			
Median	70.0	66.0	67.0	67.0			
[p25% - p75%]	[63.0;77.0]	[60.0;73.0]	[61.0;73.0]	[61.0;73.0]			
[Min - Max]	[18.0;101.0]	[19.0;95.0]	[23.0;93.0]	[23.0;94.0]			
Age at index date (in categories), n (%)							
< 65 years	6077 (29.7)	4831 (41.4)	3915 (37.9)	3963 (38.3)			
[65-80[	10925 (53.4)	6330 (54.3)	5968 (57.7)	5905 (57.1)			
≥ 80	3459 (16.9)	502 (4.3)	459 (4.4)	474 (4.6)			

For 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 (80.2 ± 9.2 years and 78.7 ± 9.4 years, 62% and 55% aged 80 years or more, 47% and 49% of men, respectively) (**Tables 5 and 6**; 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 80.4 ± 8.6 years and 47% of men in both matched groups for the comparison with VKA, and about 80 ± 7.9 years and 47% of men in both groups for the comparison with dabigatran. Similar results were found for the sensitive population.

Table 5. 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 = 12723	VKA n = 53218	Rivaroxaban 15 mg n = 12018	VKA n = 12018	Crude	Adjusted	Matched
Gender, n (%)					9.8	-1.0	0.0
Male	5957 (46.8)	27522 (51.7)	5687 (47.3)	5687 (47.3)			
Female	6766 (53.2)	25696 (48.3)	6331 (52.7)	6331 (52.7)			
Age at index date (in years)					20.8	0.0	0.1
Size (missing data)	12723 (0)	53218 (0)	12018 (0)	12018 (0)			
Mean (± SD)	80.2 (9.2)	78.0 (11.1)	80.4 (8.6)	80.4 (8.6)			
Median	82.0	80.0	82.0	82.0			
[p25% - p75%]	[76.0;86.0]	[71.0;86.0]	[76.0;86.0]	[76.0;86.0]			
[Min - Max]	[20.0;103.0]	[18.0;107.0]	[33.0;101.0]	[33.0;102.0]			
Age at index date (in categories), n (%)							
< 65 years	803 (6.3)	6732 (12.6)	676 (5.6)	681 (5.7)			
[65-80[	4095 (32.2)	18184 (34.2)	3938 (32.8)	3869 (32.2)			
≥ 80	7825 (61.5)	28302 (53.2)	7404 (61.6)	7468 (62.1)			

Table 6. 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 = 12743	Dabigatran 110 mg n = 17533	Rivaroxaban 15 mg n = 9952	Dabigatran 110 mg n = 9952	Crude	Adjusted	Matched
Gender, n (%)					4.4	0.0	0.0
Male	5963 (46.8)	8587 (49.0)	4702 (47.2)	4702 (47.2)			
Female	6780 (53.2)	8946 (51.0)	5250 (52.8)	5250 (52.8)			
Age at index date (in years)					15.7	3.8	0.0
Size (missing data)	12743 (0)	17533 (0)	9952 (0)	9952 (0)			
Mean (± SD)	80.2 (9.2)	78.7 (9.4)	80.5 (7.9)	80.4 (7.9)			
Median	82.0	80.0	82.0	82.0			
[p25% - p75%]	[76.0;86.0]	[74.0;85.0]	[77.0;86.0]	[77.0;86.0]			
[Min - Max]	[20.0;103.0]	[22.0;105.0]	[34.0;101.0]	[33.0;102.0]			
Age at index date (in categories), n (%)							
< 65 years	800 (6.3)	1435 (8.2)	460 (4.6)	461 (4.6)			
[65-80[	4094 (32.1)	6421 (36.6)	3327 (33.4)	3256 (32.7)			
≥ 80	7849 (61.6)	9677 (55.2)	6165 (61.9)	6235 (62.7)			

10.2.4. History of clinical characteristics

History of long-term diseases and hospitalisations

During the 3 years before index date, 64% of patients in the rivaroxaban 20 mg group and 77% 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 tumors, malignant lymphatic or hematopoietic tissue), LTD 13 (coronary heart disease) and LTD 12 (severe arterial hypertension) (**Table 7**; 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, 44% of patients in the rivaroxaban 20 mg group and 57% in the VKA group had at least one hospitalisation (**Table 7**;

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 8**; Appendix 1-5, Tables 7 and 9).

Table 7. 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 = 20452		VKA n = 53249		Rivaroxaban 20 mg n = 15680		VKA n = 15680		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**13036**	**(63.7)**	**41156**	**(77.3)**	**10583**	**(67.5)**	**11108**	**(70.8)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	6036	(29.5)	16064	(30.2)	4750	(30.3)	4924	(31.4)	-1.4	2.6	-2.4
LTD 8: Type 1 diabetes , type 2 diabetes	2744	(13.4)	9298	(17.5)	2277	(14.5)	2371	(15.1)	-11.2	3.0	-1.7
LTD 30: Malignant tumors, malignant lymphatic or hematopoietic tissue	2382	(11.6)	7944	(14.9)	1972	(12.6)	2125	(13.6)	-9.7	1.6	-2.9
LTD 13: Coronary heart disease	2000	(9.8)	8293	(15.6)	1791	(11.4)	1846	(11.8)	-17.5	5.3	-1.1
LTD 12: Severe arterial hypertension	1969	(9.6)	7613	(14.3)	1650	(10.5)	1695	(10.8)	-14.4	2.3	-0.9
At least one hospitalisation within 3 years before, n (%)	**15424**	**(75.4)**	**47329**	**(88.9)**	**12168**	**(77.6)**	**12219**	**(77.9)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	9633	(47.1)	33262	(62.5)	7764	(49.5)	7687	(49.0)	-31.2	1.3	1.0
Factors influencing health status and contact with health services	2719	(13.3)	10857	(20.4)	2214	(14.1)	2329	(14.9)	-19.0	2.0	-2.1
Diseases of the digestive system	2808	(13.7)	7647	(14.4)	2150	(13.7)	2079	(13.3)	-1.8	1.5	1.3
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2256	(11.0)	9601	(18.0)	1854	(11.8)	1764	(11.3)	-20.0	3.3	1.8
Neoplasms	2023	(9.9)	5718	(10.7)	1586	(10.1)	1665	(10.6)	-2.8	1.4	-1.7
Diseases of the eye and adnexa	1778	(8.7)	6384	(12.0)	1525	(9.7)	1534	(9.8)	-10.8	3.4	-0.2
Injury, poisoning and certain other consequences of external causes	1088	(5.3)	5444	(10.2)	904	(5.8)	935	(6.0)	-18.4	0.6	-0.8
Diseases of the respiratory system	1169	(5.7)	7307	(13.7)	1036	(6.6)	1112	(7.1)	-27.3	2.2	-1.9
At least one hospitalisation within 3 months before, n (%)	**10309**	**(50.4)**	**38406**	**(72.1)**	**8361**	**(53.3)**	**8798**	**(56.1)**			
At least one hospitalisation within 1 month before, n (%)	**8998**	**(44.0)**	**30547**	**(57.4)**	**7259**	**(46.3)**	**7404**	**(47.2)**			

Table 8. 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 = 20461	Dabigatran 150 mg n = 11663	Rivaroxaban 20 mg n = 10342	Dabigatran 150 mg n = 10342	Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**13037 (63.7)**	**6972 (59.8)**	**6201 (60.0)**	**6204 (60.0)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)							
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	6035 (29.5)	3356 (28.8)	2969 (28.7)	3004 (29.0)	1.6	-0.1	-0.7
LTD 8: Type 1 diabetes , type 2 diabetes	2743 (13.4)	1551 (13.3)	1408 (13.6)	1374 (13.3)	0.3	0.4	1.0
LTD 30: Malignant tumors, malignant lymphatic or hematopoietic tissue	2381 (11.6)	1133 (9.7)	1011 (9.8)	1022 (9.9)	6.2	-1.1	-0.4
At least one hospitalisation within 3 years before, n (%)	**15433 (75.4)**	**8721 (74.8)**	**7540 (72.9)**	**7597 (73.5)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)							
Diseases of the circulatory system	9642 (47.1)	5884 (50.5)	4816 (46.6)	5009 (48.4)	-6.7	0.4	-3.7
Factors influencing health status and contact with health services	2720 (13.3)	1423 (12.2)	1203 (11.6)	1216 (11.8)	3.3	-1.4	-0.4
Diseases of the digestive system	2808 (13.7)	1350 (11.6)	1310 (12.7)	1212 (11.7)	6.5	3.0	2.9
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2259 (11.0)	1022 (8.8)	968 (9.4)	892 (8.6)	7.6	2.6	2.6
At least one hospitalisation within 3 months before, n (%)	**10316 (50.4)**	**6247 (53.6)**	**5217 (50.4)**	**5316 (51.4)**			
At least one hospitalisation within 1 month before, n (%)	**9004 (44.0)**	**5712 (49.0)**	**4721 (45.6)**	**4840 (46.8)**			

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 (71% vs. 77%, and 81% vs. 89%, respectively). The difference was more important for the occurrence of hospitalisations within 3-month and 1-month before index date (54% vs. 72%, and 44% vs. 57%, respectively) (**Table 9**; 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 (54% vs. 60%, and 44% vs. 51%, respectively) (**Table 10**; Appendix 1-7, Tables 7 and 9) with really weak standardized differences after adjustment and matching.

Table 9. 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 = 12723		VKA n = 53218		Rivaroxaban 15 mg n = 12018		VKA n = 12018		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**9089**	**(71.4)**	**41132**	**(77.3)**	**8638**	**(71.9)**	**8921**	**(74.2)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	3887	(30.6)	16054	(30.2)	3677	(30.6)	3804	(31.7)	0.8	-2.7	-2.3
LTD 8: Type 1 diabetes , type 2 diabetes	1696	(13.3)	9296	(17.5)	1632	(13.6)	1650	(13.7)	-11.5	0.1	-0.4
LTD 30: Malignant tumors, malignant lymphatic or hematopoietic tissue	1895	(14.9)	7940	(14.9)	1785	(14.9)	1889	(15.7)	-0.1	-0.7	-2.4
LTD 13: Coronary heart disease	1784	(14.0)	8285	(15.6)	1711	(14.2)	1729	(14.4)	-4.4	2.1	-0.4
LTD 12: Severe arterial hypertension	1717	(13.5)	7609	(14.3)	1649	(13.7)	1612	(13.4)	-2.3	0.5	0.9
At least one hospitalisation within 3 years before, n (%)	**10341**	**(81.3)**	**47301**	**(88.9)**	**9803**	**(81.6)**	**9777**	**(81.4)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	6367	(50.0)	33249	(62.5)	6085	(50.6)	6018	(50.1)	-25.3	2.1	1.1
Factors influencing health status and contact with health services	1908	(15.0)	10849	(20.4)	1809	(15.1)	1890	(15.7)	-14.2	0.4	-1.9
Diseases of the digestive system	1823	(14.3)	7640	(14.4)	1702	(14.2)	1592	(13.2)	-0.1	2.4	2.7
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1931	(15.2)	9593	(18.0)	1828	(15.2)	1799	(15.0)	-7.7	3.4	0.7
Neoplasms	1324	(10.4)	5711	(10.7)	1256	(10.5)	1250	(10.4)	-1.1	2.4	0.2
Diseases of the eye and adnexa	1843	(14.5)	6372	(12.0)	1719	(14.3)	1712	(14.2)	7.4	-0.8	0.2
Injury, poisoning and certain other consequences of external causes	1155	(9.1)	5442	(10.2)	1096	(9.1)	1027	(8.5)	-3.9	1.8	2.0
Diseases of the respiratory system	1245	(9.8)	7305	(13.7)	1211	(10.1)	1179	(9.8)	-12.3	2.7	0.9
At least one hospitalisation within 3 months before, n (%)	**6860**	**(53.9)**	**38395**	**(72.1)**	**6591**	**(54.8)**	**6839**	**(56.9)**			
At least one hospitalisation within 1 month before, n (%)	**5629**	**(44.2)**	**30538**	**(57.4)**	**5419**	**(45.1)**	**5405**	**(45.0)**			

Table 10. 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 = 12743		Dabigatran 110 mg n = 17533		Rivaroxaban 15 mg n = 9952		Dabigatran 110 mg n = 9952		Crude	Adjusted	Matched
At least one LTD declared or ongoing within 3 years before, n (%)	**9089**	**(71.3)**	**12296**	**(70.1)**	**7041**	**(70.7)**	**6949**	**(69.8)**			
Type of LTD (several pathologies possible), (frequency ≥ 10%), n (%)											
LTD 5: Severe heart failure, arrythmias, valvular cardiomyopathy, congenital cardiomyopathy	3882	(30.5)	5226	(29.8)	3035	(30.5)	3041	(30.6)	1.4	-1.1	-0.1
LTD 8: Type 1 diabetes , type 2 diabetes	1696	(13.3)	2401	(13.7)	1336	(13.4)	1327	(13.3)	-1.1	0.3	0.3
LTD 30: Malignant tumors, malignant lymphatic or hematopoietic tissue	1895	(14.9)	2496	(14.2)	1455	(14.6)	1451	(14.6)	1.8	-0.5	0.1
LTD 13: Coronary heart disease	1784	(14.0)	2223	(12.7)	1371	(13.8)	1308	(13.1)	3.9	0.7	1.9
LTD 12: Severe arterial hypertension	1711	(13.4)	2250	(12.8)	1355	(13.6)	1280	(12.9)	1.8	-0.1	2.2
At least one hospitalisation within 3 years before, n (%)	**10349**	**(81.2)**	**14578**	**(83.1)**	**8041**	**(80.8)**	**8068**	**(81.1)**			
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)											
Diseases of the circulatory system	6351	(49.8)	9596	(54.7)	4930	(49.5)	5019	(50.4)	-9.8	-4.0	-1.8
Factors influencing health status and contact with health services	1905	(14.9)	2389	(13.6)	1372	(13.8)	1329	(13.4)	3.8	0.3	1.3
Diseases of the digestive system	1826	(14.3)	2318	(13.2)	1385	(13.9)	1351	(13.6)	3.2	1.0	1.0
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1928	(15.1)	2574	(14.7)	1435	(14.4)	1426	(14.3)	1.3	-1.2	0.3
Neoplasms	1326	(10.4)	1764	(10.1)	1027	(10.3)	1004	(10.1)	1.1	-0.7	0.8
Diseases of the eye and adnexa	1855	(14.6)	2334	(13.3)	1507	(15.1)	1410	(14.2)	3.6	0.8	2.8
At least one hospitalisation within 3 months before, n (%)	**6855**	**(53.8)**	**10516**	**(60.0)**	**5412**	**(54.4)**	**5485**	**(55.1)**			
At least one hospitalisation within 1 month before, n (%)	**5630**	**(44.2)**	**8894**	**(50.7)**	**4501**	**(45.2)**	**4559**	**(45.8)**			

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 68% and 90% of patients, respectively, and HAS-BLED score ≥ 3 for 21% and 47% of patients, respectively (**Table 11**; 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 (34% vs 18%, respectively) and age > 65 years (67% vs 54%, respectively): 68% with a CHA_2DS_2-VASc score ≥ 2 in the rivaroxaban 20 mg group and 58% in the dabigatran 150 mg group; 21% with HAS-BLED score ≥ 3 in the rivaroxaban 20 mg group and 16% in the dabigatran 150 mg group (**Table 12**; 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 (79% vs 68%, respectively), women gender (53% vs 48%, respectively), and age > 65 years (93% vs 86%, respectively), with a CHA_2DS_2-VASc score ≥ 2 for 93% and 90% of patients, respectively, and HAS-BLED score ≥ 3 for 38% and 47% of patients, respectively (**Table 13**; 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 14**; Appendix 1-7, Tables 10 and 12). Similar results were found for the sensitive population (Appendices 1-12, Table 5).

Table 11. 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 = 20452		VKA n = 53249		Rivaroxaban 20 mg n = 15680		VKA n = 15680		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	2564	(12.5)	18684	(35.1)	2378	(15.2)	2415	(15.4)	-54.9	0.3	-0.7
Hypertension	6987	(34.2)	29387	(55.2)	5986	(38.2)	6166	(39.3)	-43.3	2.9	-2.4
Age ≥ 75 years	6936	(33.9)	36413	(68.4)	6509	(41.5)	6562	(41.8)	-73.5	-1.7	-0.7
Diabetes mellitus	4304	(21.0)	14345	(26.9)	3568	(22.8)	3699	(23.6)	-13.8	4.0	-2.0
Stroke or transient ischemic attack (TIA) history	1895	(9.3)	7928	(14.9)	1719	(11.0)	1767	(11.3)	-17.3	7.5	-1.0
Vascular disease history	2353	(11.5)	12187	(22.9)	2121	(13.5)	2214	(14.1)	-30.5	3.9	-1.7
Age 65-74 years	7445	(36.4)	10105	(19.0)	5466	(34.9)	5372	(34.3)	39.7	10.0	1.3
Women	7510	(36.7)	25717	(48.3)	5969	(38.1)	5969	(38.1)	-23.6	-0.1	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	2457	(12.0)	1661	(3.1)	1288	(8.2)	1329	(8.5)			
1	4002	(19.6)	3577	(6.7)	2494	(15.9)	2452	(15.6)			
≥ 2	13993	(68.4)	48011	(90.2)	11898	(75.9)	11899	(75.9)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	6987	(34.2)	29387	(55.2)	5986	(38.2)	6166	(39.3)	-43.3	2.9	-2.4
Abnormal renal function	463	(2.3)	9385	(17.6)	439	(2.8)	514	(3.3)	-53.1	-4.4	-2.8
Abnormal liver function	266	(1.3)	1708	(3.2)	238	(1.5)	256	(1.6)	-12.9	3.2	-0.9
Stroke history	1572	(7.7)	6885	(12.9)	1448	(9.2)	1519	(9.7)	-17.3	7.7	-1.5
Bleeding history	336	(1.6)	1749	(3.3)	289	(1.8)	308	(2.0)	-10.6	1.8	-0.9
Age > 65 years	13617	(66.6)	45641	(85.7)	11443	(73.0)	11458	(73.1)	-46.1	2.1	-0.2
Medication use predisposing to bleeding	11272	(55.1)	35322	(66.3)	9406	(60.0)	9581	(61.1)	-23.1	12.6	-2.3
HAS-BLED score (in categories), n (%)											
0	2683	(13.1)	1472	(2.8)	1322	(8.4)	1140	(7.3)			
1	6322	(30.9)	8671	(16.3)	4406	(28.1)	4322	(27.6)			
2	7088	(34.7)	17991	(33.8)	5922	(37.8)	6061	(38.7)			
3	3511	(17.2)	16573	(31.1)	3210	(20.5)	3353	(21.4)			
> 3	848	(4.1)	8542	(16.0)	820	(5.2)	804	(5.1)			

[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 12. 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 = 20461		Dabigatran 150 mg n = 11663		Rivaroxaban 20 mg n = 10342		Dabigatran 150 mg n = 10342		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	2563	(12.5)	1476	(12.7)	1162	(11.2)	1207	(11.7)	-0.4	3.4	-1.4
Hypertension	6988	(34.2)	3729	(32.0)	3204	(31.0)	3245	(31.4)	4.6	1.6	-0.9
Age ≥ 75 years	6936	(33.9)	2083	(17.9)	1969	(19.0)	1961	(19.0)	37.3	6.5	0.2
Diabetes mellitus	4303	(21.0)	2450	(21.0)	2204	(21.3)	2158	(20.9)	0.1	-0.1	1.1
Stroke or transient ischemic attack (TIA) history	1897	(9.3)	994	(8.5)	805	(7.8)	861	(8.3)	2.6	0.9	-2.0
Vascular disease history	2352	(11.5)	1082	(9.3)	944	(9.1)	982	(9.5)	7.3	-0.2	-1.3
Age 65-74 years	7448	(36.4)	4749	(40.7)	4458	(43.1)	4418	(42.7)	-8.9	-6.0	0.8
Women	7510	(36.7)	3629	(31.1)	3164	(30.6)	3164	(30.6)	11.8	-0.4	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	2463	(12.0)	2017	(17.3)	1677	(16.2)	1731	(16.7)			
1	4004	(19.6)	2875	(24.7)	2549	(24.6)	2515	(24.3)			
≥ 2	13994	(68.4)	6771	(58.1)	6116	(59.1)	6096	(58.9)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	6988	(34.2)	3729	(32.0)	3204	(31.0)	3245	(31.4)	4.6	1.6	-0.9
Abnormal renal function	463	(2.3)	163	(1.4)	136	(1.3)	128	(1.2)	6.5	0.2	0.7
Abnormal liver function	266	(1.3)	145	(1.2)	116	(1.1)	116	(1.1)	0.5	0.6	0.0
Stroke history	1573	(7.7)	832	(7.1)	664	(6.4)	713	(6.9)	2.1	1.3	-1.9
Bleeding history	336	(1.6)	139	(1.2)	123	(1.2)	121	(1.2)	3.8	0.1	0.2
Age > 65 years	13620	(66.6)	6326	(54.2)	5946	(57.5)	5912	(57.2)	25.4	2.1	0.7
Medication use predisposing to bleeding	11274	(55.1)	5844	(50.1)	5376	(52.0)	5253	(50.8)	10.0	-1.3	2.4
HAS-BLED score (in categories), n (%)											
0	2688	(13.1)	2225	(19.1)	1773	(17.1)	1847	(17.9)			
1	6324	(30.9)	3966	(34.0)	3542	(34.2)	3526	(34.1)			
2	7089	(34.6)	3554	(30.5)	3350	(32.4)	3242	(31.3)			
3	3512	(17.2)	1586	(13.6)	1409	(13.6)	1446	(14.0)			
> 3	849	(4.1)	332	(2.8)	268	(2.6)	281	(2.7)			

[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 15 mg and VKA groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs VKA		
	Rivaroxaban 15 mg n = 12723		VKA n = 53218		Rivaroxaban 15 mg n = 12018		VKA n = 12018		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	3064	(24.1)	18682	(35.1)	2976	(24.8)	2962	(24.6)	-24.3	-0.1	0.3
Hypertension	5923	(46.6)	29372	(55.2)	5661	(47.1)	5751	(47.9)	-17.3	0.0	-1.5
Age ≥ 75 years	10077	(79.2)	36381	(68.4)	9566	(79.6)	9563	(79.6)	24.8	2.1	0.1
Diabetes mellitus	2709	(21.3)	14341	(26.9)	2610	(21.7)	2632	(21.9)	-13.2	0.0	-0.4
Stroke or transient ischemic attack (TIA) history	1434	(11.3)	7926	(14.9)	1378	(11.5)	1435	(11.9)	-10.8	2.9	-1.5
Vascular disease history	2193	(17.2)	12178	(22.9)	2122	(17.7)	2158	(18.0)	-14.1	1.9	-0.8
Age 65-74 years	1843	(14.5)	10105	(19.0)	1776	(14.8)	1774	(14.8)	-12.1	-0.5	0.0
Women	6766	(53.2)	25696	(48.3)	6331	(52.7)	6331	(52.7)	9.8	-1.0	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	255	(2.0)	1662	(3.1)	216	(1.8)	213	(1.8)			
1	660	(5.2)	3577	(6.7)	599	(5.0)	572	(4.8)			
≥ 2	11808	(92.8)	47979	(90.2)	11203	(93.2)	11233	(93.5)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	5923	(46.6)	29372	(55.2)	5661	(47.1)	5751	(47.9)	-17.3	0.0	-1.5
Abnormal renal function	979	(7.7)	9384	(17.6)	958	(8.0)	1039	(8.6)	-30.2	1.2	-2.4
Abnormal liver function	205	(1.6)	1708	(3.2)	196	(1.6)	208	(1.7)	-10.4	-1.0	-0.8
Stroke history	1191	(9.4)	6883	(12.9)	1146	(9.5)	1194	(9.9)	-11.4	2.6	-1.3
Bleeding history	318	(2.5)	1748	(3.3)	298	(2.5)	327	(2.7)	-4.7	2.1	-1.5
Age > 65 years	11806	(92.8)	45609	(85.7)	11231	(93.5)	11233	(93.5)	23.0	1.6	-0.1
Medication use predisposing to bleeding	8075	(63.5)	35300	(66.3)	7679	(63.9)	7726	(64.3)	-6.0	1.7	-0.8
HAS-BLED score (in categories), n (%)											
0	288	(2.3)	1473	(2.8)	226	(1.9)	201	(1.7)			
1	2594	(20.4)	8666	(16.3)	2408	(20.0)	2243	(18.7)			
2	5033	(39.6)	17975	(33.8)	4762	(39.6)	4837	(40.2)			
3	3595	(28.3)	16565	(31.1)	3447	(28.7)	3549	(29.5)			
> 3	1213	(9.5)	8539	(16.0)	1175	(9.8)	1188	(9.9)			

[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 dabigatran 110 mg groups

	All patients				Matched patients				Standardized difference (%) Rivaroxaban 15 mg vs dabigatran 110 mg		
	Rivaroxaban 15 mg n = 12743		Dabigatran 110 mg n = 17533		Rivaroxaban 15 mg n = 9952		Dabigatran 110 mg n = 9952		Crude	Adjusted	Matched
Stroke risk factors[1] (score), n (%)											
Congestive heart failure	3053	(24.0)	3959	(22.6)	2276	(22.9)	2219	(22.3)	3.3	-0.4	1.4
Hypertension	5922	(46.5)	8190	(46.7)	4554	(45.8)	4509	(45.3)	-0.5	-0.5	0.9
Age ≥ 75 years	10104	(79.3)	13112	(74.8)	8080	(81.2)	8089	(81.3)	10.7	0.6	-0.2
Diabetes mellitus	2714	(21.3)	3832	(21.9)	2134	(21.4)	2075	(20.9)	-1.4	0.1	1.5
Stroke or transient ischemic attack (TIA) history	1432	(11.2)	2339	(13.3)	1130	(11.4)	1158	(11.6)	-6.4	0.6	-0.9
Vascular disease history	2185	(17.1)	2711	(15.5)	1622	(16.3)	1563	(15.7)	4.6	0.0	1.6
Age 65-74 years	1839	(14.4)	2986	(17.0)	1412	(14.2)	1402	(14.1)	-7.1	-0.3	0.3
Women	6780	(53.2)	8946	(51.0)	5250	(52.8)	5250	(52.8)	4.4	0.0	0.0
CHA_2DS_2-VASc score (in categories), n (%)											
0	255	(2.0)	426	(2.4)	158	(1.6)	165	(1.7)			
1	658	(5.2)	1047	(6.0)	447	(4.5)	436	(4.4)			
≥ 2	11830	(92.8)	16060	(91.6)	9347	(93.9)	9351	(94.0)			
Bleeding risk factors[1] (score), n (%)											
Hypertension	5922	(46.5)	8190	(46.7)	4554	(45.8)	4509	(45.3)	-0.5	-0.5	0.9
Abnormal renal function	955	(7.5)	874	(5.0)	581	(5.8)	563	(5.7)	10.4	-0.1	0.8
Abnormal liver function	202	(1.6)	292	(1.7)	152	(1.5)	124	(1.2)	-0.6	0.1	2.4
Stroke history	1188	(9.3)	1995	(11.4)	939	(9.4)	950	(9.5)	-6.8	0.7	-0.4
Bleeding history	318	(2.5)	413	(2.4)	233	(2.3)	242	(2.4)	0.9	0.2	-0.6
Age > 65 years	11829	(92.8)	15872	(90.5)	9408	(94.5)	9412	(94.6)	8.3	1.4	-0.2
Medication use predisposing to bleeding	8070	(63.3)	10500	(59.9)	6245	(62.8)	6168	(62.0)	7.1	0.0	1.6
HAS-BLED score (in categories), n (%)											
0	288	(2.3)	520	(3.0)	163	(1.6)	160	(1.6)			
1	2612	(20.5)	3849	(22.0)	2100	(21.1)	2119	(21.3)			
2	5050	(39.6)	6885	(39.3)	4041	(40.6)	4119	(41.4)			
3	3595	(28.2)	4787	(27.3)	2800	(28.1)	2716	(27.3)			
> 3	1198	(9.4)	1492	(8.5)	848	(8.5)	838	(8.4)			

[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 (85% and 91%, respectively) (**Table 15**; 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 16**; 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 17 and 18**; Appendices 1-6 and 1-7, Tables 13 and 14).

Table 15. Drugs 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 = 20452		VKA n = 53249		Rivaroxaban 20 mg n = 15680		VKA n = 15680		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**20289**	**(99.2)**	**52625**	**(98.8)**	**15554**	**(99.2)**	**15448**	**(98.5)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	18946	(92.6)	49802	(93.5)	14564	(92.9)	14365	(91.6)	-3.5	3.8	4.7
Alimentary tract and metabolism (A)	18080	(88.4)	48697	(91.5)	13925	(88.8)	13987	(89.2)	-10.1	-0.1	-1.3
General antiinfectives for systemic use (J)	17894	(87.5)	47668	(89.5)	13801	(88.0)	13762	(87.8)	-6.4	-0.1	0.8
Musculo-skeletal system (M)	16465	(80.5)	41418	(77.8)	12541	(80.0)	12339	(78.7)	6.7	2.5	3.2
Cardiovascular system (C)	17341	(84.8)	48309	(90.7)	13623	(86.9)	13575	(86.6)	-18.2	2.4	0.9
C09 - Agents acting on the renin-angiotensin system	*10845*	*(53.0)*	*33875*	*(63.6)*	*8862*	*(56.5)*	*8860*	*(56.5)*	*-21.6*	*3.8*	*0.0*
C10 - Lipid modifying agents	*9543*	*(46.7)*	*27405*	*(51.5)*	*7785*	*(49.6)*	*7802*	*(49.8)*	*-9.6*	*9.3*	*-0.2*
C07 - Beta blocking agents	*8920*	*(43.6)*	*26054*	*(48.9)*	*7014*	*(44.7)*	*7137*	*(45.5)*	*-10.7*	*1.2*	*-1.6*
C03 - Diuretics	*4997*	*(24.4)*	*24384*	*(45.8)*	*4326*	*(27.6)*	*4399*	*(28.1)*	*-45.9*	*1.4*	*-1*
C01 - Cardiac therapy	*7249*	*(35.4)*	*22200*	*(41.7)*	*5651*	*(36.0)*	*5546*	*(35.4)*	*-12.9*	*1.7*	*1.4*
C08 - Calcium channel blockers	*5288*	*(25.9)*	*19250*	*(36.2)*	*4388*	*(28.0)*	*4425*	*(28.2)*	*-22.4*	*2.7*	*-0.5*
C02 - Antihypertensives	*1385*	*(6.8)*	*6467*	*(12.1)*	*1190*	*(7.6)*	*1238*	*(7.9)*	*-18.4*	*2.0*	*-1.1*
C04 - Peripheral vasodilators	*857*	*(4.2)*	*3738*	*(7.0)*	*736*	*(4.7)*	*720*	*(4.6)*	*-12.3*	*1.1*	*0.5*
C05 - Vasoprotectives	*1082*	*(5.3)*	*2749*	*(5.2)*	*811*	*(5.2)*	*807*	*(5.1)*	*0.6*	*0.5*	*0.1*
Dermatologicals (D)	14703	(71.9)	39846	(74.8)	11369	(72.5)	11206	(71.5)	-6.7	2.6	2.3
Respiratory system (R)	15054	(73.6)	38468	(72.2)	11494	(73.3)	11353	(72.4)	3.1	3.0	2.0
Blood and blood forming organs (B)	12370	(60.5)	37936	(71.2)	9900	(63.1)	9820	(62.6)	-22.8	4.9	1.1
B01 - Antithrombotic agents	*11297*	*(55.2)*	*33910*	*(63.7)*	*9097*	*(58.0)*	*8872*	*(56.6)*	*-17.3*	*8.7*	*2.9*
B03 - Antianemic preparations	*1867*	*(9.1)*	*10734*	*(20.2)*	*1572*	*(10.0)*	*1701*	*(10.8)*	*-31.6*	*-1.3*	*-2.7*
B05 - Plasma substitutes and perfusion solutions	*1995*	*(9.8)*	*7750*	*(14.6)*	*1606*	*(10.2)*	*1653*	*(10.5)*	*-14.7*	*1.4*	*-1.0*
B02 - Antihemorrhagics	*220*	*(1.1)*	*750*	*(1.4)*	*169*	*(1.1)*	*205*	*(1.3)*	*-3.0*	*-0.1*	*-2.1*
Systemic hormonal prep, excluding sex hormones (H)	10568	(51.7)	27220	(51.1)	8013	(51.1)	7990	(51.0)	1.1	0.4	0.3
Sensory organs (S)	10056	(49.2)	28490	(53.5)	7884	(50.3)	7766	(49.5)	-8.7	1.2	1.5
Genito urinary system and sex hormones (G)	5679	(27.8)	14663	(27.5)	4406	(28.1)	4165	(26.6)	0.5	3.9	3.4
Various (V)	5671	(27.7)	14858	(27.9)	4390	(28.0)	4361	(27.8)	-0.4	4.7	0.4
Antiparasitic products (P)	1503	(7.3)	3421	(6.4)	1118	(7.1)	1057	(6.7)	3.7	0.2	1.5
Antineoplastic and immunomodulating agents (L)	945	(4.6)	3927	(7.4)	798	(5.1)	924	(5.9)	-11.6	-0.5	-3.5

Table 16. Drugs 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 = 20461		Dabigatran 150 mg n = 11663		Rivaroxaban 20 mg n = 10342		Dabigatran 150 mg n = 10342		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**20298**	**(99.2)**	**11533**	**(98.9)**	**10243**	**(99.0)**	**10233**	**(98.9)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	18955	(92.6)	10702	(91.8)	9468	(91.5)	9468	(91.5)	3.3	-0.1	0.0
Alimentary tract and metabolism (A)	18088	(88.4)	10100	(86.6)	8944	(86.5)	8959	(86.6)	5.5	-0.6	-0.4
General antiinfectives for systemic use (J)	17902	(87.5)	10063	(86.3)	8884	(85.9)	8908	(86.1)	3.6	-1.4	-0.7
Musculo-skeletal system (M)	16475	(80.5)	9394	(80.5)	8253	(79.8)	8309	(80.3)	-0.1	-1.2	-1.4
Cardiovascular system (C)	17351	(84.8)	9339	(80.1)	8417	(81.4)	8371	(80.9)	12.4	1.0	1.1
C09 - Agents acting on the renin-angiotensin system	*10847*	*(53.0)*	*5770*	*(49.5)*	*5187*	*(50.2)*	*5190*	*(50.2)*	*7.1*	*-0.6*	*-0.1*
C10 - Lipid modifying agents	*9546*	*(46.7)*	*4960*	*(42.5)*	*4493*	*(43.4)*	*4510*	*(43.6)*	*8.3*	*-0.1*	*-0.3*
C07 - Beta blocking agents	*8925*	*(43.6)*	*4782*	*(41.0)*	*4372*	*(42.3)*	*4270*	*(41.3)*	*5.3*	*0.2*	*2.0*
C03 - Diuretics	*4998*	*(24.4)*	*2305*	*(19.8)*	*2083*	*(20.1)*	*2057*	*(19.9)*	*11.3*	*1.5*	*0.6*
C01 - Cardiac therapy	*7258*	*(35.5)*	*3351*	*(28.7)*	*3181*	*(30.8)*	*3049*	*(29.5)*	*14.5*	*0.4*	*2.8*
C08 - Calcium channel blockers	*5290*	*(25.9)*	*2562*	*(22.0)*	*2389*	*(23.1)*	*2312*	*(22.4)*	*9.1*	*1.2*	*1.8*
C02 - Antihypertensives	*1385*	*(6.8)*	*705*	*(6.0)*	*615*	*(5.9)*	*626*	*(6.1)*	*3.0*	*-0.7*	*-0.4*
C04 - Peripheral vasodilators	*858*	*(4.2)*	*358*	*(3.1)*	*349*	*(3.4)*	*329*	*(3.2)*	*6.0*	*0.8*	*1.1*
C05 - Vasoprotectives	*1084*	*(5.3)*	*620*	*(5.3)*	*526*	*(5.1)*	*535*	*(5.2)*	*-0.1*	*-1.8*	*-0.4*
Dermatologicals (D)	14710	(71.9)	8003	(68.6)	7131	(69.0)	7082	(68.5)	7.2	1.1	1.0
Respiratory system (R)	15063	(73.6)	8634	(74.0)	7540	(72.9)	7632	(73.8)	-0.9	-1.7	-2.0
Blood and blood forming organs (B)	12375	(60.5)	6324	(54.2)	5786	(55.9)	5647	(54.6)	12.7	0.1	2.7
B01 - Antithrombotic agents	*11301*	*(55.2)*	*5644*	*(48.4)*	*5250*	*(50.8)*	*5070*	*(49.0)*	*13.7*	*0.6*	*3.5*
B03 - Antianemic preparations	*1867*	*(9.1)*	*846*	*(7.3)*	*712*	*(6.9)*	*718*	*(6.9)*	*6.8*	*0.5*	*-0.2*
B05 - Plasma substitutes and perfusion solutions	*1997*	*(9.8)*	*1020*	*(8.7)*	*924*	*(8.9)*	*882*	*(8.5)*	*3.5*	*-0.6*	*1.4*
B02 - Antihemorrhagics	*220*	*(1.1)*	*140*	*(1.2)*	*89*	*(0.9)*	*114*	*(1.1)*	*-1.2*	*-2.2*	*-2.5*
Systemic hormonal prep, excluding sex hormones (H)	10575	(51.7)	5921	(50.8)	5204	(50.3)	5233	(50.6)	1.8	-0.9	-0.6
Sensory organs (S)	10061	(49.2)	5218	(44.7)	4626	(44.7)	4690	(45.3)	8.9	0.3	-1.2
Genito urinary system and sex hormones (G)	5679	(27.8)	2890	(24.8)	2569	(24.8)	2570	(24.9)	6.8	0.3	0.0
Various (V)	5676	(27.7)	2884	(24.7)	2651	(25.6)	2564	(24.8)	6.9	1.3	1.9
Antiparasitic products (P)	1503	(7.3)	835	(7.2)	775	(7.5)	729	(7.0)	0.7	0.4	1.9
Antineoplastic and immunomodulating agents (L)	945	(4.6)	419	(3.6)	383	(3.7)	360	(3.5)	5.2	-0.1	0.9

Table 17. Drugs 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 = 12723		VKA n = 53218		Rivaroxaban 15 mg n = 12018		VKA n = 12018		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**12671**	**(99.6)**	**52594**	**(98.8)**	**11968**	**(99.6)**	**11942**	**(99.4)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	12094	(95.1)	49771	(93.5)	11411	(94.9)	11357	(94.5)	6.6	2.6	2.0
Alimentary tract and metabolism (A)	11873	(93.3)	48666	(91.4)	11202	(93.2)	11142	(92.7)	7.1	2.1	2.0
General antiinfectives for systemic use (J)	11583	(91.0)	47638	(89.5)	10937	(91.0)	10941	(91.0)	5.1	-0.4	-0.1
Musculo-skeletal system (M)	10163	(79.9)	41391	(77.8)	9570	(79.6)	9607	(79.9)	5.1	-0.5	-0.8
Cardiovascular system (C)	11817	(92.9)	48278	(90.7)	11174	(93.0)	11162	(92.9)	7.9	3.7	0.4
C09 - Agents acting on the renin-angiotensin system	*7938*	*(62.4)*	*33853*	*(63.6)*	*7565*	*(62.9)*	*7696*	*(64.0)*	*-2.5*	*-0.7*	-2.3
C10 - Lipid modifying agents	*6585*	*(51.8)*	*27381*	*(51.5)*	*6278*	*(52.2)*	*6270*	*(52.2)*	*0.6*	*2.4*	0.1
C07 - Beta blocking agents	*6155*	*(48.4)*	*26037*	*(48.9)*	*5825*	*(48.5)*	*5795*	*(48.2)*	*-1.1*	*3.1*	0.5
C03 - Diuretics	*5399*	*(42.4)*	*24363*	*(45.8)*	*5134*	*(42.7)*	*5281*	*(43.9)*	*-6.7*	*0.9*	-2.5
C01 - Cardiac therapy	*5908*	*(46.4)*	*22174*	*(41.7)*	*5515*	*(45.9)*	*5484*	*(45.6)*	*9.6*	*2.4*	0.5
C08 - Calcium channel blockers	*4484*	*(35.2)*	*19235*	*(36.1)*	*4258*	*(35.4)*	*4287*	*(35.7)*	*-1.9*	*1.1*	-0.5
C02 - Antihypertensives	*1308*	*(10.3)*	*6466*	*(12.2)*	*1252*	*(10.4)*	*1209*	*(10.1)*	*-5.9*	*-0.3*	1.2
C04 - Peripheral vasodilators	*935*	*(7.3)*	*3734*	*(7.0)*	*879*	*(7.3)*	*851*	*(7.1)*	*1.3*	*1.1*	0.9
C05 - Vasoprotectives	*769*	*(6.0)*	*2747*	*(5.2)*	*718*	*(6.0)*	*720*	*(6.0)*	*3.8*	*1.5*	-0.1
Dermatologicals (D)	9783	(76.9)	39816	(74.8)	9240	(76.9)	9284	(77.3)	4.9	0.7	-0.9
Respiratory system (R)	9351	(73.5)	38443	(72.2)	8800	(73.2)	8789	(73.1)	2.8	-0.7	0.2
Blood and blood forming organs (B)	9316	(73.2)	37906	(71.2)	8791	(73.1)	8680	(72.2)	4.5	5.5	2.1
B01 - Antithrombotic agents	*8502*	*(66.8)*	*33883*	*(63.7)*	*8023*	*(66.8)*	*7852*	*(65.3)*	*6.6*	*7.4*	*3.0*
B03 - Antianemic preparations	*2207*	*(17.3)*	*10727*	*(20.2)*	*2082*	*(17.3)*	*2111*	*(17.6)*	*-7.2*	*0.9*	*-0.6*
B05 - Plasma substitutes and perfusion solutions	*1630*	*(12.8)*	*7746*	*(14.6)*	*1539*	*(12.8)*	*1530*	*(12.7)*	*-5.1*	*0.8*	*0.2*
B02 - Antihemorrhagics	*147*	*(1.2)*	*749*	*(1.4)*	*143*	*(1.2)*	*175*	*(1.5)*	*-2.2*	*-1.1*	*-2.3*
Systemic hormonal prep, excluding sex hormones (H)	6741	(53.0)	27197	(51.1)	6320	(52.6)	6401	(53.3)	3.8	-0.2	-1.4
Sensory organs (S)	7454	(58.6)	28464	(53.5)	7007	(58.3)	6916	(57.5)	10.3	-0.6	1.5
Genito urinary system and sex hormones (G)	3880	(30.5)	14653	(27.5)	3636	(30.3)	3627	(30.2)	6.5	2.5	0.2
Various (V)	3450	(27.1)	14842	(27.9)	3239	(27.0)	3304	(27.5)	-1.7	-0.4	-1.2
Antiparasitic products (P)	854	(6.7)	3418	(6.4)	791	(6.6)	757	(6.3)	1.2	1.6	1.2
Antineoplastic and immunomodulating agents (L)	822	(6.5)	3925	(7.4)	769	(6.4)	900	(7.5)	-3.6	-2.4	-4.3

Table 18. Drugs 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 = 12743		Dabigatran 110 mg n = 17533		Rivaroxaban 15 mg n = 9952		Dabigatran 110 mg n = 9952		Crude	Adjusted	Matched
At least one dispensing of drugs, n (%)	**12691**	**(99.6)**	**17435**	**(99.4)**	**9905**	**(99.5)**	**9909**	**(99.6)**			
ATC classification (several answers possible), n (%)											
Nervous system (N)	12114	(95.1)	16593	(94.6)	9430	(94.8)	9450	(95.0)	1.9	-0.1	-0.9
Alimentary tract and metabolism (A)	11894	(93.3)	16134	(92.0)	9262	(93.1)	9246	(92.9)	5.1	1.2	0.6
General antiinfectives for systemic use (J)	11601	(91.0)	15821	(90.2)	9037	(90.8)	9054	(91.0)	2.8	-0.2	-0.6
Musculo-skeletal system (M)	10180	(79.9)	14068	(80.2)	7904	(79.4)	8003	(80.4)	-0.9	-3.0	-2.5
Cardiovascular system (C)	11836	(92.9)	15984	(91.2)	9230	(92.7)	9205	(92.5)	6.3	0.9	1.0
C09 - Agents acting on the renin-angiotensin system	7949	(62.4)	10602	(60.5)	6200	(62.3)	6121	(61.5)	3.9	-0.6	1.6
C10 - Lipid modifying agents	6596	(51.8)	8941	(51.0)	5241	(52.7)	5090	(51.1)	1.5	0.3	3.0
C07 - Beta blocking agents	6150	(48.3)	8080	(46.1)	4769	(47.9)	4618	(46.4)	4.4	1.0	3.0
C03 - Diuretics	5394	(42.3)	6644	(37.9)	4013	(40.3)	4005	(40.2)	9.1	-0.1	0.2
C01 - Cardiac therapy	5924	(46.5)	7240	(41.3)	4457	(44.8)	4432	(44.5)	10.5	0.5	0.5
C08 - Calcium channel blockers	4482	(35.2)	5830	(33.3)	3464	(34.8)	3407	(34.2)	4.0	1.1	1.2
C02 - Antihypertensives	1309	(10.3)	1755	(10.0)	1019	(10.2)	1043	(10.5)	0.9	-1.6	-0.8
C04 - Peripheral vasodilators	933	(7.3)	1240	(7.1)	715	(7.2)	745	(7.5)	1.0	-1.0	-1.2
C05 - Vasoprotectives	770	(6.0)	987	(5.6)	588	(5.9)	581	(5.8)	1.8	0.6	0.3
Dermatologicals (D)	9801	(76.9)	13184	(75.2)	7586	(76.2)	7632	(76.7)	4	-0.6	-1.1
Respiratory system (R)	9363	(73.5)	12959	(73.9)	7270	(73.1)	7379	(74.1)	-1.0	-2.3	-2.5
Blood and blood forming organs (B)	9328	(73.2)	12118	(69.1)	7193	(72.3)	7059	(70.9)	9.0	1.6	3.0
B01 - Antithrombotic agents	*8513*	*(66.8)*	*10979*	*(62.6)*	*6566*	*(66.0)*	*6463*	*(64.9)*	*8.8*	*1.1*	*2.2*
B03 - Antianemic preparations	*2199*	*(17.3)*	*2564*	*(14.6)*	*1634*	*(16.4)*	*1518*	*(15.3)*	*7.2*	*2.5*	*3.2*
B05 - Plasma substitutes and perfusion solutions	*1625*	*(12.8)*	*2106*	*(12.0)*	*1202*	*(12.1)*	*1209*	*(12.1)*	*2.2*	*0*	*-0.2*
B02 - Antihemorrhagics	*147*	*(1.2)*	*222*	*(1.3)*	*106*	*(1.1)*	*125*	*(1.3)*	*-1.0*	*-1.8*	*-1.8*
Systemic hormonal prep, excluding sex hormones (H)	6750	(53.0)	9238	(52.7)	5197	(52.2)	5238	(52.6)	0.6	-1.1	-0.8
Sensory organs (S)	7476	(58.7)	10090	(57.5)	5824	(58.5)	5894	(59.2)	2.3	-1.8	-1.4
Genito urinary system and sex hormones (G)	3889	(30.5)	5163	(29.4)	2963	(29.8)	2951	(29.7)	2.3	0.6	0.3
Various (V)	3459	(27.1)	4693	(26.8)	2635	(26.5)	2636	(26.5)	0.9	-1.4	0.0
Antiparasitic products (P)	861	(6.8)	1102	(6.3)	636	(6.4)	597	(6.0)	1.9	0.6	1.6
Antineoplastic and immunomodulating agents (L)	820	(6.4)	1087	(6.2)	607	(6.1)	666	(6.7)	1.0	-1.3	-2.4

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 23 in the rivaroxaban 20 mg group, and 27 in the VKA group for the specific population (**Table 19**; 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 19**), 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 20**; 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 21 and 22**; Appendices 1-6 and 1-7, Tables 19 to 24, and 26 to 28).

Table 19. 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 = 20452	VKA n = 53249	Rivaroxaban 20 mg n = 15680	VKA n = 15680	Crude	Adjusted	Matched
At least one medical visit, n (%)	**20323 (99.4)**	**52888 (99.3)**	**15584 (99.4)**	**15551 (99.2)**			
Number per patient					-20.2	2.5	1.6
Mean (± SD)	26.7 (20.0)	31.2 (24.0)	27.3 (20.4)	26.9 (19.4)			
Median	23.0	27.0	23.0	23.0			
[p25% - p75%]	[15.0;34.0]	[17.0;40.0]	[15.0;35.0]	[15.0;35.0]			
At least one general practitioner visit, n (%)	**19903 (97.3)**	**51764 (97.2)**	**15260 (97.3)**	**15204 (97.0)**			
Number per patient					-25.8	1.2	-0.1
Mean (± SD)	19.3 (15.0)	23.6 (18.1)	19.9 (15.3)	19.9 (15.2)			
Median	17.0	20.0	17.0	17.0			
[p25% - p75%]	[10.0;25.0]	[13.0;31.0]	[11.0;26.0]	[11.0;26.0]			
At least one cardiologist visit, n (%)	**10859 (53.1)**	**25723 (48.3)**	**8206 (52.3)**	**7566 (48.3)**			
Number per patient					-5.0	1.4	4.1
Mean (± SD)	1.5 (2.3)	1.6 (3.1)	1.5 (2.4)	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 (%)	**17430 (85.2)**	**43159 (81.1)**	**13230 (84.4)**	**13100 (83.5)**			
Number per patient					-0.3	2.5	2.6
Mean (± SD)	5.9 (9.1)	6.0 (13.8)	5.9 (9.3)	5.7 (8.7)			
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;7.0]			
At least one lab test, n (%)	**19709 (96.4)**	**51481 (96.7)**	**15110 (96.4)**	**15067 (96.1)**			

Table 20. 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 = 20461	Dabigatran 150 mg n = 11663	Rivaroxaban 20 mg n = 10342	Dabigatran 150 mg n = 10342	Crude	Adjusted	Matched
At least one medical visit, n (%)	**20332 (99.4)**	**11577 (99.3)**	**10266 (99.3)**	**10270 (99.3)**			
Number per patient					12.4	0.2	-0.4
Mean (± SD)	26.7 (20.0)	24.3 (18.3)	24.2 (17.9)	24.2 (18.0)			
Median	23.0	21.0	21.0	21.0			
[p25% - p75%]	[15.0;34.0]	[13.0;31.0]	[13.0;31.0]	[13.0;31.0]			
At least one general practitioner visit, n (%)	**19912 (97.3)**	**11362 (97.4)**	**10041 (97.1)**	**10078 (97.4)**			
Number per patient					11.2	-0.2	-1.5
Mean (± SD)	19.3 (15.0)	17.7 (13.5)	17.4 (13.1)	17.6 (13.1)			
Median	17.0	15.0	15.0	15.0			
[p25% - p75%]	[10.0;25.0]	[9.0;23.0]	[9.0;23.0]	[9.0;23.0]			
At least one cardiologist visit, n (%)	**10866 (53.1)**	**5561 (47.7)**	**5289 (51.1)**	**5010 (48.4)**			
Number per patient					12.6	2.6	5.2
Mean (± SD)	1.5 (2.3)	1.2 (2.0)	1.3 (2.1)	1.2 (2.0)			
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 (%)	**17439 (85.2)**	**9807 (84.1)**	**8707 (84.2)**	**8731 (84.4)**			
Number per patient					5.8	0.1	0.2
Mean (± SD)	5.9 (9.1)	5.4 (8.7)	5.4 (8.4)	5.4 (8.6)			
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 (%)	**19718 (96.4)**	**11127 (95.4)**	**9879 (95.5)**	**9902 (95.7)**			

Table 21. 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 = 12723	VKA n = 53218	Rivaroxaban 15 mg n = 12018	VKA n = 12018	Crude	Adjusted	Matched
At least one medical visit, n (%)	**12681 (99.7)**	**52857 (99.3)**	**11979 (99.7)**	**11970 (99.6)**			
Number per patient					4.3	0.0	0.2
Mean (± SD)	32.1 (20.0)	31.2 (24.0)	32.0 (19.9)	31.9 (20.8)			
Median	28.0	27.0	28.0	28.0			
[p25% - p75%]	[19.0;42.0]	[17.0;40.0]	[19.0;41.0]	[18.0;41.0]			
At least one general practitioner visit, n (%)	**12443 (97.8)**	**51734 (97.2)**	**11749 (97.8)**	**11739 (97.7)**			
Number per patient					2.0	-0.3	-2.2
Mean (± SD)	24.0 (16.5)	23.6 (18.1)	23.9 (16.4)	24.3 (17.7)			
Median	20.0	20.0	20.0	21.0			
[p25% - p75%]	[14.0;31.0]	[13.0;31.0]	[14.0;31.0]	[14.0;31.0]			
At least one cardiologist visit, n (%)	**7307 (57.4)**	**25695 (48.3)**	**6823 (56.8)**	**6484 (54.0)**			
Number per patient					11.8	5.2	6.6
Mean (± SD)	2.0 (3.3)	1.6 (3.1)	1.9 (3.3)	1.7 (2.9)			
Median	1.0	0.0	1.0	1.0			
[p25% - p75%]	[0.0;3.0]	[0.0;2.0]	[0.0;3.0]	[0.0;2.0]			
At least one other specialist visit, n (%)	**10849 (85.3)**	**43129 (81.0)**	**10208 (84.9)**	**10160 (84.5)**			
Number per patient					2.0	-0.8	2.6
Mean (± SD)	6.2 (7.6)	6.0 (13.8)	6.1 (7.5)	5.9 (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 (%)	**12490 (98.2)**	**51450 (96.7)**	**11792 (98.1)**	**11764 (97.9)**			

Table 22. 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 = 12743	Dabigatran 110 mg n = 17533	Rivaroxaban 15 mg n = 9952	Dabigatran 110 mg n = 9952	Crude	Adjusted	Matched
At least one medical visit, n (%)	**12701 (99.7)**	**17448 (99.5)**	**9914 (99.6)**	**9912 (99.6)**			
Number per patient					6.7	-1.3	-1.3
Mean (± SD)	32.2 (20.0)	30.8 (20.4)	31.4 (19.5)	31.6 (19.8)			
Median	28.0	27.0	27.0	28.0			
[p25% - p75%]	[19.0;42.0]	[18.0;40.0]	[18.0;41.0]	[18.0;41.0]			
At least one general practitioner visit, n (%)	**12464 (97.8)**	**17133 (97.7)**	**9730 (97.8)**	**9741 (97.9)**			
Number per patient					5.6	-1.0	-2
Mean (± SD)	24.0 (16.5)	23.0 (16.2)	23.4 (16.0)	23.7 (16.1)			
Median	20.0	20.0	20.0	20.0			
[p25% - p75%]	[14.0;31.0]	[13.0;30.0]	[14.0;30.0]	[14.0;31.0]			
At least one cardiologist visit, n (%)	**7323 (57.5)**	**9384 (53.5)**	**5645 (56.7)**	**5513 (55.4)**			
Number per patient					8.4	0.5	2.7
Mean (± SD)	2.0 (3.3)	1.7 (3.0)	1.9 (3.2)	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 (%)	**10873 (85.3)**	**14789 (84.3)**	**8488 (85.3)**	**8462 (85.0)**			
Number per patient					2.0	-1.4	-0.2
Mean (± SD)	6.2 (7.6)	6.1 (9.1)	6.1 (7.5)	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 (%)	**12509 (98.2)**	**17080 (97.4)**	**9762 (98.1)**	**9754 (98.0)**			

For each comparison of the main analysis, the standardized differences for all variables independent from the hdPS selection are presented for all patients with crude and adjusted analyses, and for matched patients in Appendices 1-4 to 1-7, Figures 5 to 7.

10.2.5. Usage patterns of anticoagulant treatment during the 2-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 about 14 months for both treatment groups for all and matched patients. The number of person-years (PY) during the first drug exposure was 23 768 and 59 588, respectively for all rivaroxaban 20 mg and VKA patients, but close for matched patients, 18 524 and 18 489 PY, respectively, with a medication possession ratio (MPR) greater than 80% for more than 85% for all and matched patients for both treatment groups (**Table 23**; Appendix 1-4, Table 29).

With a grace period of 30 days, the mean duration was slightly more important with rivaroxaban 20 mg than VKA: 12.5 and 10.5 months for all patients, respectively, and 12.5 and 11 months for matched patients, respectively. The number of PY was 21 022 and 46 525, respectively for all patients, and 16 347 and 14 256 PY, respectively for matched patients. MPR was greater than 80% for more than 85% 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 of 13 months for all and matched patients. The number of PY during the first drug exposure was 23 775 and 12 698, respectively for all rivaroxaban 20 mg and dabigatran 150 mg patients, but close for matched patients, 12 104 and 11 395 PY, respectively, with a MPR greater than 80% for about 95% for all and matched patients for both treatment groups (**Table 24**; Appendix 1-5, Table 29).

With a grace period of 30 days, the mean duration was about 12 months for both treatment groups for all and matched patients, with 21 029 and 11 030 PY, respectively for all patients, and 10 734 and 9 921 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 about 13 months for both treatment groups for all and matched patients. The number of PY was 13 712 and 59 548, respectively for all rivaroxaban 15 mg and VKA patients, and 12 989 and 14 076 PY for matched patients, respectively. MPR was greater than 80% for more than 90% for all and matched patients for both treatment groups (**Table 25**; Appendix 1-6, Table 29).

With a grace period of 30 days, the mean duration was about 11 months for both treatment groups for all and matched patients, with 12 042 and 46 492 PY, respectively for all patients, and 11 392 and 11 012 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 more than 12 months for all and matched patients. The number of PY was 13 730 and 17 830, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients, and 10 935 and 9 995 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 1-7, Table 29).

With a grace period of 30 days, the mean duration was slightly more important with rivaroxaban 15 mg than dabigatran 110 mg: 11.5 and 10.5 months for both treatment groups for all patients, and 11.5 and 10.5 months for matched patients, respectively. The number of PY was 12 058 and 15 424, respectively for all patients, and 9 620 and 8 701 PY, respectively for matched patients. MPR was greater than 80% for more than 95% for all and matched patients for both treatment groups (Appendix 1-16, Table 6). Similar results were found for the sensitive population (Appendix 1-12, Table 6).

Table 23. 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 = 20452	**VKA n = 53249**	**Rivaroxaban 20 mg n = 15680**	**VKA n = 15680**
1st drug exposure duration per patient (in days)				
Mean (± SD)	424.5 (304.1)	408.7 (277.7)	431.5 (303.6)	430.7 (281.5)
Median	470.0	382.0	513.0	438.0
[p25% - p75%]	[93.0;730.0]	[128.7;730.0]	[98.0;730.0]	[138.0;730.0]
[Min - Max]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]
Person-years of the 1st drug exposure, n	23768	59588	18524	18489
Number of drug dispensing* per patient				
Mean (± SD)	14.9 (10.7)	11.8 (8.6)	15.1 (10.7)	12.7 (8.7)
Median	16.0	10.0	17.0	12.0
[p25% - p75%]	[3.0;26.0]	[4.0;20.0]	[4.0;26.0]	[4.0;21.0]
[Min - Max]	[1.0;55.0]	[1.0;50.0]	[1.0;55.0]	[1.0;42.0]
Number of defined daily doses* per patient				
Mean (± SD)	424.6 (304.9)	566.4 (469.5)	432.0 (304.7)	563.5 (461.1)
Median	448.0	460.0	504.0	480.0
[p25% - p75%]	[86.0;728.0]	[153.3;870.0]	[112.0;728.0]	[150.0;840.0]
[Min - Max]	[14.0;2156.0]	[10.0;3470.0]	[14.0;2156.0]	[10.0;3280.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
]20 - 40%]	63 (0.3)	149 (0.3)	52 (0.3)	29 (0.2)
]40 - 60%]	189 (0.9)	995 (1.9)	150 (1.0)	274 (1.7)
]60 - 80%]	867 (4.2)	3929 (7.4)	663 (4.2)	1461 (9.3)
]80 - 100%[	7928 (38.8)	7645 (14.4)	6037 (38.5)	2975 (19.0)
100%	11405 (55.8)	40530 (76.1)	8778 (56.0)	10941 (69.8)

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

Table 24. 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 = 20461	**Dabigatran 150 mg n = 11663**	**Rivaroxaban 20 mg n = 10342**	**Dabigatran 150 mg n = 10342**
1st drug exposure duration per patient (in days)				
Mean (± SD)	424.4 (304.1)	397.7 (299.5)	427.5 (304.4)	402.4 (299.5)
Median	470.0	332.0	482.0	347.0
[p25% - p75%]	[93.0;730.0]	[92.0;730.0]	[95.0;730.0]	[95.0;730.0]
[Min - Max]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]
Person-years of the 1st drug exposure, n	23775	12698	12104	11395
Number of drug dispensing* per patient				
Mean (± SD)	14.9 (10.7)	13.2 (10.0)	14.9 (10.6)	13.4 (10.0)
Median	16.0	11.0	16.0	11.0
[p25% - p75%]	[3.0;26.0]	[3.0;24.0]	[3.0;26.0]	[3.0;24.0]
[Min - Max]	[1.0;55.0]	[1.0;56.0]	[1.0;33.0]	[1.0;56.0]
Number of defined daily doses* per patient				
Mean (± SD)	424.5 (304.9)	400.2 (301.8)	426.1 (304.1)	405.2 (301.8)
Median	448.0	330.0	476.0	330.0
[p25% - p75%]	[86.0;728.0]	[90.0;720.0]	[112.0;728.0]	[90.0;720.0]
[Min - Max]	[14.0;2156.0]	[30.0;1710.0]	[14.0;1556.0]	[30.0;1710.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
]20 - 40%]	63 (0.3)	34 (0.3)	34 (0.3)	30 (0.3)
]40 - 60%]	189 (0.9)	100 (0.9)	90 (0.9)	86 (0.8)
]60 - 80%]	867 (4.2)	525 (4.5)	422 (4.1)	454 (4.4)
]80 - 100%[	7930 (38.8)	3483 (29.9)	4150 (40.1)	3095 (29.9)
100%	11412 (55.8)	7521 (64.5)	5646 (54.6)	6677 (64.6)

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

Table 25. 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 = 12723	**VKA n = 53218**	**Rivaroxaban 15 mg n = 12018**	**VKA n = 12018**
1st drug exposure duration per patient (in days)				
Mean (± SD)	393.6 (300.1)	408.7 (277.7)	394.8 (299.9)	427.8 (276.0)
Median	349.0	382.0	351.0	428.0
[p25% - p75%]	[81.0;730.0]	[128.3;730.0]	[82.0;730.0]	[145.0;730.0]
[Min - Max]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]
Person-years of the 1st drug exposure, n	13712	59548	12989	14076
Number of drug dispensing* per patient				
Mean (± SD)	13.7 (10.5)	11.8 (8.6)	13.7 (10.5)	12.1 (8.4)
Median	12.0	10.0	12.0	11.0
[p25% - p75%]	[3.0;25.0]	[4.0;20.0]	[3.0;25.0]	[4.0;20.0]
[Min - Max]	[1.0;38.0]	[1.0;50.0]	[1.0;38.0]	[1.0;50.0]
Number of defined daily doses* per patient				
Mean (± SD)	397.8 (304.6)	566.3 (469.4)	398.9 (304.4)	613.6 (485.1)
Median	350.0	458.3	357.0	540.0
[p25% - p75%]	[84.0;728.0]	[150.0;870.0]	[84.0;728.0]	[180.0;960.0]
[Min - Max]	[14.0;1862.0]	[10.0;3470.0]	[14.0;1862.0]	[10.0;3280.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
]20 - 40%]	71 (0.6)	149 (0.3)	63 (0.5)	29 (0.2)
]40 - 60%]	189 (1.5)	995 (1.9)	180 (1.5)	192 (1.6)
]60 - 80%]	535 (4.2)	3927 (7.4)	502 (4.2)	791 (6.6)
]80 - 100%[	4377 (34.4)	7640 (14.4)	4162 (34.6)	1494 (12.4)
100%	7551 (59.3)	40506 (76.1)	7111 (59.2)	9512 (79.1)

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

Table 26. 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 = 12743	**Dabigatran 110 mg n = 17533**	**Rivaroxaban 15 mg n = 9952**	**Dabigatran 110 mg n = 9952**
1st drug exposure duration per patient (in days)				
Mean (± SD)	393.5 (300.1)	371.4 (296.2)	401.3 (300.4)	366.8 (296.2)
Median	348.0	278.0	371.0	269.0
[p25% - p75%]	[81.0;730.0]	[78.0;730.0]	[84.0;730.0]	[75.0;730.0]
[Min - Max]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]	[1.0;730.0]
Person-years of the 1st drug exposure, n	13730	17830	10935	9995
Number of drug dispensing* per patient				
Mean (± SD)	13.7 (10.5)	12.5 (9.9)	14.0 (10.5)	12.4 (10)
Median	12.0	9.0	13.0	9.0
[p25% - p75%]	[3.0;25.0]	[3.0;24.0]	[3.0;25.0]	[3.0;24.0]
[Min - Max]	[1.0;38.0]	[1.0;46.0]	[1.0;38.0]	[1.0;46.0]
Number of defined daily doses* per patient				
Mean (± SD)	397.7 (304.5)	372.6 (297.2)	405.2 (304.7)	368.5 (297.3)
Median	350.0	270.0	364.0	270.0
[p25% - p75%]	[84.0;728.0]	[90.0;720.0]	[84.0;728.0]	[90.0;720.0]
[Min - Max]	[14.0;1862.0]	[5.0;1170.0]	[14.0;1862.0]	[5.0;1170.0]
Medication Possession Ratio* (in categories), n (%)				
[0 - 20%]	0 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)
]20 - 40%]	71 (0.6)	56 (0.3)	49 (0.5)	34 (0.3)
]40 - 60%]	188 (1.5)	284 (1.6)	136 (1.4)	167 (1.7)
]60 - 80%]	536 (4.2)	1005 (5.7)	407 (4.1)	554 (5.6)
]80 - 100%[	4378 (34.4)	4949 (28.2)	3499 (35.2)	2779 (27.9)
100%	7570 (59.4)	11237 (64.1)	5861 (58.9)	6418 (64.5)

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

Discontinuation and switch

The cumulative incidence of discontinuation or switch for matched patients of the specific population and 60-day grace period showed a higher rate for rivaroxaban 20 mg compared to VKA after one month of treatment, but the difference decreased along the time to become lower for rivaroxaban after 2 years of follow-up (50.7%, 34.7% of discontinuations and 24.6% of switches) than VKA (56.7%, 45.5% of discontinuations and 20.6% of switches). Switches were mainly towards VKA (51.4%), then heparins, dabigatran and apixaban (22.6%, 19.7%, and 6.2%, respectively) for the rivaroxaban 20 mg group, and towards rivaroxaban (43.2%), then heparins, dabigatran and apixaban (28.9%, 21.8%, and 6.1%, respectively) for the VKA group (**Figure 5** and **Table 27**; Appendix 1-4, Tables 36 to 42, Figures 8 to 13).

With a grace period of 30 days, the 2-year cumulative incidence of discontinuation or switch was 62.1% for rivaroxaban 20 mg (48.7% discontinuations and 26.0% switches) and 75.8% for VKA (68.4% of discontinuations and 23.4% of switches) (Appendix 1-13, Tables 7 to 13, Figures 8 to 13). Similar results were found for the sensitive population with a 60-day grace period (Appendix 1-9, Tables 7 to 13, Figures 8 to 13).

For rivaroxaban 20 mg and dabigatran 150 mg, the 2-year cumulative incidence of discontinuation or switch for matched patients of the specific population and 60-day grace period was 51.5% (36.8% of discontinuations and 23.2% of switches) and 57.3% (38.4% of discontinuations and 30.6% of switches), respectively. Switches were mainly towards VKA (47.7%), then dabigatran, heparins, and apixaban (25.1%, 21.5% and 5.7%, respectively) for the rivaroxaban 20 mg group, and mainly towards VKA (44.0%), then rivaroxaban, heparins and apixaban (34.2%, 16.1%, 5.6%, respectively) for the dabigatran 150 mg group (**Figure 6** and **Table 28**; Appendix 1-5, Tables 36 to 42, Figures 8 to 13).

With a grace period of 30 days, the 2-year cumulative incidence of discontinuation or switch was 62.9% for rivaroxaban 20 mg (50.5% of discontinuations and 25.0% of switches) and 69.0% for dabigatran 150 mg (54.3% of discontinuations and 32.2% of switches) (Appendix 1-14, Tables 8 to 13, 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 to 13, Figures 8 to 13).

The cumulative incidence of discontinuation or switch for matched patients of the specific population and 60-day grace period showed a higher rate for rivaroxaban 15 mg compared to VKA after one month of treatment, but the difference decreased along the time to become close after 2 years of follow-up (55.1%, 37.2% of discontinuations and 28.5% of switches and 55.2%, 46.9% of discontinuations and 15.7% of switches, respectively). Switches were mainly towards VKA (58.0%), then heparins, dabigatran, and apixaban (20.0%, 14.8% and 7.1%, respectively) for the rivaroxaban 15 mg group, and mainly towards rivaroxaban (42.4%), then heparins, dabigatran and apixaban (30.8%, 20.5% and 6.3%, respectively) for the VKA group (**Figure 7** and **Table 29**; Appendix 1-6, Tables 36 to 42, Figures 8 to 13).

With a grace period of 30 days, the 2-year cumulative incidence of discontinuation or switch was 66.9% for rivaroxaban 15 mg (53.3% of discontinuations and 29.1% of switches) and 75.3% for VKA (69.9% of discontinuations and 17.9% of switches) (Appendix 1-15, Tables 8 to 13, 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, Tables 7 to 13, Figures 8 to 13).

For rivaroxaban 15 mg and dabigatran 110 mg, the 2-year cumulative incidence of discontinuation or switch for matched patients of the specific population and 60-day grace period was 54.5% (36.5% of discontinuations and 28.3% of switches) and 61.4% (37.0% of discontinuations and 38.7% of switches), respectively. Switches were mainly towards VKA (57.2%), then heparins, dabigatran, and apixaban (19.8%, 16.1% and 6.9%, respectively) for rivaroxaban 15 mg and also mainly towards VKA (50.9%), then rivaroxaban, heparins, and apixaban (28.1%, 16.3% and 4.7%, respectively) for dabigatran 110 mg (**Figure 8** and **Table 30**; Appendix 1-7, Tables 36 to 42, Figures 8 to 13).

With a grace period of 30 days, the 2-year cumulative incidence of discontinuation or switch was 65.9% for rivaroxaban 15 mg (52.2% of discontinuations and 28.6% of switches) and 72.1% for dabigatran 110 mg (54.3% of discontinuations and 39.0% of switches) (Appendix 1-16, Tables 8 to 13, 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, Tables 7 to 13, Figures 8 to 13).

Table 27. Discontinuation or switch of initial treatment during the 2-year follow-up period in rivaroxaban 20 mg and VKA groups, grace period of 60 days

	All patients				Matched patients			
	Rivaroxaban 20 mg n = 20452		VKA n = 53249		Rivaroxaban 20 mg n = 15680		VKA n = 15680	
Discontinuation or switch of initial treatment, n (%)	**10514**	**(51.4)**	**27368**	**(51.4)**	**7794**	**(49.7)**	**8548**	**(54.5)**
[95% CI]	[50.7 ; 52.1]		[51.0 ; 51.8]		[48.9 ; 50.5]		[53.7 ; 55.3]	
Discontinuation of initial treatment, n (%)	**6418**	**(31.4)**	**21150**	**(39.7)**	**4596**	**(29.3)**	**5942**	**(37.9)**
[95% CI]	[30.7 ; 32.0]		[39.3 ; 40.1]		[28.6 ; 30.0]		[37.1 ; 38.7]	
Switch of initial treatment, n (%)	**4096**	**(20.0)**	**6218**	**(11.7)**	**3198**	**(20.4)**	**2606**	**(16.6)**
[95% CI]	[19.5 ; 20.6]		[11.4 ; 11.9]		[19.8 ; 21.0]		[16.0 ; 17.2]	
Drugs of switch of initial treatment [1], n (%)								
VKA	2035	(49.7)	0	(0.0)	1644	(51.4)	0	(0.0)
Heparin group	905	(22.1)	2274	(36.6)	724	(22.6)	753	(28.9)
Dabigatran	899	(21.9)	1154	(18.6)	631	(19.7)	569	(21.8)
Rivaroxaban	0	(0.0)	2445	(39.3)	0	(0.0)	1125	(43.2)
Apixaban	257	(6.3)	345	(5.5)	199	(6.2)	159	(6.1)

[1] *Among concerned patients*

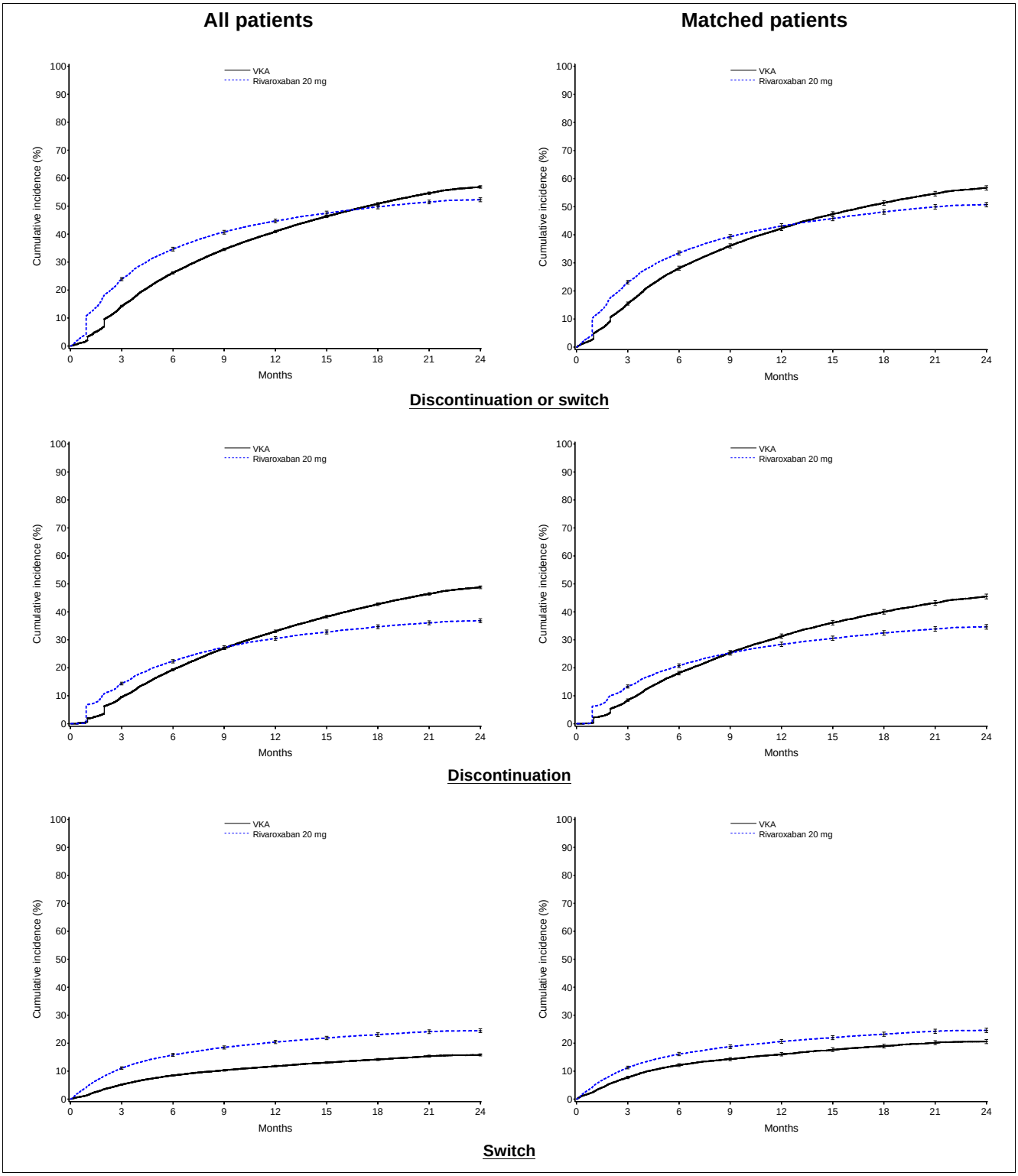


Figure 5. Two-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 20 mg and VKA groups, grace period of 60 days

Table 28. Discontinuation or switch of initial treatment during the 2-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 = 20461	Dabigatran 150 mg n = 11663	Rivaroxaban 20 mg n = 10342	Dabigatran 150 mg n = 10342
Discontinuation or switch of initial treatment, n (%)	**10520 (51.4)**	**6788 (58.2)**	**5352 (51.8)**	**5945 (57.5)**
[95% CI]	[50.7 ; 52.1]	[57.3 ; 59.1]	[50.8 ; 52.7]	[56.5 ; 58.4]
Discontinuation of initial treatment, n (%)	**6421 (31.4)**	**3915 (33.6)**	**3348 (32.4)**	**3350 (32.4)**
[95% CI]	[30.7 ; 32.0]	[32.7 ; 34.4]	[31.5 ; 33.3]	[31.5 ; 33.3]
Switch of initial treatment, n (%)	**4099 (20.0)**	**2873 (24.6)**	**2004 (19.4)**	**2595 (25.1)**
[95% CI]	[19.5 ; 20.6]	[23.9 ; 25.4]	[18.6 ; 20.1]	[24.3 ; 25.9]
Drugs of switch of initial treatment [1], n (%)				
VKA	2036 (49.7)	1239 (43.1)	955 (47.7)	1142 (44.0)
Heparin group	905 (22.1)	472 (16.4)	431 (21.5)	419 (16.1)
Dabigatran	901 (22.0)	0 (0.0)	504 (25.1)	0 (0.0)
Rivaroxaban	0 (0.0)	1007 (35.1)	0 (0.0)	888 (34.2)
Apixaban	257 (6.3)	155 (5.4)	114 (5.7)	146 (5.6)

[1] *Among concerned patients*

Table 29. Discontinuation or switch of initial treatment during the 2-year follow-up period in rivaroxaban 15 mg and VKA groups, grace period of 60 days

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 12723	VKA n = 53218	Rivaroxaban 15 mg n = 12018	VKA n = 12018
Discontinuation or switch of initial treatment, n (%)	**6671 (52.4)**	**27356 (51.4)**	**6277 (52.2)**	**6089 (50.7)**
[95% CI]	[51.6 ; 53.3]	[51.0 ; 51.8]	[51.3 ; 53.1]	[49.8 ; 51.6]
Discontinuation of initial treatment, n (%)	**3847 (30.2)**	**21141 (39.7)**	**3608 (30.0)**	**4649 (38.7)**
[95% CI]	[29.4 ; 31.0]	[39.3 ; 40.1]	[29.2 ; 30.8]	[37.8 ; 39.6]
Switch of initial treatment, n (%)	**2824 (22.2)**	**6215 (11.7)**	**2669 (22.2)**	**1440 (12.0)**
[95% CI]	[21.5 ; 22.9]	[11.4 ; 12.0]	[21.5 ; 23.0]	[11.4 ; 12.6]
Drugs of switch of initial treatment [1], n (%)				
VKA	1629 (57.7)	0 (0.0)	1548 (58.0)	0 (0.0)
Heparin group	570 (20.2)	2274 (36.6)	535 (20.0)	444 (30.8)
Dabigatran	425 (15.0)	1152 (18.5)	396 (14.8)	295 (20.5)
Rivaroxaban	0 (0.0)	2444 (39.3)	0 (0.0)	611 (42.4)
Apixaban	200 (7.1)	345 (5.6)	190 (7.1)	90 (6.3)

[1] *Among concerned patients*

Table 30. Discontinuation or switch of initial treatment during the 2-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 = 12743	Dabigatran 110 mg n = 17533	Rivaroxaban 15 mg n = 9952	Dabigatran 110 mg n = 9952
Discontinuation or switch of initial treatment, n (%)	**6685 (52.5)**	**10219 (58.3)**	**5170 (51.9)**	**5840 (58.7)**
[95% CI]	[51.6 ; 53.3]	[57.6 ; 59.0]	[51.0 ; 52.9]	[57.7 ; 59.6]
Discontinuation of initial treatment, n (%)	**3858 (30.3)**	**5170 (29.5)**	**2956 (29.7)**	**2783 (28.0)**
[95% CI]	[29.5 ; 31.1]	[28.8 ; 30.2]	[28.8 ; 30.6]	[27.1 ; 28.8]
Switch of initial treatment, n (%)	**2827 (22.2)**	**5049 (28.8)**	**2214 (22.2)**	**3057 (30.7)**
[95% CI]	[21.5 ; 22.9]	[28.1 ; 29.5]	[21.4 ; 23.1]	[29.8 ; 31.6]
Drugs of switch of initial treatment [1], n (%)				
VKA	1631 (57.7)	2485 (49.2)	1266 (57.2)	1555 (50.9)
Heparin group	570 (20.2)	812 (16.1)	439 (19.8)	498 (16.3)
Dabigatran	427 (15.1)	0 (0.0)	356 (16.1)	0 (0.0)
Rivaroxaban	0 (0.0)	1512 (29.9)	0 (0.0)	860 (28.1)
Apixaban	199 (7.0)	240 (4.8)	153 (6.9)	144 (4.7)

[1] *Among concerned patients*

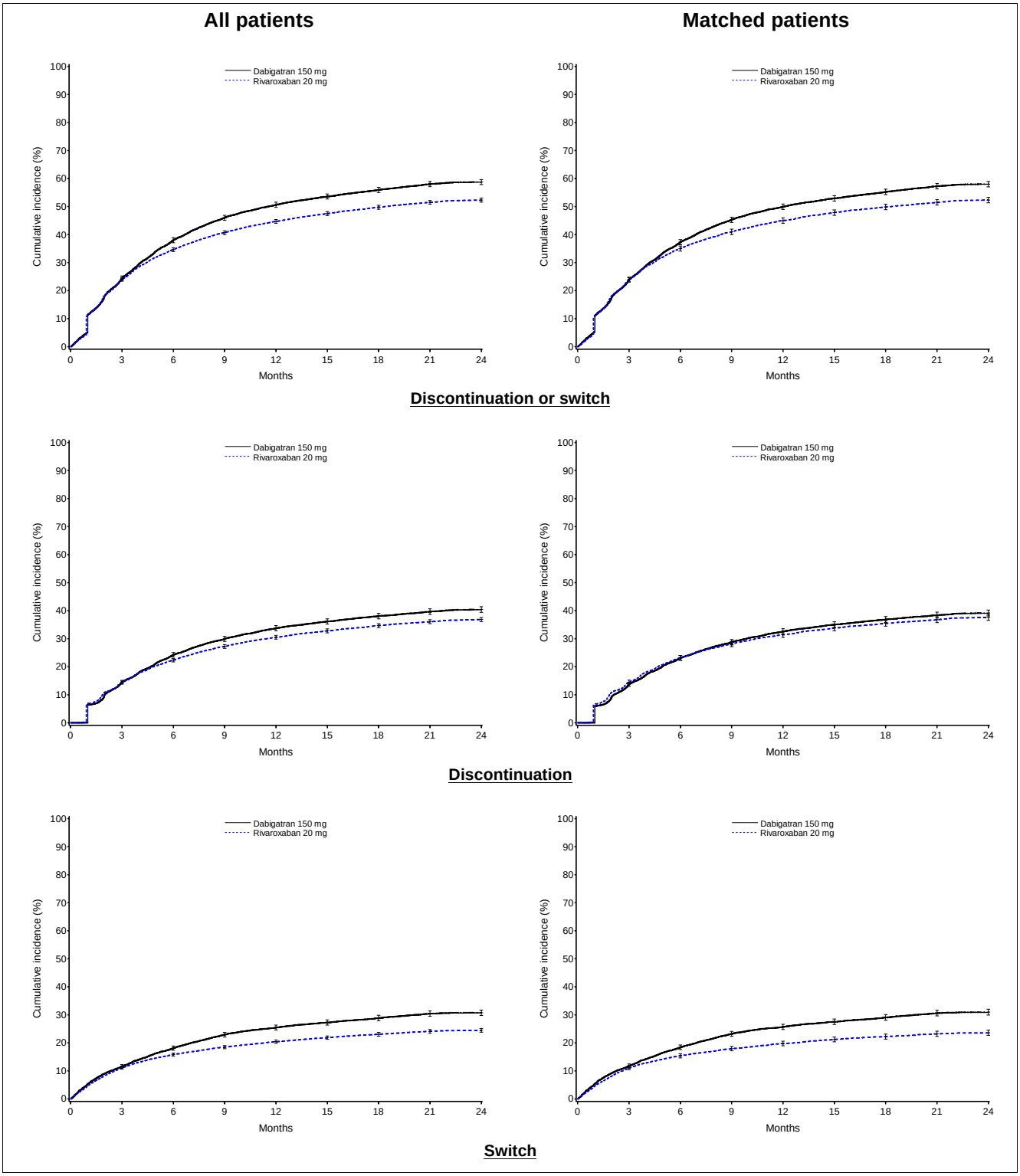


Figure 6. Two-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 20 mg and dabigatran 150 mg groups, grace period of 60 days

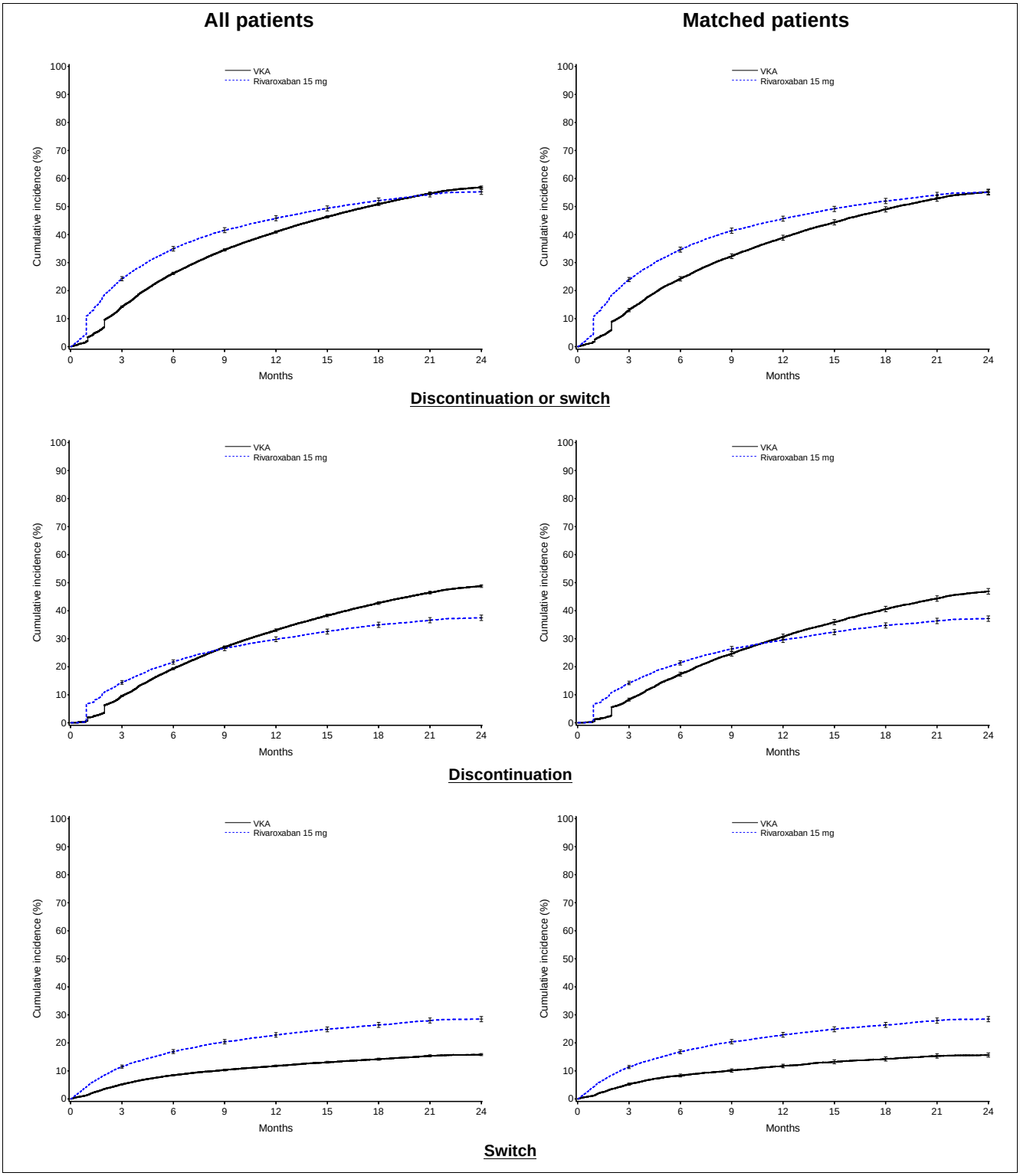


Figure 7. Two-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 15 mg and VKA groups, grace period of 60 days

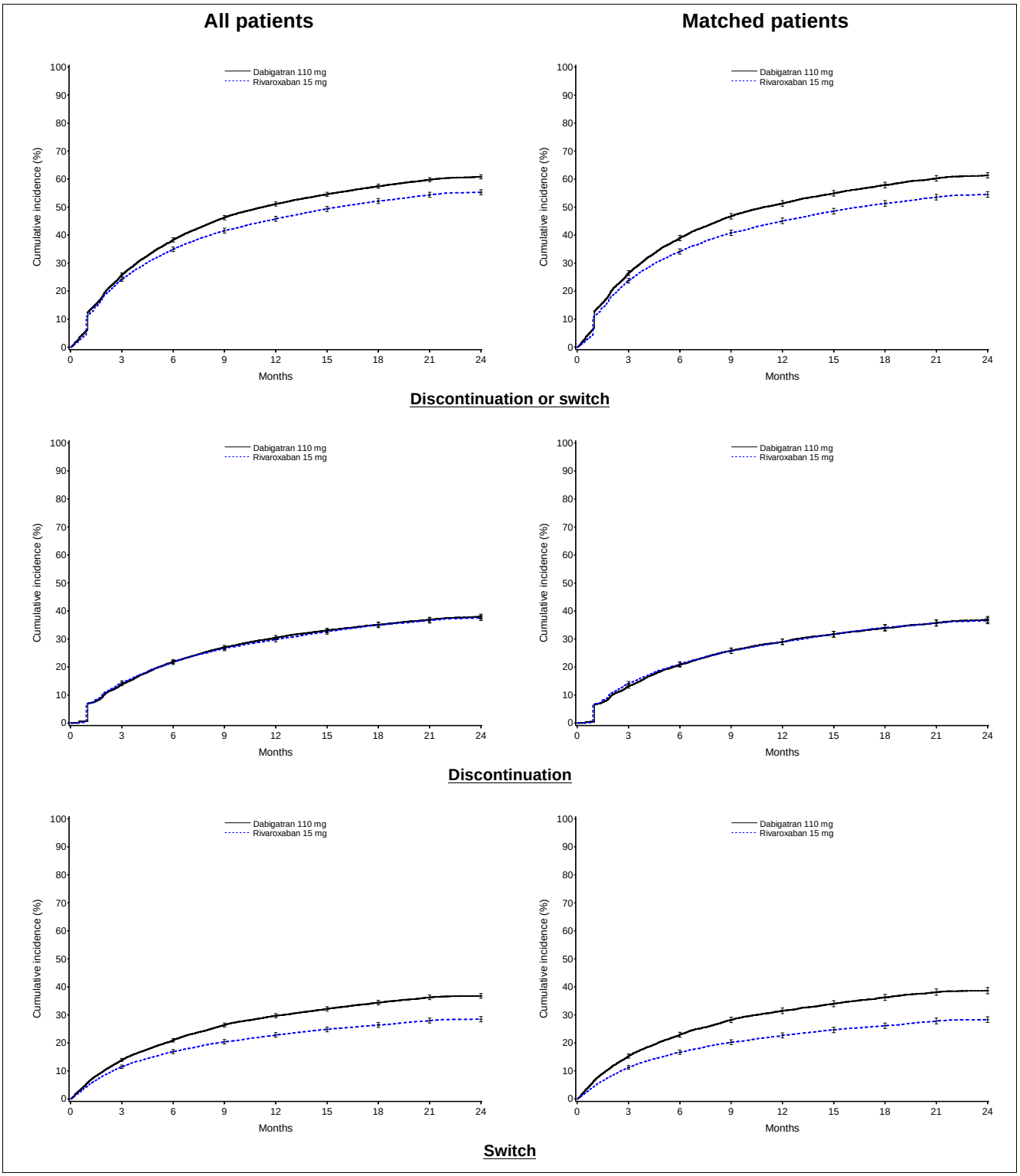


Figure 8. Two-year cumulative incidence (Kaplan-Meier curve) of discontinuation or switch of initial treatment during the follow-up period for all and matched patients in rivaroxaban 15 mg and dabigatran 110 mg groups, grace period of 60 days

10.2.6. Healthcare resource use during the drug exposure on the 2-year follow-up period

Hospitalisations, medical visits and lab tests

More than 6 patients out of 10 in the rivaroxaban 20 mg group (62%) and in the VKA group (69%) for the specific population had at least one hospitalisation during the drug exposure for rivaroxaban, dabigatran, and VKA on the 2-year follow-up period. The most frequent primary diagnosis was diseases of the circulatory system (39% for both groups), followed by ill-defined disorders: factors influencing health status and contact with health services (11% and 16%, respectively) or symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (8% and 14%, respectively) (**Table 31**; Appendix 1-4, Table 30).

Nearly all patients had physician visit reimbursements during the drug exposure on the 2-year follow-up period, with a median of 13 visits in the rivaroxaban 20 mg group and 14 in the VKA group: medians of 8 and 10 visits with GP, respectively, of 1 and 0 visit with a cardiologist, and of 1 visit with another specialist (**Table 31**, Appendix 1-4, Tables 33 and 34). Lab tests were also widely used (**Table 31**) and concerned 88% 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 2-year follow-up period were almost the same as for rivaroxaban 20 mg (**Table 32**, 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 33 and 34**; Appendices 1-6 and 1-7, Tables 33 to 35).

Table 31. Hospitalisations, medicals visits and lab tests during the drug exposure on the 2-year follow-up period in rivaroxaban 20 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 20452	**VKA n = 53249**	**Rivaroxaban 20 mg n = 15680**	**VKA n = 15680**
At least one hospitalisation, n (%)	**12654 (61.9)**	**36603 (68.7)**	**9778 (62.4)**	**10488 (66.9)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	7928 (38.8)	20614 (38.7)	5902 (37.6)	6701 (42.7)
Factors influencing health status and contact with health services	2250 (11.0)	8421 (15.8)	1818 (11.6)	2204 (14.1)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1635 (8.0)	7272 (13.7)	1367 (8.7)	1566 (10.0)
At least one medical visit, n (%)	**19780 (96.7)**	**51670 (97.0)**	**15180 (96.8)**	**15369 (98.0)**
Mean per patient, mean (± SD)	15.7 (14.9)	17.5 (16.5)	16.0 (15.2)	17.4 (14.7)
Median per patient	13.0	14.0	13.0	14.0
[p25% - p75%]	[5.0;23.0]	[6.0;25.0]	[5.0;23.0]	[6.0;24.0]
At least one general practitioner visit, n (%)	**18736 (91.6)**	**50111 (94.1)**	**14449 (92.1)**	**14866 (94.8)**
Mean per patient, mean (± SD)	10.5 (10.9)	13.3 (12.8)	11.0 (11.2)	12.5 (11.5)
Median per patient	8.0	10.0	9.0	10.0
[p25% - p75%]	[3.0;15.0]	[4.0;19.0]	[3.0;16.0]	[4.0;17.0]
At least one cardiologist visit, n (%)	**13200 (64.5)**	**24462 (45.9)**	**9638 (61.5)**	**9323 (59.5)**
Mean per patient, mean (± SD)	2.2 (3.0)	1.4 (2.9)	2.0 (3.0)	1.9 (3.0)
Median per patient	1.0	0.0	1.0	1.0
[p25% - p75%]	[0.0;3.0]	[0.0;2.0]	[0.0;3.0]	[0.0;3.0]
At least one other specialist visit, n (%)	**13261 (64.8)**	**30264 (56.8)**	**10088 (64.3)**	**10076 (64.3)**
Mean per patient, mean (± SD)	3.0 (5.3)	2.8 (7.7)	3.0 (5.4)	2.9 (5.2)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;4.0]	[0.0;3.0]	[0.0;4.0]	[0.0;4.0]
At least one lab test, n (%)	**18031 (88.2)**	**51774 (97.2)**	**13933 (88.9)**	**15383 (98.1)**

Table 32. Hospitalisations, medicals visits and lab tests during the drug exposure on the 2-year follow-up period in rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 20461	Dabigatran 150 mg n = 11663	Rivaroxaban 20 mg n = 10342	Dabigatran 150 mg n = 10342
At least one hospitalisation, n (%)	**12657 (61.9)**	**7446 (63.8)**	**6334 (61.2)**	**6621 (64.0)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	7930 (38.8)	5541 (47.5)	4208 (40.7)	4950 (47.9)
Factors influencing health status and contact with health services	2250 (11.0)	1209 (10.4)	1132 (10.9)	1043 (10.1)
At least one medical visit, n (%)	**19789 (96.7)**	**11264 (96.6)**	**10014 (96.8)**	**10014 (96.8)**
Mean per patient, mean (± SD)	15.7 (14.9)	14.2 (12.8)	15.2 (15.2)	14.3 (12.5)
Median per patient	13.0	11.0	12.0	11.0
[p25% - p75%]	[5.0;23.0]	[4.0;21.0]	[4.0;22.0]	[4.0;21.0]
At least one general practitioner visit, n (%)	**18744 (91.6)**	**10671 (91.5)**	**9429 (91.2)**	**9492 (91.8)**
Mean per patient, mean (± SD)	10.5 (10.8)	9.5 (9.5)	10.0 (10.8)	9.5 (9.2)
Median per patient	8.0	7.0	8.0	7.0
[p25% - p75%]	[3.0;15.0]	[2.0;14.0]	[2.0;14.0]	[2.0;14.0]
At least one cardiologist visit, n (%)	**13208 (64.6)**	**7671 (65.8)**	**6931 (67.0)**	**6919 (66.9)**
Mean per patient, mean (± SD)	2.2 (3.0)	2.2 (2.8)	2.3 (3.1)	2.3 (2.9)
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 (%)	**13265 (64.8)**	**7392 (63.4)**	**6775 (65.5)**	**6617 (64.0)**
Mean per patient, mean (± SD)	3.0 (5.3)	2.5 (4.3)	2.9 (5.1)	2.6 (4.3)
Median per patient	1.0	1.0	1.0	1.0
[p25% - p75%]	[0.0;4.0]	[0.0;3.0]	[0.0;4.0]	[0.0;3.0]
At least one lab test, n (%)	**18039 (88.2)**	**10128 (86.8)**	**9076 (87.8)**	**9037 (87.4)**

Table 33. Hospitalisations, medicals visits and lab tests during the drug exposure on the 2-year follow-up period in rivaroxaban 15 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 12723	VKA n = 53218	Rivaroxaban 15 mg n = 12018	VKA n = 12018
At least one hospitalisation, n (%)	**7950 (62.5)**	**36581 (68.7)**	**7524 (62.6)**	**8233 (68.5)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	4145 (32.6)	20601 (38.7)	3896 (32.4)	4682 (39.0)
Factors influencing health status and contact with health services	1339 (10.5)	8417 (15.8)	1274 (10.6)	1584 (13.2)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1360 (10.7)	7265 (13.7)	1301 (10.8)	1554 (12.9)
At least one medical visit, n (%)	**12271 (96.4)**	**51639 (97.0)**	**11589 (96.4)**	**11770 (97.9)**
Mean per patient, mean (± SD)	15.8 (14.6)	17.5 (16.5)	15.8 (14.5)	18.8 (15.9)
Median per patient	12.0	14.0	12.0	15.0
[p25% - p75%]	[4.0;23.0]	[6.0;25.0]	[4.0;23.0]	[7.0;26.0]
At least one general practitioner visit, n (%)	**11767 (92.5)**	**50080 (94.1)**	**11124 (92.6)**	**11441 (95.2)**
Mean per patient, mean (± SD)	11.5 (11.6)	13.3 (12.8)	11.5 (11.6)	14.1 (13.0)
Median per patient	9.0	10.0	9.0	11.0
[p25% - p75%]	[3.0;16.0]	[4.0;19.0]	[3.0;17.0]	[5.0;20.0]
At least one cardiologist visit, n (%)	**7071 (55.6)**	**24435 (45.9)**	**6545 (54.5)**	**6651 (55.3)**
Mean per patient, mean (± SD)	1.7 (2.9)	1.4 (2.9)	1.7 (2.8)	1.8 (3.2)
Median per patient	1.0	0.0	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 (%)	**7391 (58.1)**	**30240 (56.8)**	**6932 (57.7)**	**7423 (61.8)**
Mean per patient, mean (± SD)	2.6 (4.6)	2.8 (7.7)	2.6 (4.6)	2.8 (5.5)
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;4.0]
At least one lab test, n (%)	**11251 (88.4)**	**51743 (97.2)**	**10635 (88.5)**	**11754 (97.8)**

Table 34. Hospitalisations, medicals visits and lab tests during the drug exposure on the 2-year follow-up period in rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 12743	Dabigatran 110 mg n = 17533	Rivaroxaban 15 mg n = 9952	Dabigatran 110 mg n = 9952
At least one hospitalisation, n (%)	**7967 (62.5)**	**10720 (61.1)**	**6163 (61.9)**	**6116 (61.5)**
Primary diagnosis (ICD-10 code main chapter classification) (several pathologies possible), (frequency ≥ 10%) n (%)				
Diseases of the circulatory system	4144 (32.5)	5917 (33.7)	3156 (31.7)	3344 (33.6)
Factors influencing health status and contact with health services	1343 (10.5)	1667 (9.5)	1045 (10.5)	898 (9.0)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1362 (10.7)	1658 (9.5)	1065 (10.7)	941 (9.5)
At least one medical visit, n (%)	**12294 (96.5)**	**16908 (96.4)**	**9593 (96.4)**	**9622 (96.7)**
Mean per patient, mean (± SD)	15.8 (14.6)	14.6 (13.4)	15.9 (14.4)	14.7 (13.5)
Median per patient	12.0	11.0	13.0	11.0
[p25% - p75%]	[4.0;23.0]	[4.0;21.0]	[5.0;23.0]	[4.0;22.0]
At least one general practitioner visit, n (%)	**11791 (92.5)**	**16159 (92.2)**	**9208 (92.5)**	**9188 (92.3)**
Mean per patient, mean (± SD)	11.5 (11.6)	10.5 (10.5)	11.5 (11.4)	10.6 (10.6)
Median per patient	9.0	8.0	9.0	8.0
[p25% - p75%]	[3.0;16.0]	[3.0;15.0]	[3.0;17.0]	[3.0;16.0]
At least one cardiologist visit, n (%)	**7090 (55.6)**	**9436 (53.8)**	**5489 (55.2)**	**5507 (55.3)**
Mean per patient, mean (± SD)	1.7 (2.9)	1.7 (2.7)	1.7 (2.8)	1.7 (2.8)
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 (%)	**7410 (58.1)**	**9785 (55.8)**	**5845 (58.7)**	**5562 (55.9)**
Mean per patient, mean (± SD)	2.6 (4.6)	2.4 (4.6)	2.6 (4.7)	2.4 (4.5)
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 lab test, n (%)	**11270 (88.4)**	**15357 (87.6)**	**8802 (88.4)**	**8752 (87.9)**

Drug dispensing

The four most frequent drugs dispensed (first level of the ATC classification) during the drug exposure on the 2-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 35**; 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 16 and 10, respectively, with 1/4 of patients with at least 26 and 20 specific drug 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 36**; Appendix 1-5, Table 31). The median number of specific drug dispensing was more important in the rivaroxaban 20 mg group than the dabigatran 150 mg group, 16 and 11, 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 37**; 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 12 and 10, respectively, with 1/4 of patients with at least 25 and 20 specific drug 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 38**; Appendix 1-7, Table 31), and with 1/4 of patients with at least 25 and 24 specific drug dispensing, respectively (Appendix 1-7, Table 32).

Table 35. Drugs dispensing during the drug exposure on the 2-year follow-up period in rivaroxaban 20 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 20452	**VKA n = 53249**	**Rivaroxaban 20 mg n = 15680**	**VKA n = 15680**
At least one dispensing of drugs*, n (%)	**20452 (100.0)**	**53249 (100.0)**	**15680 (100.0)**	**15680 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	20452 (100.0)	53249 (100.0)	15680 (100.0)	15680 (100.0)
B01 - Antithrombotic agents	*20452 (100.0)*	*53249 (100.0)*	*15680 (100.0)*	*15680 (100.0)*
B03 - Antianemic preparations	*1745 (8.5)*	*10888 (20.4)*	*1513 (9.6)*	*1915 (12.2)*
B05 - Plasma substitutes and perfusion solutions	*1479 (7.2)*	*7492 (14.1)*	*1236 (7.9)*	*1517 (9.7)*
B02 - Antihemorrhagics	*278 (1.4)*	*3542 (6.7)*	*218 (1.4)*	*892 (5.7)*
Cardiovascular system (C)	19778 (96.7)	52010 (97.7)	15179 (96.8)	15242 (97.2)
C07 - Beta blocking agents	*13274 (64.9)*	*35198 (66.1)*	*10182 (64.9)*	*10621 (67.7)*
C09 - Agents acting on the renin-angiotensin system	*11326 (55.4)*	*31305 (58.8)*	*9147 (58.3)*	*9270 (59.1)*
C01 - Cardiac therapy	*14417 (70.5)*	*34089 (64.0)*	*10751 (68.6)*	*10732 (68.4)*
C10 - Lipid modifying agents	*8815 (43.1)*	*24610 (46.2)*	*7202 (45.9)*	*7604 (48.5)*
C03 - Diuretics	*6950 (34.0)*	*32641 (61.3)*	*5952 (38.0)*	*7005 (44.7)*
C08 - Calcium channel blockers	*4700 (23.0)*	*16051 (30.1)*	*3869 (24.7)*	*4262 (27.2)*
C02 - Antihypertensives	*946 (4.6)*	*3778 (7.1)*	*813 (5.2)*	*911 (5.8)*
Nervous system (N)	15723 (76.9)	46399 (87.1)	12301 (78.5)	12902 (82.3)
Alimentary tract and metabolism (A)	15713 (76.8)	47258 (88.7)	12386 (79.0)	12859 (82.0)
General antiinfectives for systemic use (J)	12943 (63.3)	38026 (71.4)	10165 (64.8)	10606 (67.6)
Dermatologicals (D)	10017 (49.0)	29769 (55.9)	7881 (50.3)	8244 (52.6)
Respiratory system (R)	10067 (49.2)	27021 (50.7)	7878 (50.2)	7920 (50.5)
Musculo-skeletal system (M)	9375 (45.8)	23156 (43.5)	7374 (47.0)	6910 (44.1)
Systemic hormonal prep, excluding sex hormones (H)	6963 (34.0)	19016 (35.7)	5410 (34.5)	5298 (33.8)
Sensory organs (S)	6392 (31.3)	18743 (35.2)	5072 (32.3)	5275 (33.6)
Genito urinary system and sex hormones (G)	3949 (19.3)	10827 (20.3)	3137 (20.0)	3098 (19.8)
Various (V)	4145 (20.3)	10182 (19.1)	3179 (20.3)	3349 (21.4)
Antineoplastic and immunomodulating agents (L)	746 (3.6)	3033 (5.7)	614 (3.9)	783 (5.0)
Antiparasitic products (P)	711 (3.5)	1782 (3.3)	515 (3.3)	504 (3.2)

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

Table 36. Drugs dispensing during the drug exposure on the 2-year follow-up period in rivaroxaban 20 mg and dabigatran 150 mg groups

	All patients		Matched patients	
	Rivaroxaban 20 mg n = 20461	**Dabigatran 150 mg n = 11663**	**Rivaroxaban 20 mg n = 10342**	**Dabigatran 150 mg n = 10342**
At least one dispensing of drugs*, n (%)	**20461 (100.0)**	**11663 (100.0)**	**10342 (100.0)**	**10342 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	20461 (100.0)	11663 (100.0)	10342 (100.0)	10342 (100.0)
B01 - Antithrombotic agents	*20461 (100.0)*	*11663 (100.0)*	*10342 (100.0)*	*10342 (100.0)*
B03 - Antianemic preparations	*1745 (8.5)*	*656 (5.6)*	*714 (6.9)*	*563 (5.4)*
B05 - Plasma substitutes and perfusion solutions	*1479 (7.2)*	*705 (6.0)*	*651 (6.3)*	*601 (5.8)*
B02 - Antihemorrhagics	*278 (1.4)*	*128 (1.1)*	*136 (1.3)*	*115 (1.1)*
Cardiovascular system (C)	19786 (96.7)	11328 (97.1)	10013 (96.8)	10057 (97.2)
C07 - Beta blocking agents	*13279 (64.9)*	*8143 (69.8)*	*6944 (67.1)*	*7221 (69.8)*
C09 - Agents acting on the renin-angiotensin system	*11328 (55.4)*	*6349 (54.4)*	*5669 (54.8)*	*5692 (55.0)*
C01 - Cardiac therapy	*14424 (70.5)*	*8519 (73.0)*	*7437 (71.9)*	*7588 (73.4)*
C10 - Lipid modifying agents	*8817 (43.1)*	*4701 (40.3)*	*4312 (41.7)*	*4244 (41.0)*
C03 - Diuretics	*6950 (34.0)*	*3636 (31.2)*	*3119 (30.2)*	*3201 (31.0)*
C08 - Calcium channel blockers	*4702 (23.0)*	*2428 (20.8)*	*2184 (21.1)*	*2194 (21.2)*
C02 - Antihypertensives	*946 (4.6)*	*509 (4.4)*	*441 (4.3)*	*467 (4.5)*
Nervous system (N)	15727 (76.9)	8507 (72.9)	7728 (74.7)	7551 (73.0)
Alimentary tract and metabolism (A)	15716 (76.8)	8453 (72.5)	7666 (74.1)	7528 (72.8)
General antiinfectives for systemic use (J)	12946 (63.3)	6702 (57.5)	6314 (61.1)	5994 (58.0)
Dermatologicals (D)	10018 (49.0)	5216 (44.7)	4918 (47.6)	4691 (45.4)
Respiratory system (R)	10070 (49.2)	5344 (45.8)	4983 (48.2)	4735 (45.8)
Musculo-skeletal system (M)	9375 (45.8)	5037 (43.2)	4669 (45.1)	4500 (43.5)
Systemic hormonal prep, excluding sex hormones (H)	6964 (34.0)	3519 (30.2)	3356 (32.5)	3110 (30.1)
Sensory organs (S)	6392 (31.2)	3099 (26.6)	2977 (28.8)	2818 (27.2)
Genito urinary system and sex hormones (G)	3949 (19.3)	1920 (16.5)	1802 (17.4)	1747 (16.9)
Various (V)	4148 (20.3)	2185 (18.7)	2155 (20.8)	1948 (18.8)
Antineoplastic and immunomodulating agents (L)	746 (3.6)	316 (2.7)	328 (3.2)	274 (2.6)
Antiparasitic products (P)	712 (3.5)	315 (2.7)	368 (3.6)	273 (2.6)

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

Table 37. Drugs dispensing during the drug exposure on the 2-year follow-up period in rivaroxaban 15 mg and VKA groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 12723	VKA n = 53218	Rivaroxaban 15 mg n = 12018	VKA n = 12018
At least one dispensing of drugs*, n (%)	**12723 (100.0)**	**53218 (100.0)**	**12018 (100.0)**	**12018 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	12723 (100.0)	53218 (100.0)	12018 (100.0)	12018 (100.0)
B01 - Antithrombotic agents	*12723 (100.0)*	*53218 (100.0)*	*12018 (100.0)*	*12018 (100.0)*
B03 - Antianemic preparations	*1903 (15.0)*	*10882 (20.4)*	*1803 (15.0)*	*2147 (17.9)*
B05 - Plasma substitutes and perfusion solutions	*1212 (9.5)*	*7489 (14.1)*	*1156 (9.6)*	*1527 (12.7)*
B02 - Antihemorrhagics	*192 (1.5)*	*3540 (6.7)*	*183 (1.5)*	*798 (6.6)*
Cardiovascular system (C)	12329 (96.9)	51979 (97.7)	11649 (96.9)	11772 (98.0)
C07 - Beta blocking agents	*7705 (60.6)*	*35182 (66.1)*	*7286 (60.6)*	*7810 (65.0)*
C09 - Agents acting on the renin-angiotensin system	*7316 (57.5)*	*31287 (58.8)*	*6969 (58.0)*	*7227 (60.1)*
C01 - Cardiac therapy	*8450 (66.4)*	*34065 (64.0)*	*7936 (66.0)*	*8067 (67.1)*
C10 - Lipid modifying agents	*5348 (42.0)*	*24597 (46.2)*	*5098 (42.4)*	*5442 (45.3)*
C03 - Diuretics	*6632 (52.1)*	*32622 (61.3)*	*6302 (52.4)*	*7108 (59.1)*
C08 - Calcium channel blockers	*3524 (27.7)*	*16042 (30.1)*	*3369 (28.0)*	*3678 (30.6)*
C02 - Antihypertensives	*804 (6.3)*	*3777 (7.1)*	*765 (6.4)*	*786 (6.5)*
Nervous system (N)	10312 (81.1)	46369 (87.1)	9751 (81.1)	10411 (86.6)
Alimentary tract and metabolism (A)	10610 (83.4)	47228 (88.7)	10037 (83.5)	10577 (88.0)
General antiinfectives for systemic use (J)	8317 (65.4)	38000 (71.4)	7895 (65.7)	8729 (72.6)
Dermatologicals (D)	6542 (51.4)	29750 (55.9)	6190 (51.5)	6761 (56.3)
Respiratory system (R)	6034 (47.4)	26999 (50.7)	5724 (47.6)	6147 (51.1)
Musculo-skeletal system (M)	5844 (45.9)	23137 (43.5)	5541 (46.1)	5556 (46.2)
Systemic hormonal prep, excluding sex hormones (H)	4456 (35.0)	18991 (35.7)	4207 (35.0)	4464 (37.1)
Sensory organs (S)	4600 (36.2)	18723 (35.2)	4337 (36.1)	4704 (39.1)
Genito urinary system and sex hormones (G)	2640 (20.7)	10817 (20.3)	2500 (20.8)	2632 (21.9)
Various (V)	2003 (15.7)	10171 (19.1)	1872 (15.6)	2165 (18.0)
Antineoplastic and immunomodulating agents (L)	596 (4.7)	3033 (5.7)	569 (4.7)	699 (5.8)
Antiparasitic products (P)	360 (2.8)	1779 (3.3)	341 (2.8)	376 (3.1)

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

Table 38. Drugs dispensing during the drug exposure on the 2-year follow-up period in rivaroxaban 15 mg and dabigatran 110 mg groups

	All patients		Matched patients	
	Rivaroxaban 15 mg n = 12743	Dabigatran 110 mg n = 17533	Rivaroxaban 15 mg n = 9952	Dabigatran 110 mg n = 9952
At least one dispensing of drugs*, n (%)	**12743 (100.0)**	**17533 (100.0)**	**9952 (100.0)**	**9952 (100.0)**
Drugs according to ATC classification* (several answers possible), n (%)				
Blood and blood forming organs (B)	12743 (100.0)	17533 (100.0)	9952 (100.0)	9952 (100.0)
B01 - Antithrombotic agents	*12743 (100.0)*	*17533 (100.0)*	*9952 (100.0)*	*9952 (100.0)*
B03 - Antianemic preparations	*1899 (14.9)*	*2102 (12.0)*	*1434 (14.4)*	*1256 (12.6)*
B05 - Plasma substitutes and perfusion solutions	*1208 (9.5)*	*1580 (9.0)*	*905 (9.1)*	*865 (8.7)*
B02 - Antihemorrhagics	*190 (1.5)*	*144 (0.8)*	*148 (1.5)*	*85 (0.9)*
Cardiovascular system (C)	12352 (96.9)	17018 (97.1)	9681 (97.3)	9665 (97.1)
C07 - Beta blocking agents	*7708 (60.5)*	*10876 (62.0)*	*6074 (61.0)*	*6130 (61.6)*
C09 - Agents acting on the renin-angiotensin system	*7332 (57.5)*	*10069 (57.4)*	*5795 (58.2)*	*5680 (57.1)*
C01 - Cardiac therapy	*8479 (66.5)*	*11649 (66.4)*	*6557 (65.9)*	*6695 (67.3)*
C10 - Lipid modifying agents	*5357 (42.0)*	*7603 (43.4)*	*4312 (43.3)*	*4209 (42.3)*
C03 - Diuretics	*6634 (52.1)*	*8548 (48.8)*	*5105 (51.3)*	*5072 (51.0)*
C08 - Calcium channel blockers	*3537 (27.8)*	*4695 (26.8)*	*2791 (28.0)*	*2680 (26.9)*
C02 - Antihypertensives	*805 (6.3)*	*1040 (5.9)*	*637 (6.4)*	*609 (6.1)*
Nervous system (N)	10331 (81.1)	14063 (80.2)	8096 (81.4)	7971 (80.1)
Alimentary tract and metabolism (A)	10634 (83.4)	14510 (82.8)	8281 (83.2)	8205 (82.4)
General antiinfectives for systemic use (J)	8338 (65.4)	10920 (62.3)	6532 (65.6)	6241 (62.7)
Dermatologicals (D)	6552 (51.4)	8615 (49.1)	5117 (51.4)	4901 (49.2)
Respiratory system (R)	6051 (47.5)	8128 (46.4)	4744 (47.7)	4523 (45.4)
Musculo-skeletal system (M)	5853 (45.9)	7636 (43.6)	4590 (46.1)	4346 (43.7)
Systemic hormonal prep, excluding sex hormones (H)	4462 (35.0)	5899 (33.6)	3500 (35.2)	3373 (33.9)
Sensory organs (S)	4619 (36.2)	6010 (34.3)	3644 (36.6)	3525 (35.4)
Genito urinary system and sex hormones (G)	2644 (20.7)	3482 (19.9)	2083 (20.9)	2006 (20.2)
Various (V)	2005 (15.7)	2625 (15.0)	1570 (15.8)	1425 (14.3)
Antineoplastic and immunomodulating agents (L)	594 (4.7)	763 (4.4)	446 (4.5)	460 (4.6)
Antiparasitic products (P)	357 (2.8)	477 (2.7)	267 (2.7)	267 (2.7)

** 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) were assessed during the drug exposure (rivaroxaban, dabigatran or VKA) on the 2-year follow-up period (on treatment) for the specific population of new anticoagulant users in 2013 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 population with a 60-day grace period.

10.4. Main results

10.4.1. Incidence rate of outcomes (all patients)

The overall incidence rates of different outcomes (first event) for the specific population during the drug exposure period with a 60-day grace period are presented in **Tables 39, 40 and 41**.

For SSE, it was 1.3 [95%CI: 1.2 to 1.4] per 100 person-years (PY) for the rivaroxaban 20 mg group, 1.1 [0.9 to 1.3] for the dabigatran 150 mg group and 2.6 [2.5 to 2.7] for the VKA group, 1.2 [1.1; 1.3], 0.5 [0.4; 0.6] and 3.1 [3.0; 3.2] for major bleeds, respectively, 3.0 [2.8; 3.2], 1.7 [1.5; 1.9] and 13.0 [12.7; 13.3] for death, respectively, and 5.1 [4.8; 5.4], 3.1 [2.8; 3.4] and 17.0 [16.7; 17.3] for the composite criterion (SSE, major bleeding, death), respectively; death being the most frequent event (Appendix 1-4 and 1-5, Tables 46, 54, 60, 66, 86, 94, 102, 122, 140, 146, 152, 158, 164, 178, 184, and 190).

Table 39. 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)	**318**	**23 610**	**1.3 [1.2; 1.4]**	**141**	**12 617**	**1.1 [0.9; 1.3]**
Ischemic or undefined stroke	200	23 693	0.8 [0.7; 0.9]	83	12 659	0.7 [0.6; 0.8]
Other SE or surgical procedure for SE	121	23 692	0.5 [0.4; 0.6]	59	12 656	0.5 [0.4; 0.6]
Major bleeding	**286**	**23 713**	**1.2 [1.1; 1.3]**	**60**	**12 684**	**0.5 [0.4; 0.6]**
Clinically relevant bleeding (CRB)	**681**	**23 485**	**2.9 [2.7; 3.1]**	**166**	**12 618**	**1.3 [1.1; 1.5]**
Haemorrhagic stroke	94	23 767	0.4 [0.3; 0.5]	11	12 698	0.1 [0.0; 0.2]
Other critical organ or site bleeding	44	23 758	0.2 [0.1; 0.3]	18	12 690	0.1 [0.0; 0.2]
Gastro-intestinal bleeding	259	23 652	1.1 [1.0; 1.2]	75	12 665	0.6 [0.5; 0.7]
Urogenital bleeding	142	23 697	0.6 [0.5; 0.7]	35	12 681	0.3 [0.2; 0.4]
Other bleeding	164	23 703	0.7 [0.6; 0.8]	33	12 676	0.3 [0.2; 0.4]
Death (all causes)	**718**	**23 775**	**3.0 [2.8; 3.2]**	**214**	**12 698**	**1.7 [1.5; 1.9]**
Composite criterion (SSE, major bleeding, and death)	**1206**	**23 552**	**5.1 [4.8; 5.4]**	**393**	**12 603**	**3.1 [2.8; 3.4]**
Acute coronary syndrome (ACS)	**225**	**23 648**	**1.0 [0.9; 1.1]**	**102**	**12 648**	**0.8 [0.6; 1.0]**
ST-segment elevation MI (STEMI)	45	23 767	0.2 [0.1; 0.3]	36	12 683	0.3 [0.2; 0.4]
Non-ST-segment elevation MI (NSTEMI)	33	23 756	0.1 [0.1; 0.1]	11	12 697	0.1 [0.0; 0.2]
Unstable angina (I20.0 codes)	160	23 671	0.7 [0.6; 0.8]	64	12 663	0.5 [0.4; 0.6]

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

	VKA		
	n evt	Person-years	Inc./100 PY [95%CI]
Stroke and systemic embolism (SSE)	**1504**	**58 742**	**2.6 [2.5; 2.7]**
Ischemic or undefined stroke	854	59 140	1.4 [1.3; 1.5]
Other SE or surgical procedure for SE	670	59 183	1.1 [1.0; 1.2]
Major bleeding	**1823**	**58 982**	**3.1 [3.0; 3.2]**
Clinically relevant bleeding (CRB)	**3005**	**58 160**	**5.2 [5.0; 5.4]**
Haemorrhagic stroke	472	59 528	0.8 [0.7; 0.9]
Other critical organ or site bleeding	444	59 460	0.7 [0.6; 0.8]
Gastro-intestinal bleeding	953	59 108	1.6 [1.5; 1.7]
Urogenital bleeding	398	59 297	0.7 [0.6; 0.8]
Other bleeding	905	59 058	1.5 [1.4; 1.6]
Death (all causes)	**7757**	**59 588**	**13.0 [12.7; 13.3]**
Composite criterion (SSE, major bleeding, and death)	**9916**	**58 166**	**17.0 [16.7; 17.3]**
Acute coronary syndrome (ACS)	**968**	**59 908**	**1.6 [1.5; 1.7]**
ST-segment elevation MI (STEMI)	321	59 408	0.5 [0.4; 0.6]
Non-ST-segment elevation MI (NSTEMI)	154	59 487	0.3 [0.3; 0.3]
Unstable angina (I20.0 codes)	595	59 136	1.0 [0.9; 1.1]

For the reduced dose comparison of the specific population and a grace period of 60 days, the incidence rate of SSE was respectively 2.3 [2.0; 2.6] and 1.7 [1.5; 1.9] per 100 PY for the rivaroxaban 15 mg and dabigatran 110 mg groups, 2.3 [2.0; 2.6] and 1.6 [1.4; 1.8] for major bleeds, 8.5 [8.0; 9.0] and 7.0 [6.6; 7.4] for death, respectively, 11.8 [11.3; 12.3] and 9.5 [9.1; 9.9] for the composite criterion, respectively (Appendix 1-6 and 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 1-13, 1-14, 1-15 and 1-16, Tables 14, 20, 26, 32, 38 and 44), as well as for the sensitive population with a 60-day grace period (Appendix 1-9, 1-10, 1-11 and 1-12, Tables 14, 20, 26, 32, 38 and 44).

Table 41. 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)	**309**	**13 587**	**2.3 [2.0; 2.6]**	**295**	**17 723**	**1.7 [1.5; 1.9]**
Ischemic or undefined stroke	196	13 653	1.4 [1.2; 1.6]	208	17 765	1.2 [1.0; 1.4]
Other SE or surgical procedure for SE	115	13 663	0.8 [0.7; 0.9]	90	17 788	0.5 [0.4; 0.6]
Major bleeding	**310**	**13 675**	**2.3 [2.0; 2.6]**	**288**	**17 780**	**1.6 [1.4; 1.8]**
Clinically relevant bleeding (CRB)	**568**	**13 536**	**4.2 [3.9; 4.5]**	**520**	**17 678**	**2.9 [2.7; 3.1]**
Haemorrhagic stroke	103	13 722	0.8 [0.7; 0.9]	49	17 824	0.3 [0.2; 0.4]
Other critical organ or site bleeding	67	13 719	0.5 [0.4; 0.6]	56	17 815	0.3 [0.2; 0.4]
Gastro-intestinal bleeding	195	13 664	1.4 [1.2; 1.6]	260	17 765	1.5 [1.3; 1.7]
Urogenital bleeding	88	13 681	0.6 [0.5; 0.7]	69	17 790	0.4 [0.3; 0.5]
Other bleeding	138	13 668	1.0 [0.8; 1.2]	102	17 803	0.6 [0.5; 0.7]
Death (all causes)	**1162**	**13 730**	**8.5 [8.0; 9.0]**	**1256**	**17 830**	**7.0 [6.6; 7.4]**
Composite criterion (SSE, major bleeding, and death)	**1597**	**13 537**	**11.8 [11.3; 12.3]**	**1680**	**17 674**	**9.5 [9.1; 9.9]**
Acute coronary syndrome (ACS)	**206**	**13 631**	**1.5 [1.3; 1.7]**	**239**	**17 727**	**1.3 [1.1; 1.5]**
ST-segment elevation MI (STEMI)	66	13 713	0.5 [0.4; 0.6]	65	17 812	0.4 [0.3; 0.5]
Non-ST-segment elevation MI (NSTEMI)	26	13 716	0.2 [0.1; 0.3]	51	17 815	0.3 [0.2; 0.4]
Unstable angina (I20.0 codes)	142	13 647	1.0 [0.8; 1.2]	144	17 757	0.8 [0.7; 0.9]

10.4.1.1. Crude cumulative incidence of outcomes (all patients)

The 2-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 17, 17b, 19, 19b, 21, 21b, 23, 23b, 29, 29b, 31, 31b, 33, 33b, 39, 39b, 45, 45b, 47, 47b, 49, 49b, 51, 51b, 53, 53b, 55, 55b, 57, 57b, 59, 59b, 61, 61b).

Results were similar for the three main and secondary 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 2-year cumulative incidence of different outcomes during the drug exposure with a 60-day grace period are presented in following tables and figures for matched patients of the specific population. This cumulative incidence was lower with rivaroxaban 20 mg than VKA for two main outcomes: major bleeding (2.4% [2.1 to 2.7] *vs.* 3.5% [3.2 to 3.9]), and death (6.5% [6.0 to 7.0] *vs.* 9.7% [9.1 to 10.3]), while it was similar between the two groups for SSE (2.6% [2.3 to 2.9] *vs.* 2.7% [2.4 to 3.0]). It was also lower with rivaroxaban for the three secondary outcomes: CRB (5.5% [5.0 to 5.9] *vs.* 6.4% [5.9 to 6.9]), ACS (1.6% [1.4 to 1.9] *vs.* 2.2% [1.9 to 2.5]), and the composite criterion (10.2% [9.6 to 10.8] *vs.* 14.0% [13.3 to14.7]) (**Table 42**, **Figure 9**; Appendix 1-4, Tables 48, 68, 88, 96, 104, 166, and Figures 18, 18b, 24, 24b, 30, 30b, 32, 32b, 34, 34b, 54, 54b).

Table 42. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period (60-day grace period for treatment discontinuation) for rivaroxaban 20 mg and VKA matched patients

	Rivaroxaban 20 mg n = 15 680		VKA n = 15 680	
	n evt	% [95%CI]	n evt	% [95%CI]
Stroke and systemic embolism (SSE)	**280**	**2.6 [2.3; 2.9]**	**292**	**2.7 [2.4; 3.0]**
Major bleeding	**250**	**2.4 [2.1; 2.7]**	**372**	**3.5 [3.2; 3.9]**
Clinically relevant bleeding (CRB)	581	5.5 [5.0; 5.9]	685	6.4 [5.9; 6.9]
Death (all causes)	**661**	**6.5 [6.0; 7.0]**	**1000**	**9.7 [9.1; 10.3]**
Composite criterion (SSE, major bleeding, and death)	**1080**	**10.2 [9.6; 10.8]**	**1491**	**14.0 [13.3; 14.7]**
Acute coronary syndrome (ACS)	**180**	**1.6 [1.4; 1.9]**	**247**	**2.2 [1.9; 2.5]**

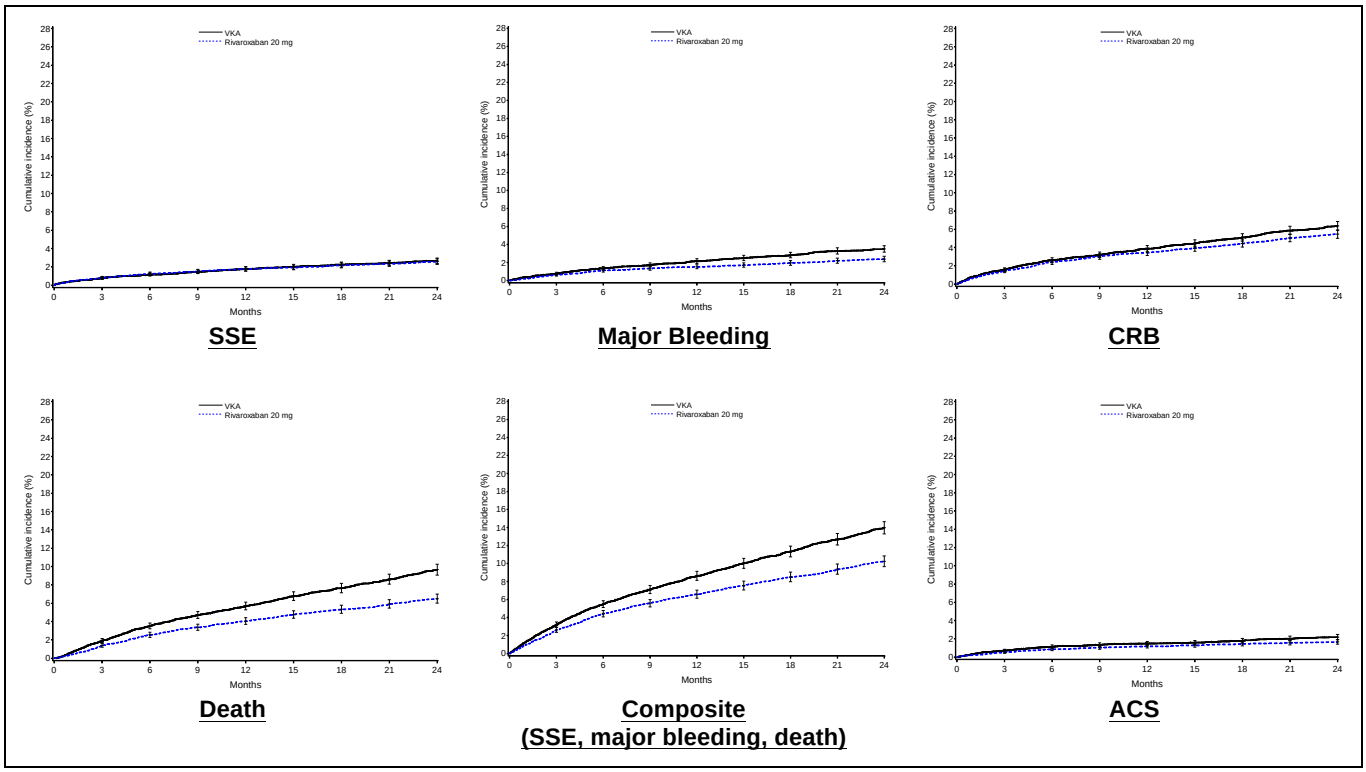


Figure 9. Two-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 20 mg and VKA matched patients

The 2-year cumulative incidence was higher with rivaroxaban 20 mg than dabigatran 150 mg for two main outcomes: major bleeding (1.7% [1.4 to 2.1] vs. 0.8% [0.6 to 1.1]), death (3.9% [3.5 to 4.4] vs. 3.0% [2.6 to 3.5]), and almost the same for SSE (2.0% [1.7 to 2.4] vs. 2.0% [1.6 to 2.3]). It was also higher with rivaroxaban for CRB (4.5% [4.0 to 5.0] vs. 2.3% [1.9 to 2.7]), the composite criterion (7.0% [6.4 to 7.6] vs. 5.6% [5.0 to 6.2]), and almost the same for ACS (1.5% [1.2 to 1.8] vs. 1.4% [1.2 to 1.8]) (**Table 43**, **Figure 10**; Appendix 1-5, Tables 48, 68, 88, 96, 104, 166, and Figures 18, 18b, 24, 24b, 30, 30b, 32, 32b, 34, 34b, 54, 54b).

Table 43. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period (60-day grace period for treatment discontinuation) for rivaroxaban 20 mg and dabigatran 150 mg matched patients

	Rivaroxaban 20 mg n = 10 342		Dabigatran 150 mg n = 10 342	
	n evt	% [95%CI]	n evt	% [95%CI]
Stroke and systemic embolism (SSE)	**140**	**2.0 [1.7; 2.4]**	**131**	**2.0 [1.6; 2.3]**
Major bleeding	**116**	**1.7 [1.4; 2.1]**	**52**	**0.8 [0.6; 1.1]**
Clinically relevant bleeding (CRB)	301	4.5 [4.0; 5.0]	144	2.3 [1.9; 2.7]
Death (all causes)	**253**	**3.9 [3.5; 4.4]**	**185**	**3.0 [2.6; 3.5]**
Composite criterion (SSE, major bleeding, and death)	**467**	**7.0 [6.4; 7.6]**	**354**	**5.6 [5.0; 6.2]**
Acute coronary syndrome (ACS)	**104**	**1.5 [1.2; 1.8]**	**93**	**1.4 [1.2; 1.8]**

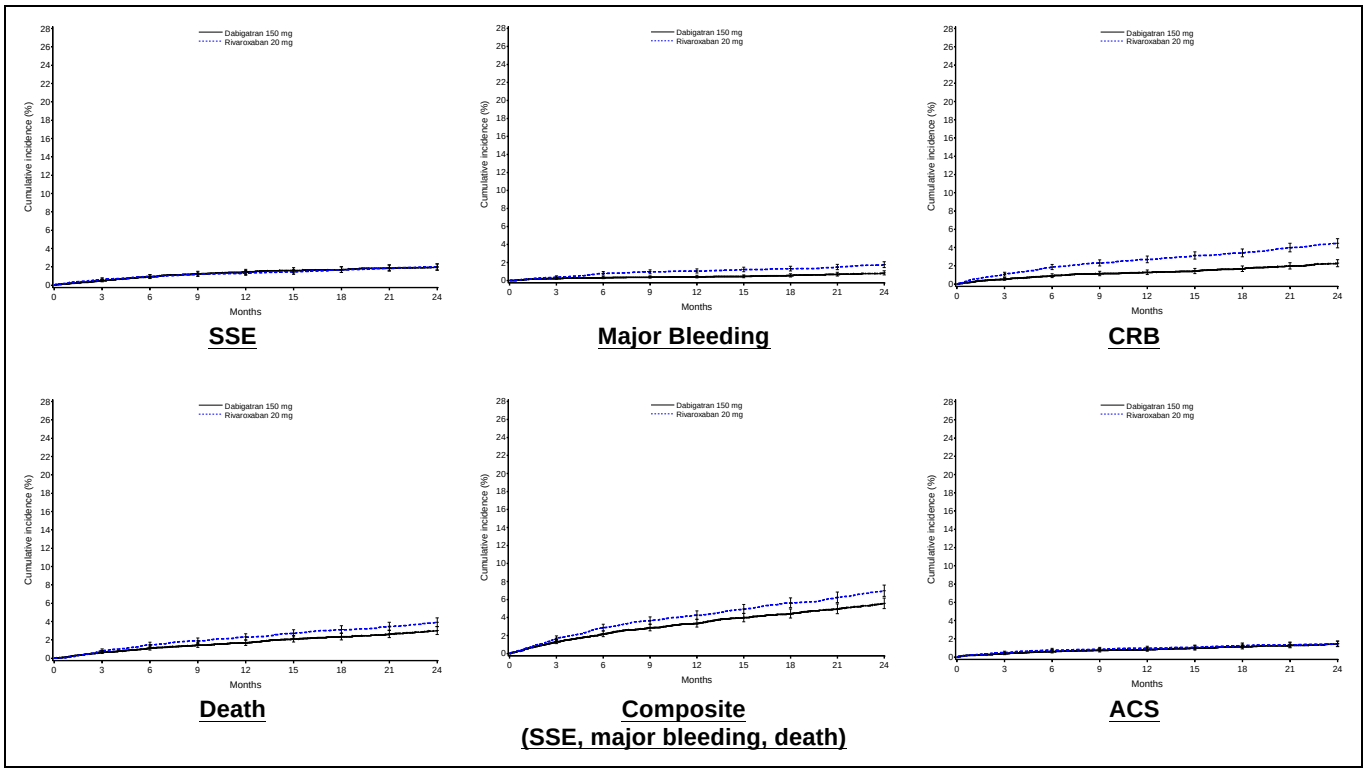


Figure 10. Two-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 20 mg and dabigatran 150 mg matched patients

The 2-year cumulative incidence was lower with rivaroxaban 15 mg than VKA for two main outcomes: major bleeding (3.7% [3.3 to 4.1] vs. 4.6% [4.2 to 5.1]), death (14.1% [13.3 to 14.9] vs. 18.3% [17.5 to 19.2]), and somewhat different for SSE but with 95%CI overlap (3.7% [3.3 to 4.1] vs. 3.2% [2.9 to 3.6]). It was also lower with rivaroxaban for CRB (6.7% [6.2 to 7.3] vs. 7.6% [7.1 to 8.2]), and the composite criterion (18.9% [18.0 to 19.8] vs. 23.2% [22.3 to 24.1], and almost the same for ACS (2.4% [2.0 to 2.7] vs. 2.3% [2.0 to 2.7]) (**Table 44**, **Figure 11**; Appendix 1-6, Tables 48, 68, 88, 96, 104, 166, and Figures 18, 18b, 24, 24b, 30, 30b, 32, 32b, 34, 34b, 54, 54b).

Table 44. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period (60-day grace period for treatment discontinuation) for rivaroxaban 15 mg and VKA matched patients

	Rivaroxaban 15 mg n = 12 018		VKA n = 12 018	
	n evt	**% [95%CI]**	**n evt**	**% [95%CI]**
Stroke and systemic embolism (SSE)	**298**	**3.7 [3.3; 4.1]**	**286**	**3.2 [2.9; 3.6]**
Major bleeding	**299**	**3.7 [3.3; 4.1]**	**406**	**4.6 [4.2; 5.1]**
Clinically relevant bleeding (CRB)	547	6.7 [6.2; 7.3]	677	7.6 [7.1; 8.2]
Death (all causes)	**1105**	**14.1 [13.3; 14.9]**	**1536**	**18.3 [17.5; 19.2]**
Composite criterion (SSE, major bleeding, and death)	**1526**	**18.9 [18.0; 19.8]**	**1998**	**23.2 [22.3; 24.1]**
Acute coronary syndrome (ACS)	**194**	**2.4 [2.0; 2.7]**	**205**	**2.3 [2.0; 2.7]**

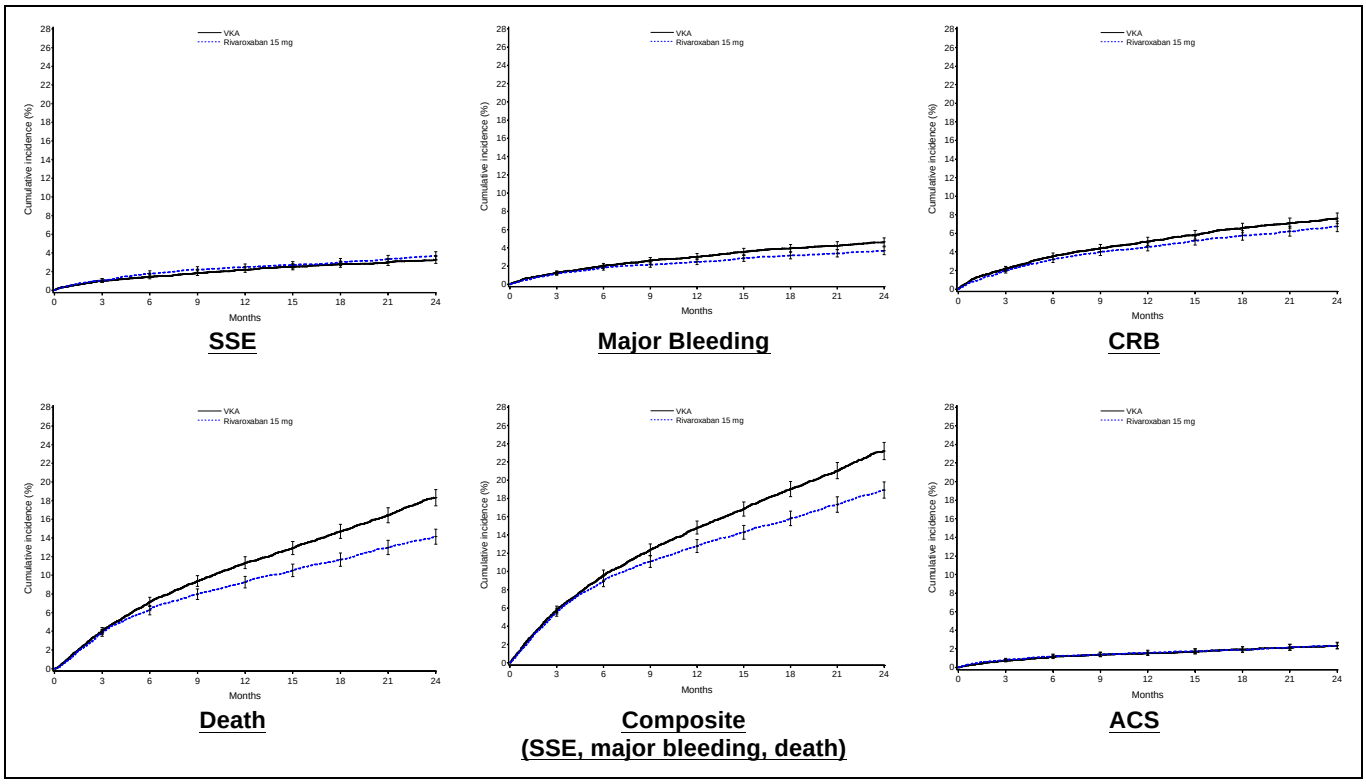


Figure 11. Two-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 15 mg and VKA matched patients

The 2-year cumulative incidence was higher with rivaroxaban 15 mg than dabigatran 110 mg for one main outcome: major bleeding (3.6% [3.2; 4.1] vs. 2.7% [2.3; 3.1]), and somewhat different for SSE and death but with 95%CI overlap (3.5% [3.0; 3.9] vs. 2.7% [2.3; 3.1], and 12.9% [12.1; 13.8] vs. 12.3% [11.4; 13.2], respectively). It was also higher with rivaroxaban for CRB (6.6% [6.0; 7.2] vs. 4.9% [4.3; 5.4]), somewhat different for the composite criterion but with 95%CI overlap (17.5% [16.6; 18.5] vs. 15.7% [14.8; 16.7]), and almost the same for ACS (2.3% [1.9; 2.6] vs. 2.2% [1.9; 2.6]) (**Table 45**, **Figure 12**; Appendix 1-7, Tables 48, 68, 88, 96, 104, 166, and Figures 18, 18b, 24, 24b, 30, 30b, 32, 32b, 34, 34b, 54, 54b).

Table 45. Cumulative incidence of outcomes (Kaplan-Meier estimate) during the drug exposure period (60-day grace period for treatment discontinuation) for rivaroxaban 15 mg and dabigatran 110 mg matched patients

	Rivaroxaban 15 mg n = 9 952		Dabigatran 110 mg n = 9 952	
	n evt	% [95%CI]	n evt	% [95%CI]
Stroke and systemic embolism (SSE)	**233**	**3.5 [3.0; 3.9]**	**163**	**2.7 [2.3; 3.1]**
Major bleeding	**244**	**3.6 [3.2; 4.1]**	**175**	**2.7 [2.3; 3.1]**
Clinically relevant bleeding (CRB)	444	6.6 [6.0; 7.2]	313	4.9 [4.3; 5.4]
Death (all causes)	**839**	**12.9 [12.1; 13.8]**	**738**	**12.3 [11.4; 13.2]**
Composite criterion (SSE, major bleeding, and death)	**1177**	**17.5 [16.6; 18.5]**	**971**	**15.7 [14.8; 16.7]**
Acute coronary syndrome (ACS)	**157**	**2.3 [1.9; 2.6]**	**141**	**2.2 [1.9; 2.6]**

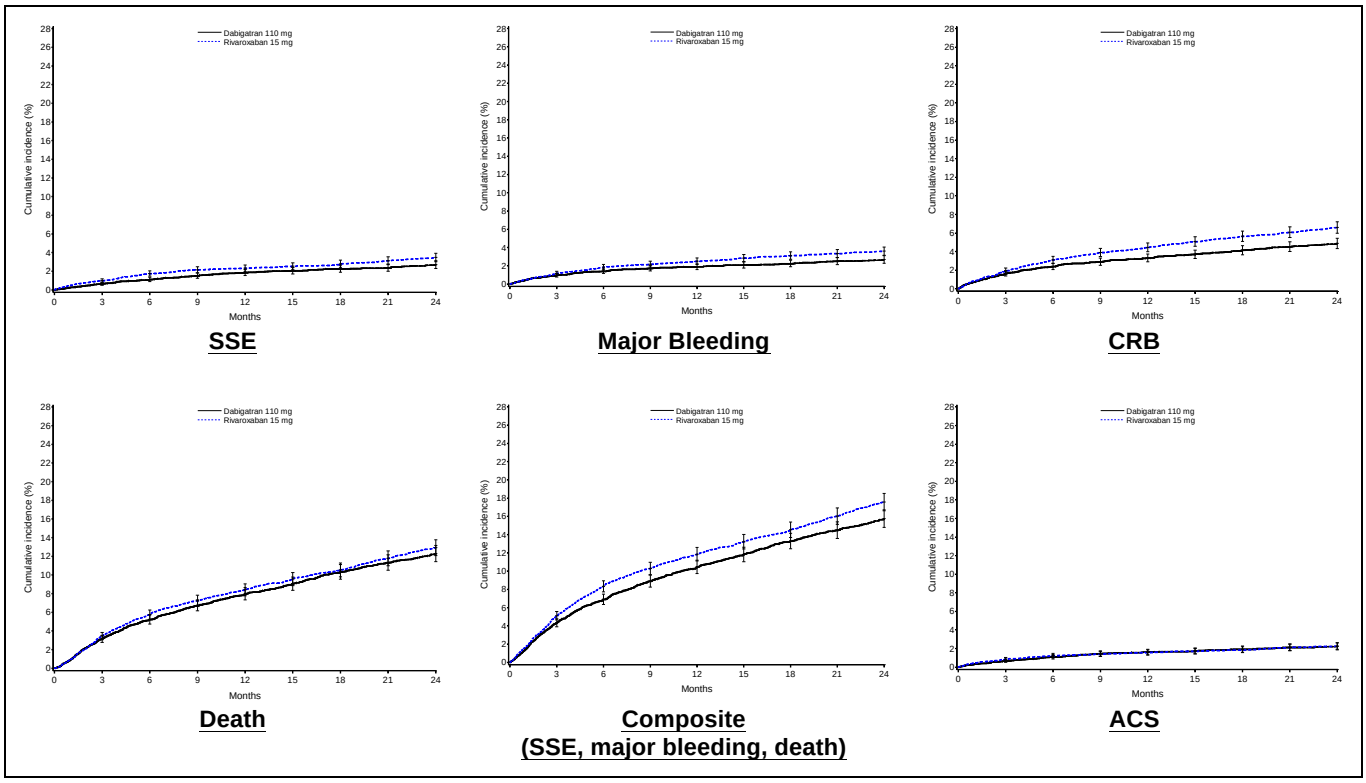


Figure 12. Two-year cumulative incidence (Kaplan-Meier estimate) of outcomes during the drug exposure period for rivaroxaban 15 mg and dabigatran 110 mg matched patients

For the 4 comparisons, results were similar with a 30-day grace period (Appendix 1-13, 1-14, 1-15 and 1-16, 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, 1-10, 1-11 and 1-12, Tables 16, 22, 28, 34, 40, 46, and Figures 16, 16b, 18, 18b, 20, 20b, 22, 22b, 24, 24b, 26, 26b).

10.4.2. Rivaroxaban 20 mg versus VKA comparison of the 2-year risk of outcomes during the exposure period (on treatment)

The main analysis was for the matched patients of the specific population with a 60-day grace period for the drug discontinuation definition. The risk at 2-year was significantly lower with rivaroxaban 20 mg than VKA for two main outcomes: major bleeding (HR: 0.69 [0.59 to 0.81]) and death (0.67 [0.61 to 0.74]), but not for SSE (0.99 [0.84 to 1.16]). It was also significantly lower with rivaroxaban for the three secondary outcomes: CRB (0.86 [0.77 to 0.97), ACS (0.75 [0.62 to 0.91]), and the composite criterion (0.73 [0.68 to 0.79]) (**Table 46** and **Figure 13**; Appendix 1-4, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 108, 164 to 171).

The two-year hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figure 13**). Beside, a complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes of matched and all patients adjusted analyses (Appendix 1-4, Tables 196 to 201).

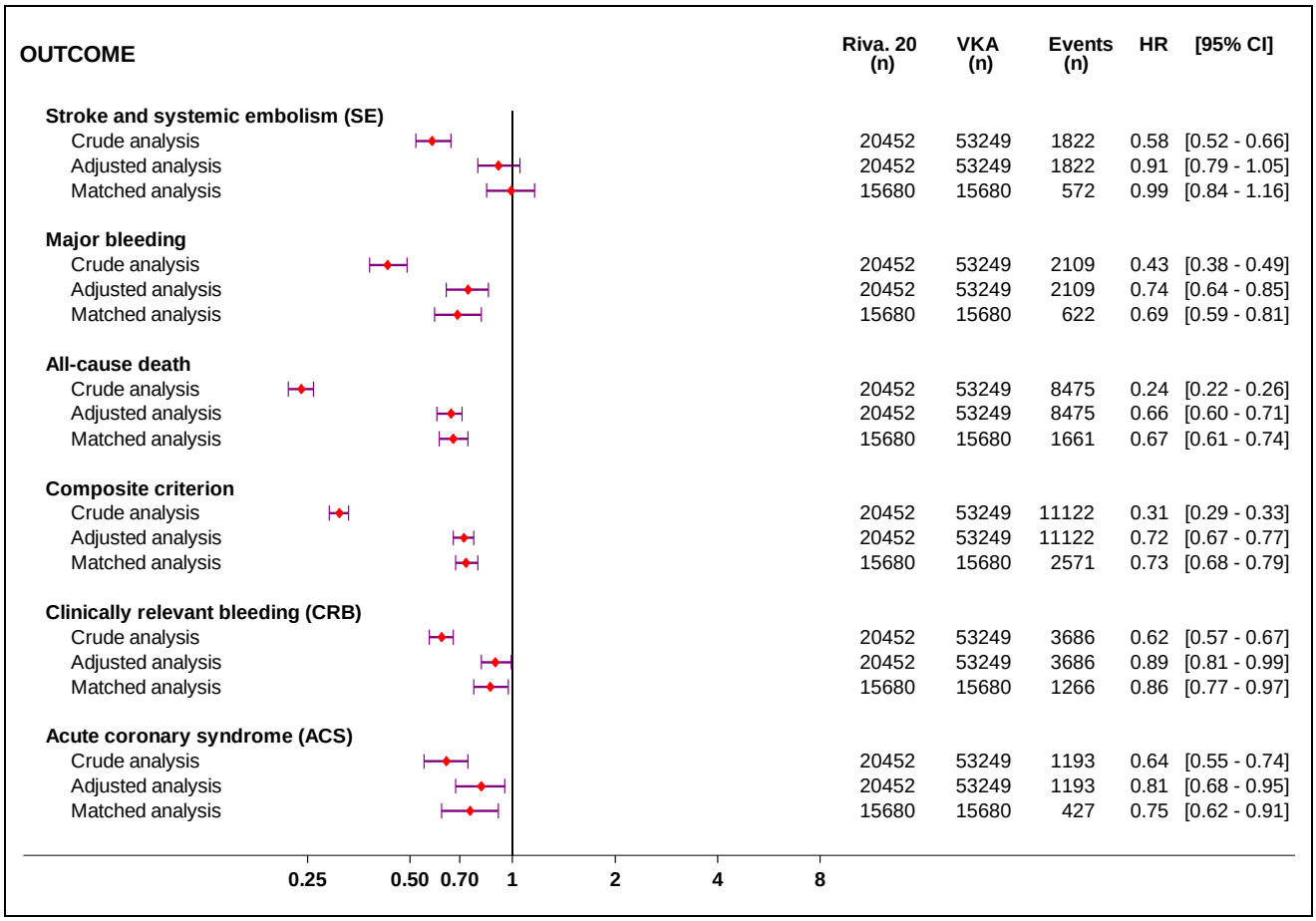
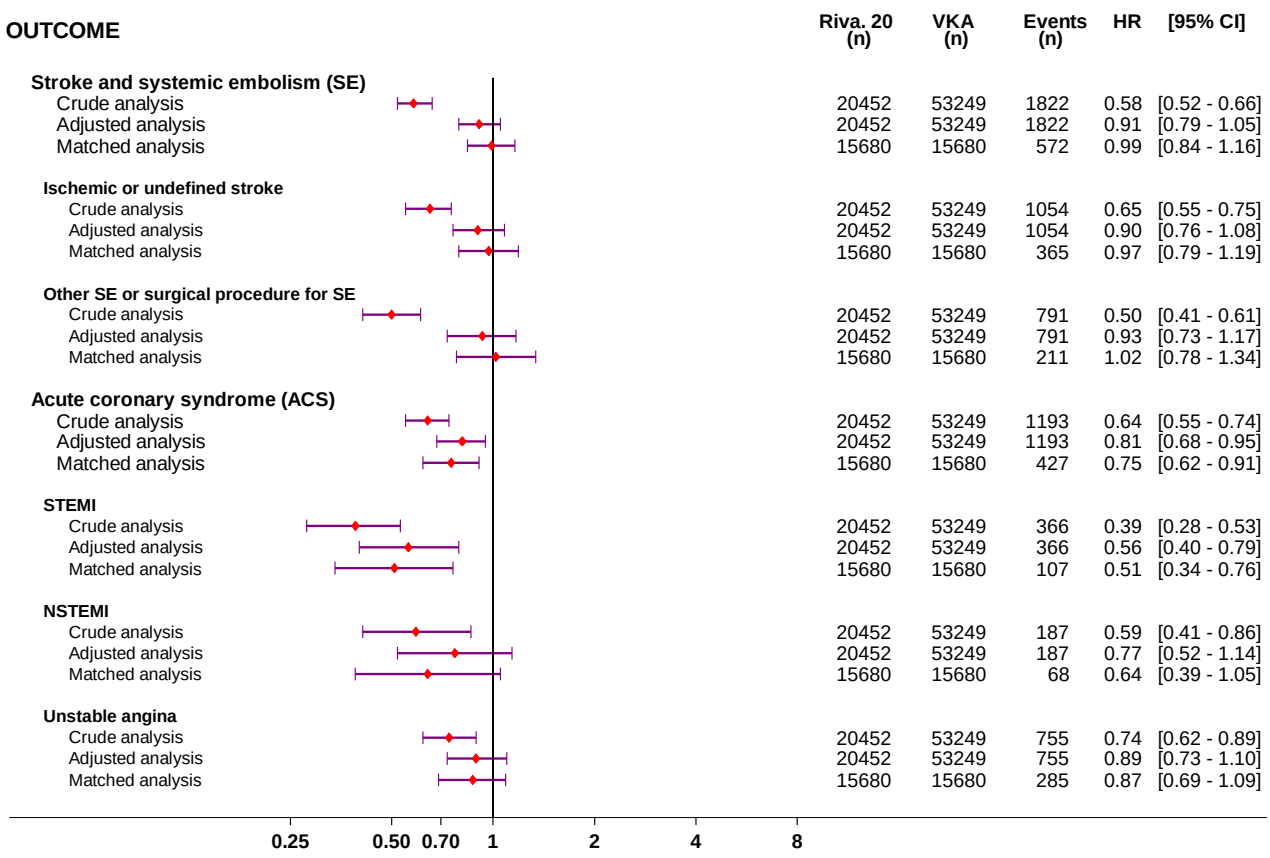


Figure 13. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban for other critical organ or site bleeding (HR: 0.38 [0.26 to 0.56]) and other bleeding (0.75 [0.60 to 0.93]), but not for haemorrhagic stroke, GI bleeding, and urogenital bleeding (0.84 [0.63 to 1.12], 1.02 [0.84 to 1.22], 1.12 [0.86 to 1.46], respectively). For other individual events of major outcomes, the risk was significantly lower with rivaroxaban for STEMI (0.51 [0.34 to 0.76]), but not for ischemic or undefined stroke (0.97 [0.79 to 1.19]), other SE or surgical procedure for SE (1.02 [0.78 to 1.34]), NSTEMI (0.64 [0.39 to 1.05]), and unstable angina (0.87 [0.69 to 1.09]) (**Figure 14**; Appendix 1-4, Tables 57 to 59, 63 to 65, 125 to 127, 143 to 145, 149 to 151, 155 to 157, 161 to 163, 181 to 183, 187 to 189, 193 to 195).



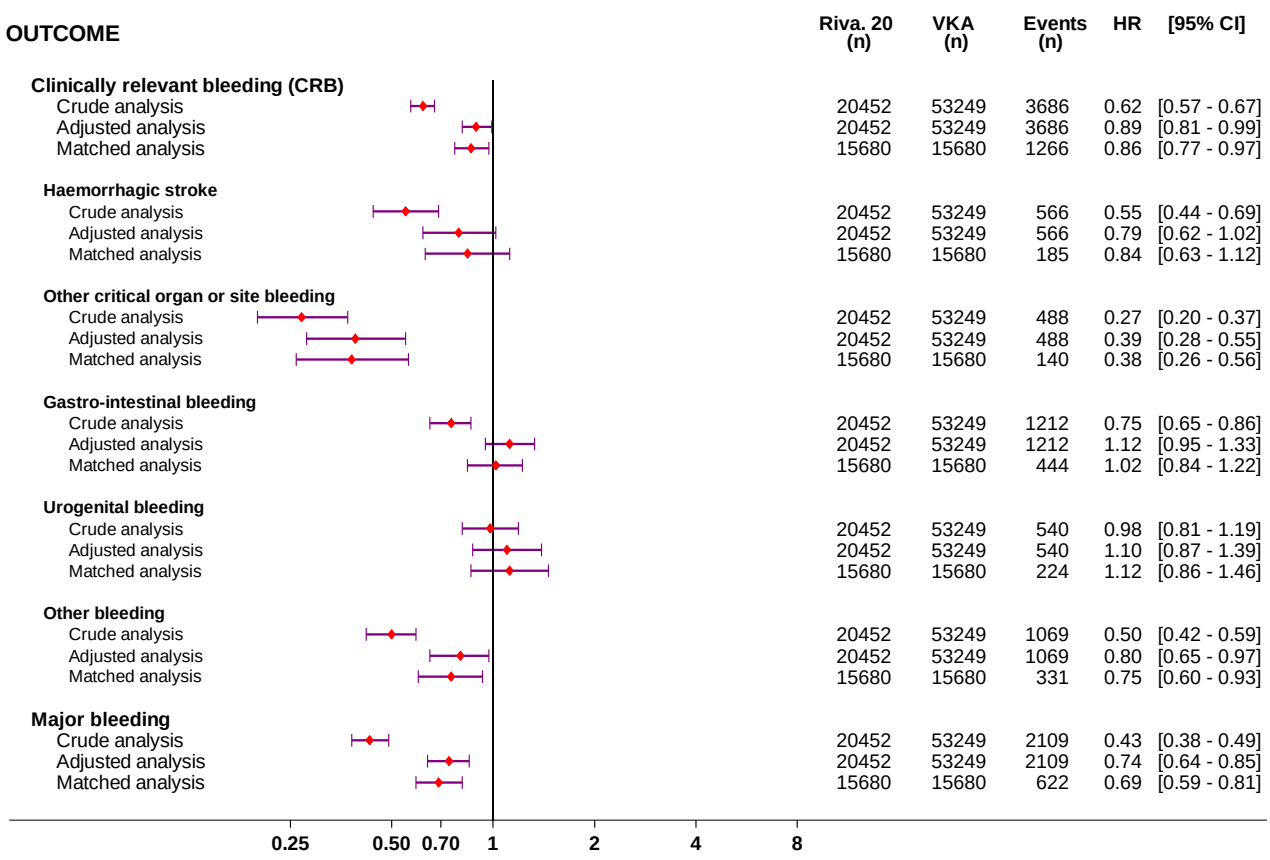


Figure 14. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of outcome details for the specific population and a 60-day grace period for drug discontinuation

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, except for the risk of SSE which reached the significant threshold in favour of rivaroxaban 20 mg (15% [1% to 27%]) (Appendix 1-9, Figure 14, Tables 17 to 19, 23 to 25, 29 to 31, 35 to 37, 41 to 43, 47 to 49).

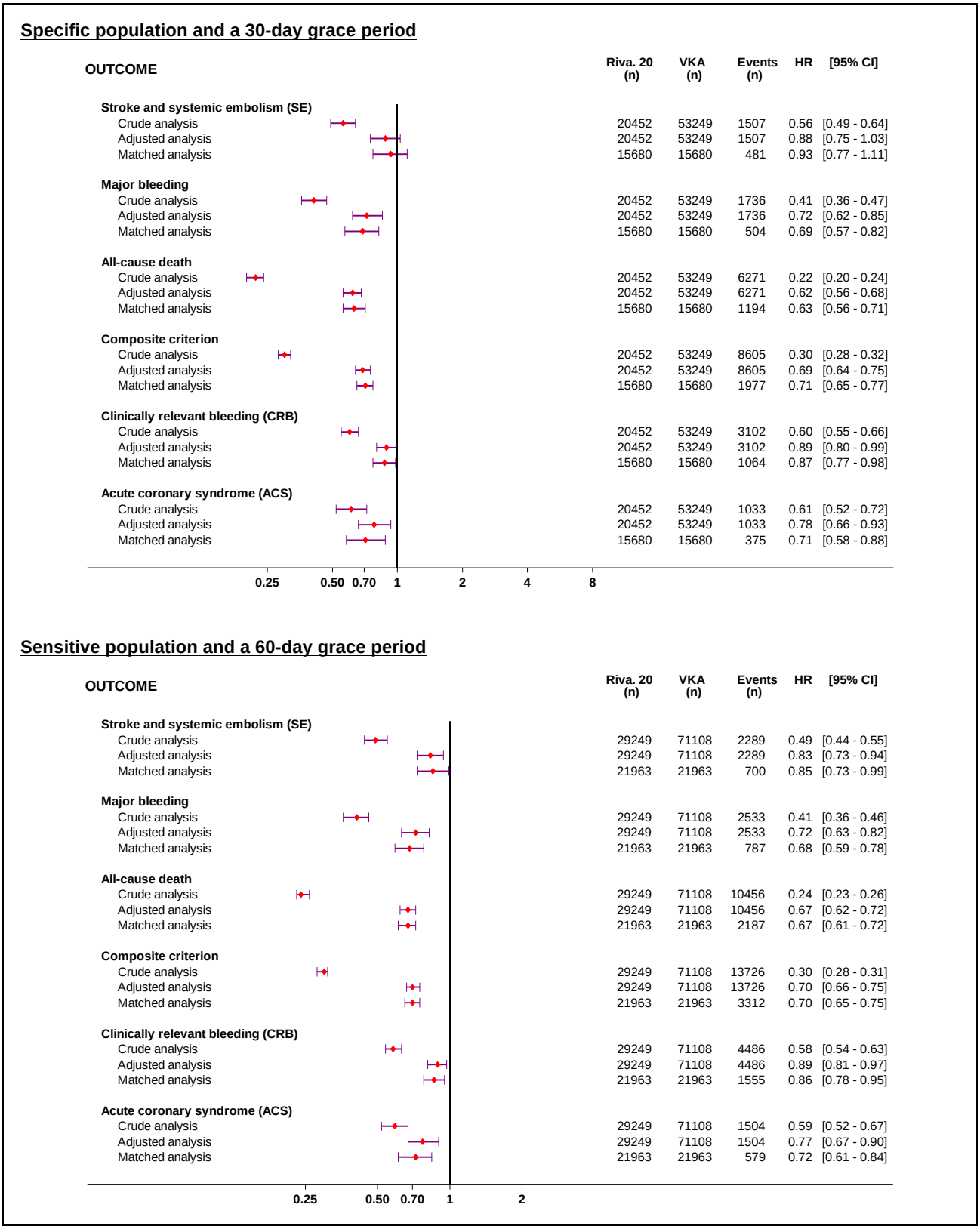


Figure 15. Rivaroxaban 20 mg versus VKA: Hazard ratio (HR) and 95% CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period

Stratified analyses were performed for the specific population and a 60-day grace period according to 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 47**; 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% non-significantly lower for the fourth quintile of logit hdPS (33%),
  - Between 10% and 24% non-significantly lower for 75-79 years old (23%), female (14%), HAS-BLED score > 3 (14%), CHA_2DS_2-VASc score 3 (11%),
  - Relatively similar with HR between 0.91 and 1.10 (symmetric of 0.91) for all matched patients (0.99), male (1.06), < 65, 65-69 and 70-74 years old (1.03, 0.97 and 1.07, respectively) CHA_2DS_2-VASc score 2 (1.04), congestive heart failure (1.01), hypertension (1.06), stroke or TIA history (1.01), vascular disease history (1.10), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (1.03 and 0.96, respectively), HAS-BLED score 2-3 (0.97), and the second and last quintiles (1.03 and 0.95, respectively),
  - Between 10% and 24% non-significantly lower with VKA for ≥ 80 years old (11%, i.e. inverse of 1.12; [1-(1/1.12)]), CHA_2DS_2-VASc scores 0-1 and ≥ 4 (24% and 10%, respectively), diabetes mellitus (19%), HAS-BLED score 0-1 (13%), and the first and third quintiles (12% and 14%, respectively),
  - With a gradient for HAS-BLED, from 0.86 to 1.15 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For major bleeding,**
  - At least 25% lower for all matched patients (31%), female (43%), < 65, 65-69, and 75-79 years old (43%, 56% and 33%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and 3 (45%, 41% and 36%, respectively), age 65-74 years as CHA_2DS_2-VASc risk factor (37%), congestive heart failure (30%), HAS-BLED scores 0-1 and 2-3 (41% and 30%, respectively), and the four last quintiles of logit hdPS (29%, 35%, 38% and 46%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 47**),
  - Between 10% and 24% significantly lower for male (24%), age ≥ 75 years old as CHA_2DS_2-VASc risk factor (24%), and non-significantly for 70-74 and ≥ 80 years old (19% for both), CHA_2DS_2-VASc scores ≥ 4 (14%), hypertension (16%), diabetes mellitus (18%), stroke or TIA history (18%), HAS-BLED score > 3 (11%), and the first quintile of logit hdPS (14%),
  - Relatively similar with HR between 0.91 and 1.10 for vascular disease history (0.94),
  - None lower with VKA,
  - With a gradient for CHA_2DS_2-VASC from 0.55 to 0.86 for scores 0-1 to ≥ 4 HR, HAS-BLED, from 0.59 to 0.89 for scores 0-1 to > 3 HR, and for quintiles from 0.54 to 0.86 for the last to the first quintile HR, and no clear systematic variation for the other factors;
- **For clinically relevant bleeding,**
  - At least 25% lower for 65-69 years old (34%), age 65-74 years as CHA_2DS_2-VASc risk factor (25%), the last quintile of logit hdPS (26%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 47**),
  - Between 10% and 24% lower for all matched patients (14%), female (23%), < 65 and 70-74 years old (12% and 17%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and 3 (16%, 22% and 21%, respectively), congestive heart failure (13%), HAS-BLED scores 0-1 and 2-3 (13% and 14%, respectively), the third and fourth quintiles (14% for both), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 47**),
  - Relatively similar with HR between 0.91 and 1.10 for male (0.92), 75-79 and ≥ 80 years old (0.91 and 0.98, respectively), CHA_2DS_2-VASc scores ≥ 4 (1.01), hypertension (0.92), diabetes mellitus (0.91), stroke or TIA history (0.91), age ≥ 75 years as CHA_2DS_2-VASc risk factor (0.95) and the two first quintiles (0.94 and 0.95, respectively),
  - Between 10% and 24% non-significantly lower with VKA for vascular disease history (12%),

- Without clear systematic variation;

– **For death,**
  - At least 25% significantly lower for all matched patients (33%), male and female (31% and 36%, respectively), < 65, 65-69, 75-79 and ≥ 80 years old (28%, 46%, 41% and 26%, respectively), all CHA_2DS_2-VASc score classes (30%, 35%, 42% and 25%, respectively), congestive heart failure (32%), hypertension (27%), diabetes mellitus (25%), vascular disease history (27%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (34% and 31%, respectively), HAS-BLED scores 0-1 and 2-3 (41% and 31%, respectively), and all quintiles of logit hdPS (25%, 31%, 26%, 32%, 53%, respectively),
  - Between 10% and 24% non-significantly lower for 70-74 years old (23%), stroke or TIA history (22%), and HAS-BLED score > 3 (18%),
  - All were at least 18% lower with rivaroxaban,
  - With a gradient for HAS-BLED from 0.59 to 0.82 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 (27%), female (33%), 65-69 and 75-79 years old (39% and 37%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and 3 (25%, 28% and 35%, respectively), congestive heart failure (26%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (27%), HAS-BLED scores 0-1 and 2-3 (30% and 26%, respectively), and the two last quintiles of logit hdPS (33% and 36%, respectively),
  - Between 10% and 24% lower with rivaroxaban for male (23%), age < 65, 70-74 and ≥ 80 years old (20%, 11% and 21%, respectively), CHA_2DS_2-VASc scores ≥ 4 (20%), hypertension (20%), diabetes mellitus (15%), stroke or TIA history (17%), vascular disease history (14%), age 65-74 years as CHA_2DS_2-VASc risk factor (24%), HAS-BLED scores > 3 (17%), the three first quintiles (19%, 23% and 21%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 47**),
  - None lower with VKA,
  - With a gradient for HAS-BLED, from 0.70 to 0.83 for scores 0-1 to scores > 3 HR, and no clear systematic variation for the other factors;

– **For ACS,**
  - At least 25% lower for all matched patients (25%), male (28%), age ≥ 80 years old (49%), CHA_2DS_2-VASc score 3 (31%), congestive failure (26%), hypertension (28%), stroke or TIA history (37%), vascular disease history (26%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (34%), HAS-BLED scores > 3 (38%), the first and last quintiles of logit hdPS (37% and 36%, respectively), and significantly when there were enough patients and events to reach statistical power,
  - Between 10% and 24% lower for female (17%), age < 65, 65-69, 70-74 and 75-79 years old (18%, 20%, 15% and 17%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and ≥ 4 (21%, 23% and 22%, respectively), diabetes mellitus (10%), age 65-74 years as CHA_2DS_2-VASc risk factor (18%), HAS-BLED scores 0-1 and 2-3 (20% and 24%, respectively), the second, third and fourth quintiles (10%, 14% and 20%, respectively), and significantly when there were enough patients and events to reach statistical power,
  - None lower with VKA,
  - With a gradient for HAS-BLED, from 0.62 to 0.80 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors.

The HR point estimate after one year of follow-up for the 2013 matched patients was quite the same for two of the three main outcomes (major bleeding and death) with some variations of the 95%CI, and a little better HR with rivaroxaban but also not significant for SSE (0.90 [0.74 to 1.08]). It was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with some variations of the 95%CI, including a non-significant 95%CI for CRB (HR: 0.90 [0.79 to 1.03]) (**Table 46**).

It was quite the same for the 2013-2014 matched patients at one-year presented in the previous report, with twice more patients: similar HR for two of the three main outcomes (major bleeding and death) with narrower 95%CI due to larger population, but a significant lower risk for SSE with rivaroxaban compared to VKA (HR: 0.79 [0.69 to 0.90] for 2013 and 2014 matched patients); The difference for SSE was more important for the only 2014 patients (0.68 [0.56 to 0.83]), as well as for almost all subgroups of the stratified analyses of these patients (see the study report "One-year of follow-up", Table 48). Result was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with narrower 95%CI due to larger population (**Table 46**).

Table 46. Rivaroxaban 20 mg versus VKA, specific population, and a 60-day grace period for drug discontinuation: Hazard ratio (HR) and 95%CI of main and secondary outcomes at 1-year and at 2-year for the 2013 matched patients, and at 1-year for the 2013-2014 matched patients

	Matched patients of the specific populations		
	New users in 2013		**New users in 2013-2014**
	Riva. 20 vs VKA at 1-year n = 15 712	**Riva. 20 vs VKA at 2-year n = 15 680**	**Riva. 20 vs VKA at 1-year n = 31 171**
	HR [95%CI]	**HR [95%CI]**	**HR [95%CI]**
Stroke and systemic embolism (SSE)	**0.90 [0.74; 1.08]**	**0.99 [0.84; 1.16]**	**0.79 [0.69; 0.90]**
Major bleeding	**0.70 [0.58; 0.85]**	**0.69 [0.59; 0.81]**	**0.67 [0.59; 0.77]**
Clinically relevant bleeding (CRB)	0.90 [0.79; 1.03]	0.86 [0.77; 0.97]	0.83 [0.76 ; 0.91]
Death (all causes)	**0.68 [0.61; 0.77]**	**0.67 [0.61; 0.74]**	**0.67 [0.61 - 0.73]**
Composite criterion (SSE, major bleeding, and death)	**0.73 [0.67; 0.80]**	**0.73 [0.68; 0.79]**	**0.70 [0.65 - 0.74]**
Acute coronary syndrome (ACS)	**0.77 [0.62; 0.95]**	**0.75 [0.62; 0.91]**	**0.80 [0.69 ; 0.93]**

Table 47. 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	15 680	15 680	0.99 [0.84 ; 1.16]	0.69 [0.59 ; 0.81]	0.86 [0.77 ; 0.97]	0.67 [0.61 - 0.74]	0.73 [0.68 - 0.79]	0.75 [0.62 ; 0.91]
Gender								
Male	9 711	9 711	1.06 [0.87 ; 1.30]	0.76 [0.63 ; 0.93]	0.92 [0.80 ; 1.05]	0.69 [0.61 - 0.78]	0.77 [0.70 - 0.85]	0.72 [0.56 ; 0.91]
Female	5 969	5 969	0.86 [0.65 ; 1.14]	0.57 [0.43 ; 0.75]	0.77 [0.64 ; 0.93]	0.64 [0.54 - 0.75]	0.67 [0.58 - 0.76]	0.83 [0.60 ; 1.16]
Age (years)								
<65	3 705	3 746	1.03 [0.68 ; 1.58]	0.57 [0.34 ; 0.97]	0.88 [0.66 ; 1.17]	0.72 [0.53 - 0.98]	0.80 [0.63 - 1.00]	0.82 [0.52 ; 1.29]
[65-70[	2 645	2 657	0.97 [0.63 ; 1.51]	0.44 [0.27 ; 0.71]	0.66 [0.49 ; 0.90]	0.54 [0.39 - 0.74]	0.61 [0.49 - 0.78]	0.80 [0.51 ; 1.26]
[70-75[	2 821	2 715	1.07 [0.73 ; 1.57]	0.81 [0.56 ; 1.17]	0.83 [0.63 ; 1.08]	0.77 [0.59 - 1.00]	0.89 [0.73 - 1.08]	0.85 [0.56 ; 1.28]
[75-80[	3 100	3 230	0.77 [0.55 ; 1.10]	0.67 [0.48 ; 0.95]	0.91 [0.72 ; 1.14]	0.59 [0.48 - 0.73]	0.63 [0.53 - 0.74]	0.83 [0.56 ; 1.24]
≥ 80	3 409	3 332	1.12 [0.83 ; 1.52]	0.81 [0.63 ; 1.05]	0.98 [0.81 ; 1.19]	0.74 [0.64 - 0.86]	0.79 [0.69 - 0.89]	0.51 [0.32 ; 0.79]
CHA_2DS_2-VASc score								
0-1	3 782	3 781	1.00 [0.64 ; 1.57]	0.55 [0.34 ; 0.89]	0.84 [0.63 ; 1.11]	0.70 [0.51 - 0.94]	0.75 [0.60 - 0.95]	0.79 [0.46 ; 1.38]
2	3 798	3 603	1.07 [0.74 ; 1.56]	0.59 [0.42 ; 0.83]	0.78 [0.62 ; 0.99]	0.65 [0.52 - 0.83]	0.72 [0.61 - 0.86]	0.77 [0.52 ; 1.14]
3	3 643	3 604	0.89 [0.63 ; 1.27]	0.64 [0.46 ; 0.89]	0.79 [0.63 ; 0.99]	0.58 [0.48 - 0.72]	0.65 [0.56 - 0.77]	0.69 [0.47 ; 1.02]
≥ 4	4 457	4 692	1.02 [0.80 ; 1.31]	0.86 [0.67 ; 1.10]	1.01 [0.84 ; 1.20]	0.75 [0.65 - 0.86]	0.80 [0.71 - 0.90]	0.78 [0.57 ; 1.07]
Risk factors								
Congestive heart failure	2 378	2 415	1.01 [0.68 ; 1.49]	0.70 [0.48 ; 1.02]	0.87 [0.66 ; 1.14]	0.68 [0.57 - 0.82]	0.74 [0.63 - 0.86]	0.74 [0.48 ; 1.13]
Hypertension	5 986	6 166	1.06 [0.83 ; 1.34]	0.84 [0.66 ; 1.07]	0.92 [0.78 ; 1.09]	0.73 [0.64 - 0.84]	0.80 [0.71 - 0.89]	0.72 [0.55 ; 0.95]
Diabetes mellitus	3 568	3 699	1.24 [0.93 ; 1.67]	0.82 [0.61 ; 1.11]	0.91 [0.73 ; 1.13]	0.75 [0.63 - 0.89]	0.85 [0.73 - 0.97]	0.90 [0.66 ; 1.23]
Stroke or TIA history	1 719	1 767	1.01 [0.71 ; 1.43]	0.82 [0.56 ; 1.20]	0.91 [0.69 ; 1.21]	0.78 [0.61 - 1.00]	0.83 [0.68 - 1.00]	0.63 [0.34 ; 1.17]
Vascular disease history	2 121	2 214	1.10 [0.80 ; 1.52]	0.94 [0.64 ; 1.39]	1.14 [0.88 ; 1.49]	0.73 [0.58 - 0.93]	0.86 [0.72 - 1.03]	0.74 [0.52 ; 1.04]
Age 65-74 years	5 466	5 372	1.03 [0.77 ; 1.37]	0.63 [0.47 ; 0.85]	0.75 [0.61 ; 0.92]	0.66 [0.54 - 0.81]	0.76 [0.66 - 0.88]	0.82 [0.61 ; 1.12]
Age ≥75 years	6 509	6 562	0.96 [0.76 ; 1.20]	0.76 [0.62 ; 0.93]	0.95 [0.82 ; 1.10]	0.69 [0.61 - 0.78]	0.73 [0.66 - 0.80]	0.66 [0.49 ; 0.89]
HAS-BLED score								
0-1	5 728	5 462	1.15 [0.82 ; 1.63]	0.59 [0.41 ; 0.83]	0.87 [0.69 ; 1.08]	0.59 [0.48 - 0.73]	0.70 [0.59 - 0.82]	0.80 [0.52 ; 1.21]
2-3	9 132	9 414	0.97 [0.79 ; 1.19]	0.70 [0.58 ; 0.85]	0.86 [0.75 ; 0.98]	0.69 [0.61 - 0.78]	0.74 [0.67 - 0.81]	0.76 [0.61 ; 0.96]
>3	820	804	0.86 [0.54 ; 1.36]	0.89 [0.55 ; 1.43]	0.97 [0.67 ; 1.39]	0.82 [0.61 - 1.10]	0.83 [0.66 - 1.06]	0.62 [0.29 ; 1.32]
Quintiles of logit (hdPS)								
Quintile 1	3 092	3 180	1.14 [0.84 ; 1.54]	0.86 [0.66 ; 1.13]	0.94 [0.76 ; 1.15]	0.75 [0.65 - 0.87]	0.81 [0.72 - 0.92]	0.63 [0.42 ; 0.94]
Quintile 2	3 015	3 257	1.03 [0.74 ; 1.44]	0.71 [0.51 ; 0.99]	0.95 [0.76 ; 1.20]	0.69 [0.56 - 0.85]	0.77 [0.65 - 0.90]	0.90 [0.61 ; 1.32]
Quintile 3	2 955	3 317	1.16 [0.80 ; 1.70]	0.65 [0.45 ; 0.95]	0.86 [0.66 ; 1.11]	0.74 [0.57 - 0.95]	0.79 [0.65 - 0.96]	0.86 [0.55 ; 1.33]
Quintile 4	3 213	3 059	0.67 [0.43 ; 1.05]	0.62 [0.39 ; 0.96]	0.86 [0.65 ; 1.14]	0.68 [0.50 - 0.92]	0.67 [0.54 - 0.84]	0.80 [0.52 ; 1.24]
Quintile 5	3 405	2 867	0.95 [0.61 ; 1.48]	0.54 [0.31 ; 0.92]	0.74 [0.54 ; 1.01]	0.47 [0.31 - 0.70]	0.64 [0.49 - 0.84]	0.64 [0.38 ; 1.09]

10.4.3. Rivaroxaban 20 mg versus dabigatran 150 mg comparison of the 2-year risk of outcomes during the exposure period (on treatment)

For matched patients, the risk at 2-year was significantly higher with rivaroxaban 20 mg than dabigatran 150 mg for two main outcomes: major bleeding (HR: 2.13 [1.53 to 2.95]), death (1.30 [1.08 to 1.57]), and almost the same for SSE (1.03 [0.81 to 1.31]). It was also significantly higher with rivaroxaban for CRB (2.0 [1.64 to 2.44]), the composite criterion (1.26 [1.10 to 1.45]), and almost the same for ACS (1.07 [0.81 to 1.42]) (**Table 48** and **Figure 16**; Appendix 1-5, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101, 105 to 109, 167 to 171).

The two-year hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figure 16**). The complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes of matched and all patients adjusted analyses (Appendix 1-5, Tables 196 to 201).

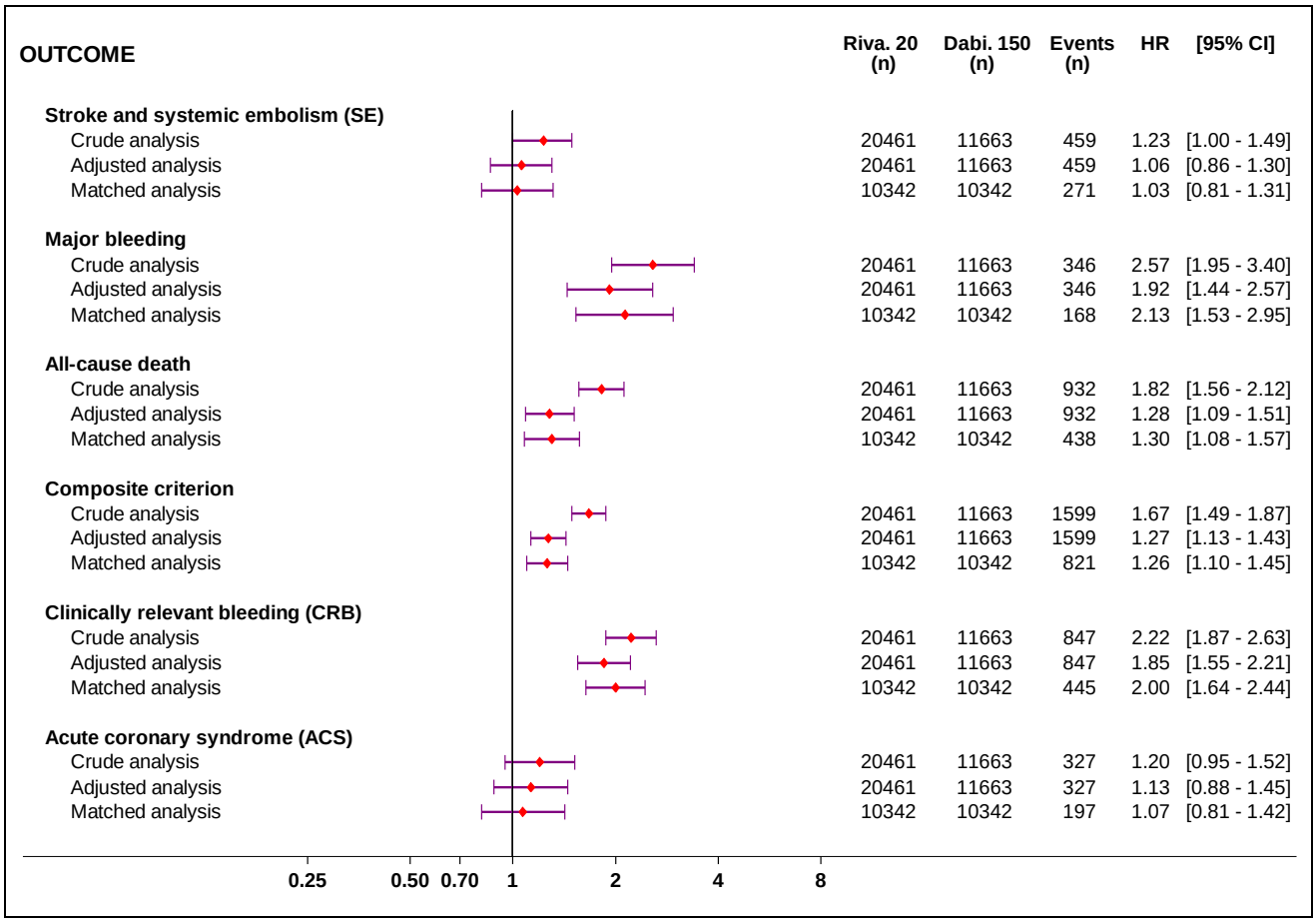
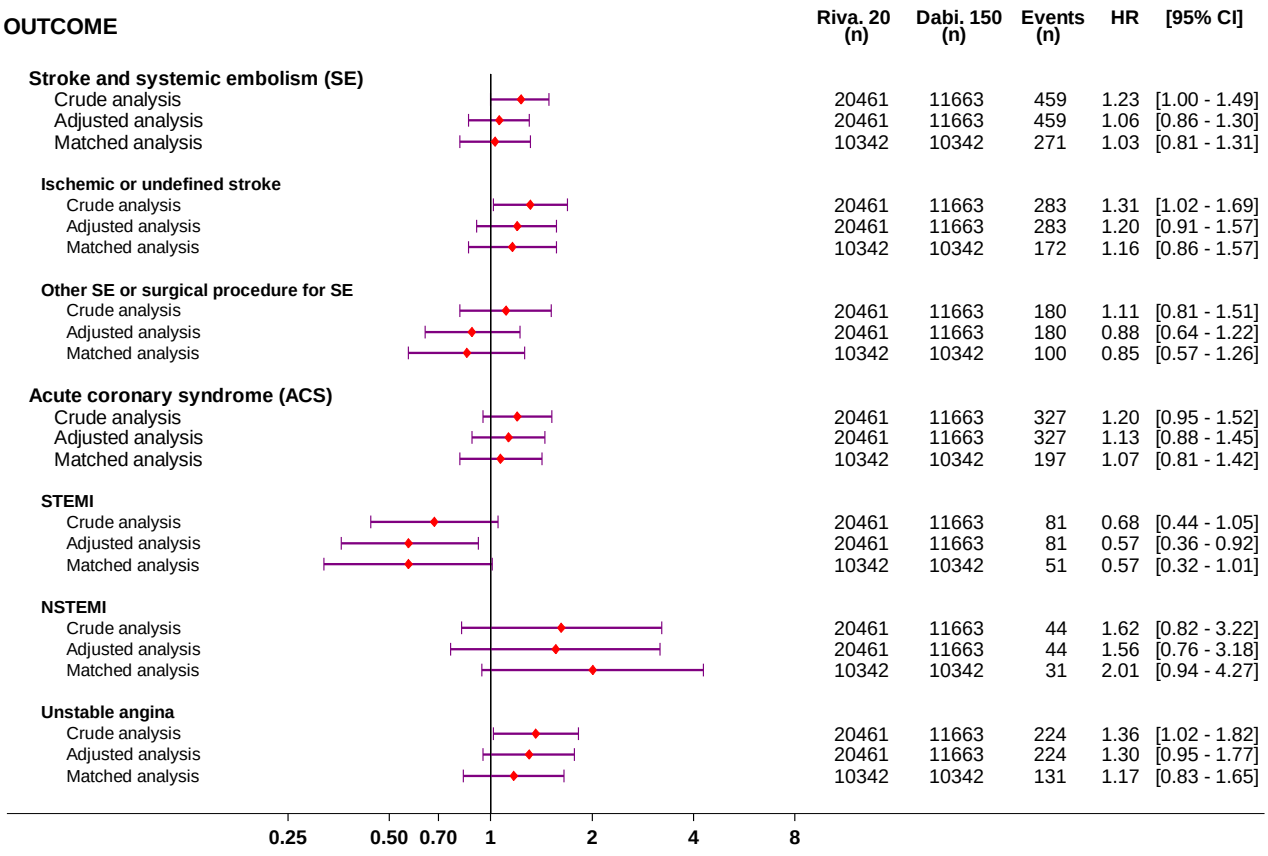


Figure 16. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation

The 2-year risk of other individual events was significantly higher with rivaroxaban 20 mg for haemorrhagic stroke (HR: 4.46 [2.18 to 9.15]), GI bleeding (1.73 [1.26 to 2.35]), urogenital bleeding (2.24 [1.46 to 3.44]), other bleeding (1.91 [1.25 to 2.92]), but not for other critical organ or site bleeding (1.13 [0.59 to 2.15]), ischemic or undefined stroke (1.16 [0.86 to 1.57]), other SE or surgical procedure for SE (0.85 [0.57 to 1.26]), STEMI (0.57 [0.32 to 1.01]), NSTEMI (2.01 [0.94 to 4.27]), and unstable angina (1.17 [0.83 to 1.65]) (**Figure 17**; Appendix 1-5, Tables 57 to 59, 63 to 65, 125 to 127, 143 to 145, 149 to 151, 155 to 157, 161 to 163, 181 to 183, 187 to 189, 193 to 195).



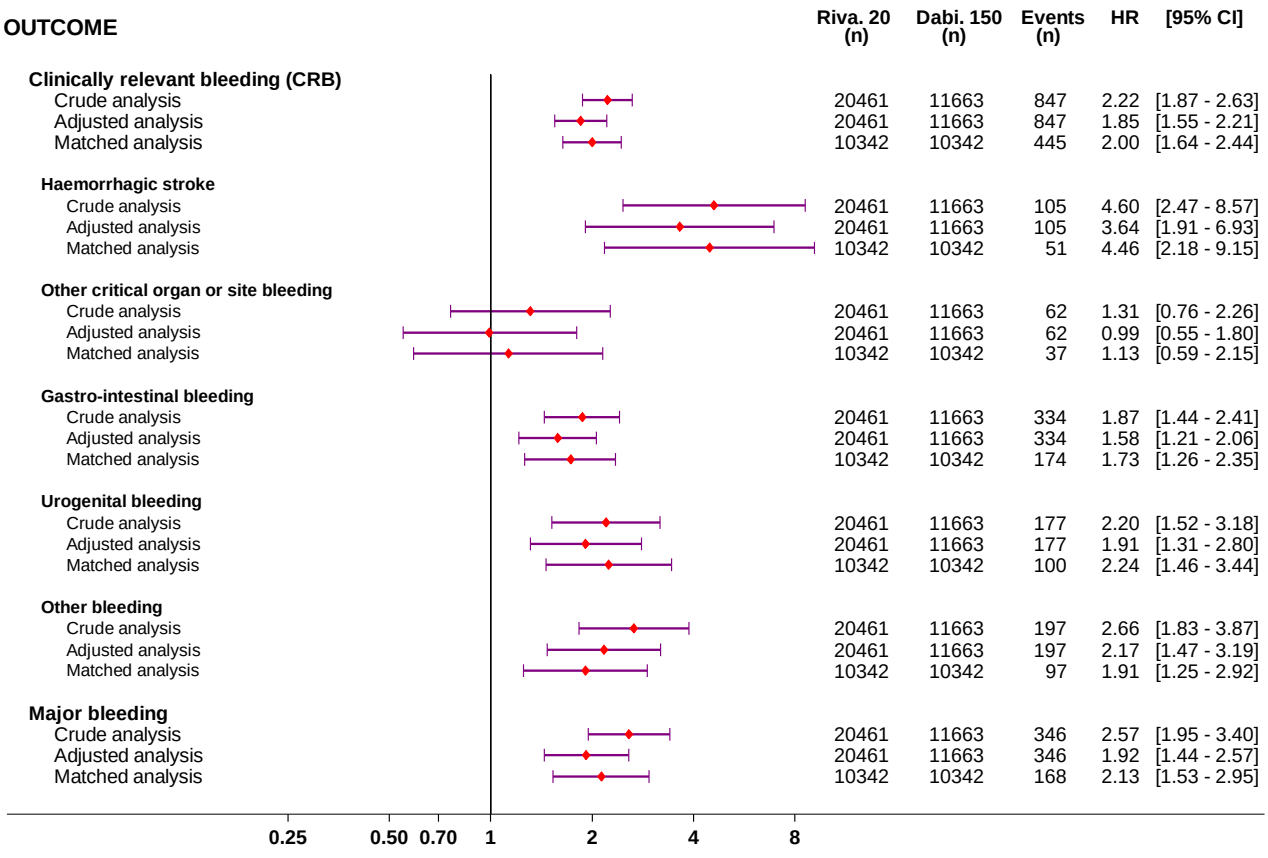
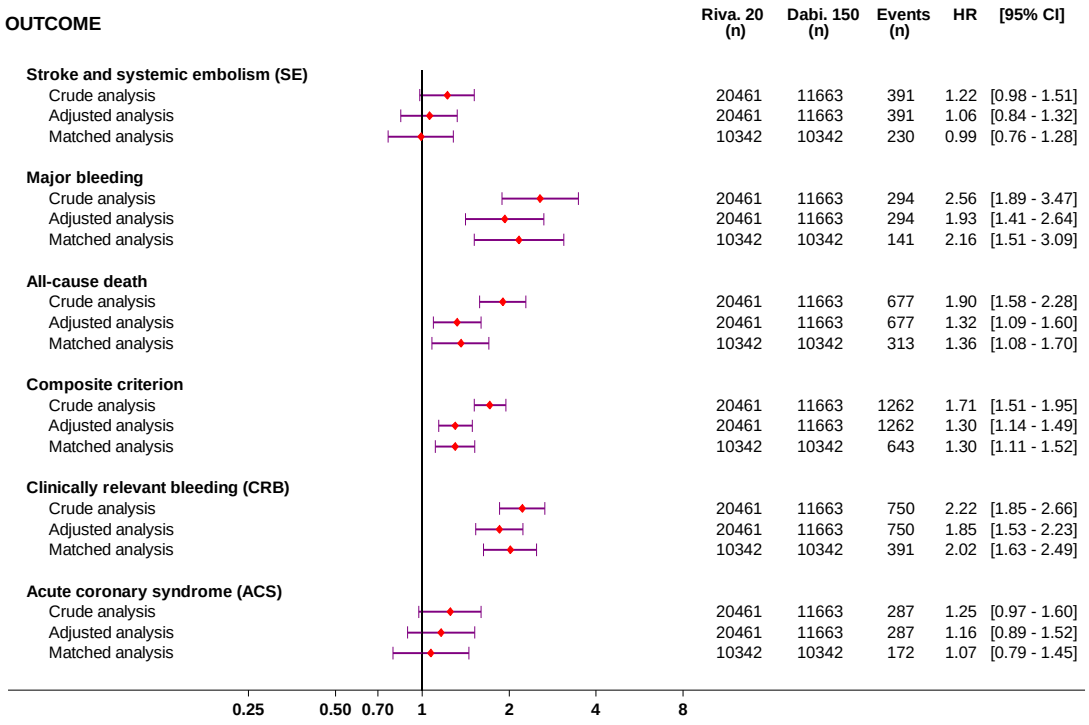


Figure 17. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95%CI of outcome details for the specific population and a 60-day grace period for drug discontinuation

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 (Appendix 1-10, 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



Sensitive population and a 60-day grace period

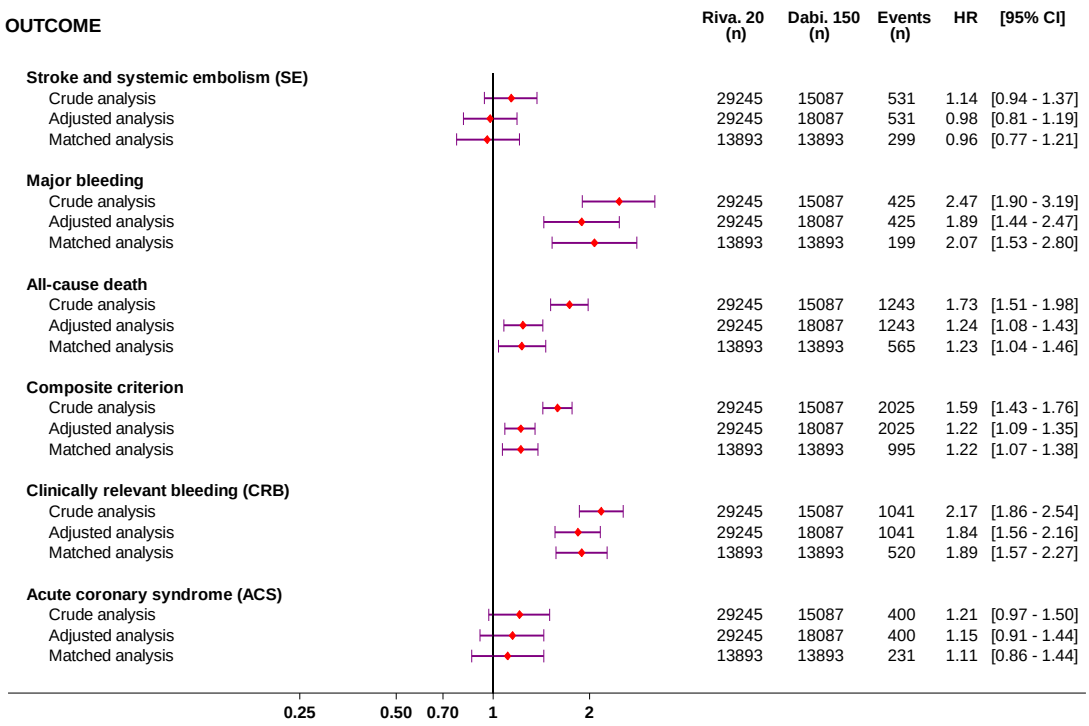


Figure 18. Rivaroxaban 20 mg versus dabigatran 150 mg: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period

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

- **For stroke and systemic embolism,**
  - At least 25% non-significantly lower with rivaroxaban for 75-79 years old (28%), CHA_2DS_2-VASc score 3 (28%), and the second quintile of logit hdPS (34%),
  - Between 10% and 24% non-significantly lower for < 65 years old (23%), vascular disease history (14%), HAS-BLED scores 0-1 (12%), and the last quintile of logit hdPS (20%),
  - Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.03), male (0.99), 65-69 years old (1.09), CHA_2DS_2-VASc scores 2 and ≥ 4 (1.03 and 1.10, respectively), hypertension (0.93), diabetes mellitus (0.99), age ≥ 75 years as CHA_2DS_2-VASc risk factor (0.93), HAS-BLED scores 2-3 (1.06), and the first quintile of logit hdPS (1.07),
  - Between 10% and 24% non-significantly lower with dabigatran for female (17% i.e. inverse of 1.20; [1-(1/1.20)]), CHA_2DS_2-VASc scores 0-1 (17%), congestive heart failure (15%), stroke or TIA history (12%), age 65-74 years as CHA_2DS_2-VASc risk factor (22%), and the third quintile of logit hdPS (21%),
  - At least 25% lower with dabigatran for 70-74 and ≥ 80 years old (35% and 36%, respectively), HAS-BLED scores > 3 (25%), the fourth quintile of logit hdPS (53%), 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 0.88 to 1.33 for scores 0-1 to scores > 3 HR, and no clear systematic variation for the other factors;
- **For major bleeding,**
  - At least 25% lower with dabigatran for all matched patients (53%), male and female (51% and 60%, respectively), all age classes (73%, 38%, 66%, 40% and 39%, respectively), all CHA_2DS_2-VASc scores (58%, 47%, 50% and 57%, respectively), congestive heart failure (52%), hypertension (60%), diabetes mellitus (59%), stroke or TIA history (47%), vascular disease history (57%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (56% and 39%, respectively), all HAS-BLED scores (55%, 55% and 37%, respectively), all quintiles (64%, 50%, 45%, 70% and 38%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - All were at least 37% lower with dabigatran,
  - None lower with rivaroxaban,
  - With a gradient for HAS-BLED, from 1.59 to 2.21 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For clinically relevant bleeding,**
  - At least 25% lower with dabigatran for all matched patients (50%), male and female (48% and 58%, respectively), all age classes (57%, 60%, 48%, 38% and 45%, respectively), all CHA_2DS_2-VASc scores (54% for all, except for CHA_2DS_2-VASc score 3, 34%), congestive heart failure (52%), hypertension (50%), diabetes mellitus (49%), stroke or TIA history (43%), vascular disease history (47%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (53% and 40%, respectively), all HAS-BLED scores (56%, 46% and 47%, respectively), all quintiles of logit hdPS (52%, 48%, 47%, 58% and 45%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 49**),
  - All were at least 34% lower with dabigatran,
  - None lower with rivaroxaban,
  - Without clear systematic variation;

- **For death,**
  - Between 10% and 24% lower with dabigatran for all matched patients (23%), male (18%), < 65, 65-69 and 75-79 years old (12%, 12% and 15%, respectively), CHA_2DS_2-VASc scores 0-1, 2 and 3 (15%, 20% and 15%, respectively), vascular disease history (11%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (21%), HAS-BLED scores 0-1 and 2-3 (16% and 22%, respectively), the two first and fourth quintiles (10%, 17% and 10%, 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 (38%), 70-74 and ≥ 80 years old (47% and 31%, respectively), CHA_2DS_2-VASc scores ≥ 4 (38%), congestive heart failure (36%), hypertension (34%), diabetes mellitus (33%), stroke or TIA history (31%), age 65-74 years as CHA_2DS_2-VASc risk factor (32%), HAS-BLED scores > 3 (50%), the third and last quintiles (35% and 32%, 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,
  - With a gradient for HAS-BLED, from 1.19 to 2.02 for scores 0-1 to scores > 3 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 < 65 and 75-79 years old (1.09 and 1.06, respectively), CHA_2DS_2-VASc score 3 (1.10), vascular disease history (1.08), and the second quintile of logit hdPS (0.95),
  - Between 10% and 24% lower with dabigatran for all matched patients (21%), male (16%), 65-69 and ≥ 80 years old (13% and 22%, respectively), CHA_2DS_2-VASc scores 0-1 and 2-3 (21% for both), stroke or TIA history (19%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (12%), HAS-BLED scores 0-1 and 2-3 (15% and 21%, respectively), the first and last quintiles of logit hdPS (17% and 15%, 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 (36%), 70-74 years old (47%), CHA_2DS_2-VASc scores ≥ 4 (29%), congestive heart failure (32%), hypertension (26%), diabetes mellitus (28%), age 65-74 years as CHA_2DS_2-VASc risk factor (33%), HAS-BLED scores > 3 (37%), the third and fourth quintiles of logit hdPS (33% and 36%, 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,
  - With a gradient for HAS-BLED, from 1.18 to 1.59 for scores 0-1 to scores > 3 HR and no clear systematic variation for the other factors;
- **For ACS,**
  - At least 25% lower with rivaroxaban for stroke or TIA history (50%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (27%), the last quintile (48%), and significantly when there were enough patients and events to reach statistical power,
  - Between 10% and 24% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc scores 0-1 and 3 (11% and 16%, respectively), and the third quintile of logit hdPS (20%),
  - Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.07), male (1.06), CHA_2DS_2-VASc scores ≥ 4 (0.99), hypertension (1.01), and HAS-BLED scores 2-3 (1.02),
  - Between 10% and 24% non-significantly lower with dabigatran for female (12%), < 65, 65-69, 70-74 and 75-79 years old (19%, 15%, 15% and 17%, respectively), diabetes mellitus (24%), vascular disease history (13%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (15%),
  - At least 25% non-significantly lower with dabigatran for CHA_2DS_2-VASc score 2 (40%), congestive heart failure (35%), HAS-BLED scores 0-1 (29%), the two first and fourth quintiles (34%, 45% and 35%, respectively),
  - Without clear systematic variation.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main outcomes (SSE, major bleeding, death) and two of the three secondary outcomes (CRB and composite criterion) with some variations of the 95%CI, while the risk of ACS was significantly lower with dabigatran (HR: 1.57 [1.15 to 2.14]) (**Table 48**).

For the 2013-2014 matched patients at one-year, HR was similar with some variations of the 95%CI for death, a little better with rivaroxaban but also not significant for SSE, and with a lower difference for major bleeding but always in favour of dabigatran. It was similar with some variations of the 95%CI for CRB, and the composite criterion, and also with a lower difference for ACS with dabigatran (HR: 1.35 [1.05 to 1.75]) (**Table 48**).

Table 48. Rivaroxaban 20 mg versus dabigatran 150 mg, specific population, and a 60-day grace period for drug discontinuation: Hazard ratio (HR) and 95%CI of main and secondary outcomes at 1-year and at 2-year for the 2013 matched patients, and at 1-year for the 2013-2014 matched patients

	Matched patients of specific populations		
	New users in 2013		New users in 2013-2014
	Riva. 20 vs Dabi. 150 at 1-year n = 10 402	Riva. 20 vs Dabi. 150 at 2-year n = 10 342	Riva. 20 vs Dabi. 150 at 1-year n = 15 323
	HR [95%CI]	HR [95%CI]	HR [95%CI]
Stroke and systemic embolism (SSE)	**0.96 [0.73; 1.26]**	**1.03 [0.81; 1.31]**	**0.90 [0.71; 1.13]**
Major bleeding	**2.24 [1.53; 3.30]**	**2.13 [1.53; 2.95]**	**1.74 [1.29; 2.36]**
Clinically relevant bleeding (CRB)	1.95 [1.54; 2.47]	2.00 [1.64; 2.44]	1.78 [1.46; 2.16]
Death (all causes)	**1.36 [1.08; 1.71]**	**1.30 [1.08; 1.57]**	**1.28 [1.06; 1.54]**
Composite criterion (SSE, major bleeding, and death)	**1.31 [1.11; 1.54]**	**1.26 [1.10; 1.45]**	**1.21 [1.05; 1.38]**
Acute coronary syndrome (ACS)	**1.57 [1.15; 2.14]**	**1.07 [0.81; 1.42]**	**1.35 [1.05; 1.75]**

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	Dabigatran 150 mg	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	10 342	10 342	1.03 [0.81 ; 1.31]	2.13 [1.53 ; 2.95]	2.00 [1.64 ; 2.44]	1.30 [1.08 - 1.57]	1.26 [1.10 - 1.45]	1.07 [0.81 ; 1.42]
Gender								
Male	7 178	7 178	0.99 [0.75 ; 1.29]	2.05 [1.42 ; 2.95]	1.91 [1.52 ; 2.39]	1.22 [0.98 - 1.52]	1.19 [1.02 - 1.39]	1.06 [0.77 ; 1.46]
Female	3 164	3 164	1.20 [0.72 ; 1.99]	2.50 [1.22 ; 5.15]	2.36 [1.56 ; 3.58]	1.62 [1.09 - 2.42]	1.57 [1.17 - 2.10]	1.13 [0.63 ; 2.03]
Age (years)								
<65	3 915	3 963	0.77 [0.49 ; 1.21]	3.73 [1.39 ; 9.99]	2.35 [1.52 ; 3.62]	1.13 [0.78 - 1.63]	1.09 [0.83 - 1.43]	1.24 [0.76 ; 2.03]
[65-70[	2 437	2 357	1.09 [0.66 ; 1.78]	1.60 [0.79 ; 3.27]	2.49 [1.56 ; 3.97]	1.13 [0.74 - 1.74]	1.15 [0.85 - 1.56]	1.17 [0.67 ; 2.06]
[70-75[	2 021	2 061	1.54 [0.94 ; 2.55]	2.95 [1.53 ; 5.67]	1.93 [1.30 ; 2.86]	1.89 [1.23 - 2.90]	1.90 [1.41 - 2.55]	1.17 [0.62 ; 2.20]
[75-80[	1 510	1 487	0.72 [0.39 ; 1.31]	1.68 [0.87 ; 3.23]	1.61 [1.08 ; 2.40]	1.18 [0.79 - 1.78]	1.06 [0.78 - 1.44]	1.21 [0.61 ; 2.37]
≥ 80	459	474	1.56 [0.68 ; 3.60]	1.65 [0.72 ; 3.75]	1.81 [0.99 ; 3.33]	1.44 [0.84 - 2.48]	1.29 [0.84 - 1.97]	-
CHA_2DS_2-VASc score								
0-1	4 226	4 246	1.20 [0.73 ; 1.96]	2.39 [1.14 ; 4.99]	2.19 [1.48 ; 3.24]	1.18 [0.81 - 1.73]	1.26 [0.95 - 1.67]	0.89 [0.52 ; 1.53]
2	2 721	2 612	1.03 [0.64 ; 1.65]	1.89 [0.99 ; 3.59]	2.17 [1.45 ; 3.24]	1.25 [0.84 - 1.85]	1.27 [0.96 - 1.68]	1.66 [0.97 ; 2.83]
3	1 772	1 806	0.72 [0.39 ; 1.35]	2.00 [0.97 ; 4.10]	1.51 [0.99 ; 2.31]	1.18 [0.79 - 1.75]	1.10 [0.81 - 1.51]	0.84 [0.46 ; 1.53]
≥ 4	1 623	1 678	1.10 [0.74 ; 1.64]	2.31 [1.31 ; 4.08]	2.16 [1.48 ; 3.15]	1.62 [1.14 - 2.30]	1.41 [1.10 - 1.80]	0.99 [0.54 ; 1.83]
Risk factors								
Congestive heart failure	1 162	1 207	1.18 [0.60 ; 2.31]	2.08 [0.94 ; 4.64]	2.10 [1.21 ; 3.64]	1.57 [1.08 - 2.29]	1.48 [1.09 - 2.01]	1.54 [0.71 ; 3.32]
Hypertension	3 204	3 245	0.93 [0.64 ; 1.36]	2.49 [1.50 ; 4.12]	1.99 [1.46 ; 2.72]	1.51 [1.13 - 2.01]	1.35 [1.09 - 1.67]	1.01 [0.66 ; 1.56]
Diabetes mellitus	2 204	2 158	0.99 [0.66 ; 1.48]	2.43 [1.36 ; 4.34]	1.97 [1.38 ; 2.83]	1.49 [1.07 - 2.07]	1.38 [1.09 - 1.75]	1.32 [0.83 ; 2.12]
Stroke or TIA history	805	861	1.13 [0.71 ; 1.79]	1.88 [0.84 ; 4.20]	1.76 [1.03 ; 3.00]	1.45 [0.84 - 2.53]	1.23 [0.88 - 1.73]	0.50 [0.17 ; 1.47]
Vascular disease history	944	982	0.86 [0.53 ; 1.39]	2.34 [1.02 ; 5.34]	1.87 [1.11 ; 3.13]	1.12 [0.70 - 1.82]	1.08 [0.79 - 1.49]	1.15 [0.65 ; 2.06]
Age 65-74 years	4 458	4 418	1.29 [0.91 ; 1.83]	2.25 [1.39 ; 3.62]	2.13 [1.58 ; 2.89]	1.47 [1.09 - 1.98]	1.49 [1.21 - 1.84]	1.17 [0.77 ; 1.79]
Age ≥75 years	1 969	1 961	0.93 [0.58 ; 1.50]	1.65 [0.99 ; 2.76]	1.66 [1.19 ; 2.32]	1.26 [0.91 - 1.75]	1.13 [0.88 - 1.45]	0.73 [0.40 ; 1.32]
HAS-BLED score								
0-1	5 315	5 373	0.88 [0.59 ; 1.32]	2.21 [1.21 ; 4.06]	2.27 [1.60 ; 3.22]	1.19 [0.87 - 1.64]	1.18 [0.93 - 1.49]	1.40 [0.86 ; 2.27]
2-3	4 759	4 688	1.06 [0.77 ; 1.47]	2.20 [1.42 ; 3.40]	1.86 [1.44 ; 2.41]	1.29 [1.00 - 1.66]	1.26 [1.04 - 1.51]	1.02 [0.72 ; 1.46]
>3	268	281	1.33 [0.64 ; 2.77]	1.59 [0.67 ; 3.76]	1.89 [0.93 ; 3.86]	2.02 [0.96 - 4.25]	1.59 [0.99 - 2.55]	-
Quintiles of logit (hdPS)								
Quintile 1	1 980	2 156	1.07 [0.60 ; 1.90]	2.76 [1.15 ; 6.63]	2.10 [1.30 ; 3.39]	1.11 [0.71 - 1.74]	1.21 [0.87 - 1.69]	1.51 [0.72 ; 3.16]
Quintile 2	2 092	2 045	0.66 [0.37 ; 1.15]	2.02 [0.77 ; 5.32]	1.92 [1.13 ; 3.28]	1.20 [0.72 - 2.00]	0.95 [0.67 - 1.36]	1.82 [0.95 ; 3.49]
Quintile 3	2 072	2 065	1.26 [0.70 ; 2.25]	1.81 [0.87 ; 3.74]	1.89 [1.23 ; 2.91]	1.53 [0.94 - 2.47]	1.49 [1.06 - 2.09]	0.80 [0.45 ; 1.43]
Quintile 4	2 105	2 032	2.12 [1.14 ; 3.97]	3.33 [1.52 ; 7.30]	2.38 [1.51 ; 3.75]	1.11 [0.73 - 1.70]	1.56 [1.13 - 2.16]	1.53 [0.79 ; 2.98]
Quintile 5	2 093	2 044	0.80 [0.52 ; 1.23]	1.60 [0.92 ; 2.77]	1.81 [1.25 ; 2.62]	1.48 [1.06 - 2.06]	1.18 [0.92 - 1.50]	0.52 [0.28 ; 0.97]

10.4.4. Rivaroxaban 15 mg versus VKA comparison of the 2-year risk of outcomes during the exposure period (on treatment)

For matched patient, the risk at 2-year was significantly lower with rivaroxaban 15 mg than VKA for two main outcomes: major bleeding (HR: 0.80 [0.69 to 0.93]), death (0.79 [0.73 to 0.85]), and not statistically different for SSE (1.14 [0.97 to 1.34]). It was also significantly lower with rivaroxaban for CRB (0.88 [0.79 to 0.99]) and the composite criterion (0.83 [0.77 to 0.88]), and almost the same for ACS (1.03 [0.85 to 1.26]) (**Table 50** and **Figure 19**; Appendix 1-6, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101, 105 to 109, 167 to 171).

The two-year hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figure 19**). The complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes of matched and all patients adjusted analyses (Appendix 1-6, Tables 196 to 201).

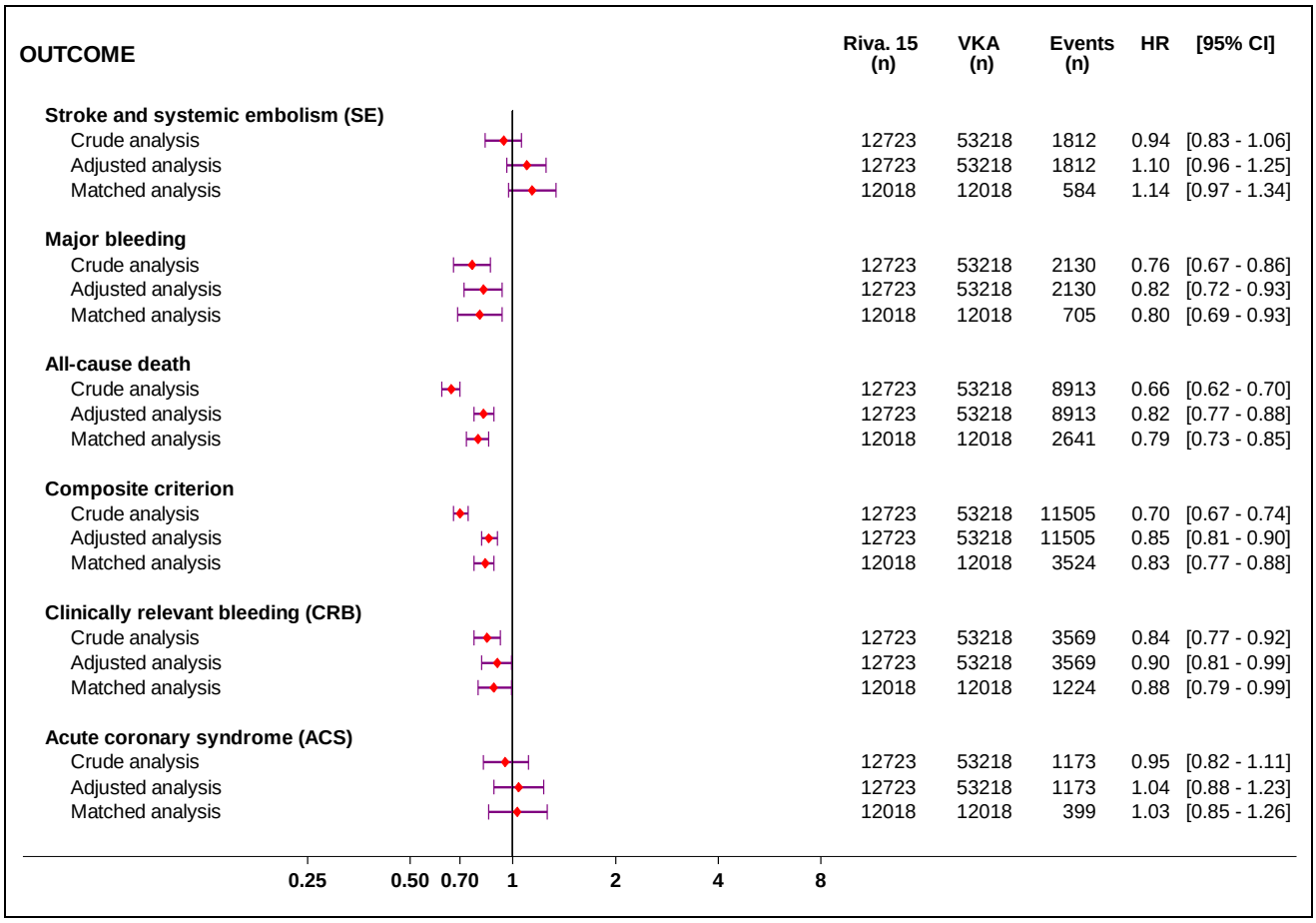
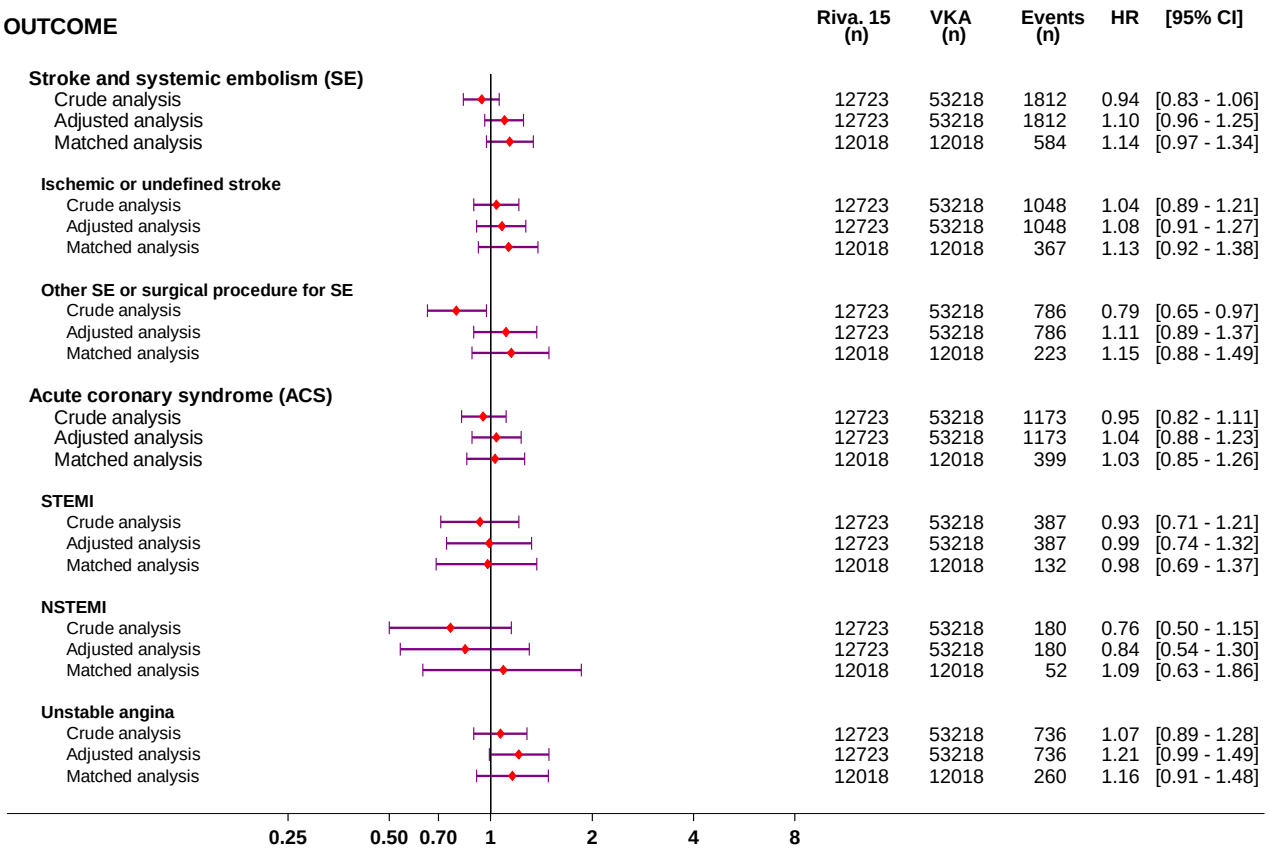


Figure 19. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban 15 mg for other critical organ or site bleeding (HR: 0.69 [0.50 to 0.94]) and other bleeding (0.74 [0.60 to 0.93]), but not for haemorrhagic stroke, GI bleeding and urogenital bleeding (0.83 [0.64 to 1.07], 1.02 [0.84 to 1.25] and 1.03 [0.77 to 1.39], respectively). For other individual events of major outcomes, the risk was not different between groups: ischemic or undefined stroke (1.13 [0.92 to 1.38]), other SE or surgical procedure for SE (1.15 [0.88 to 1.49]), STEMI (0.98 [0.69 to 1.37]), NSTEMI (1.09 [0.63 to 1.86]) and unstable angina (1.16 [0.91 to 1.48]) (**Figure 20**; Appendix 1-6, Tables 57 to 59, 63 to 65, 125 to 127, 143 to 145, 149 to 151, 155 to 157, 161 to 163, 181 to 183, 187 to 189, 193 to 195).



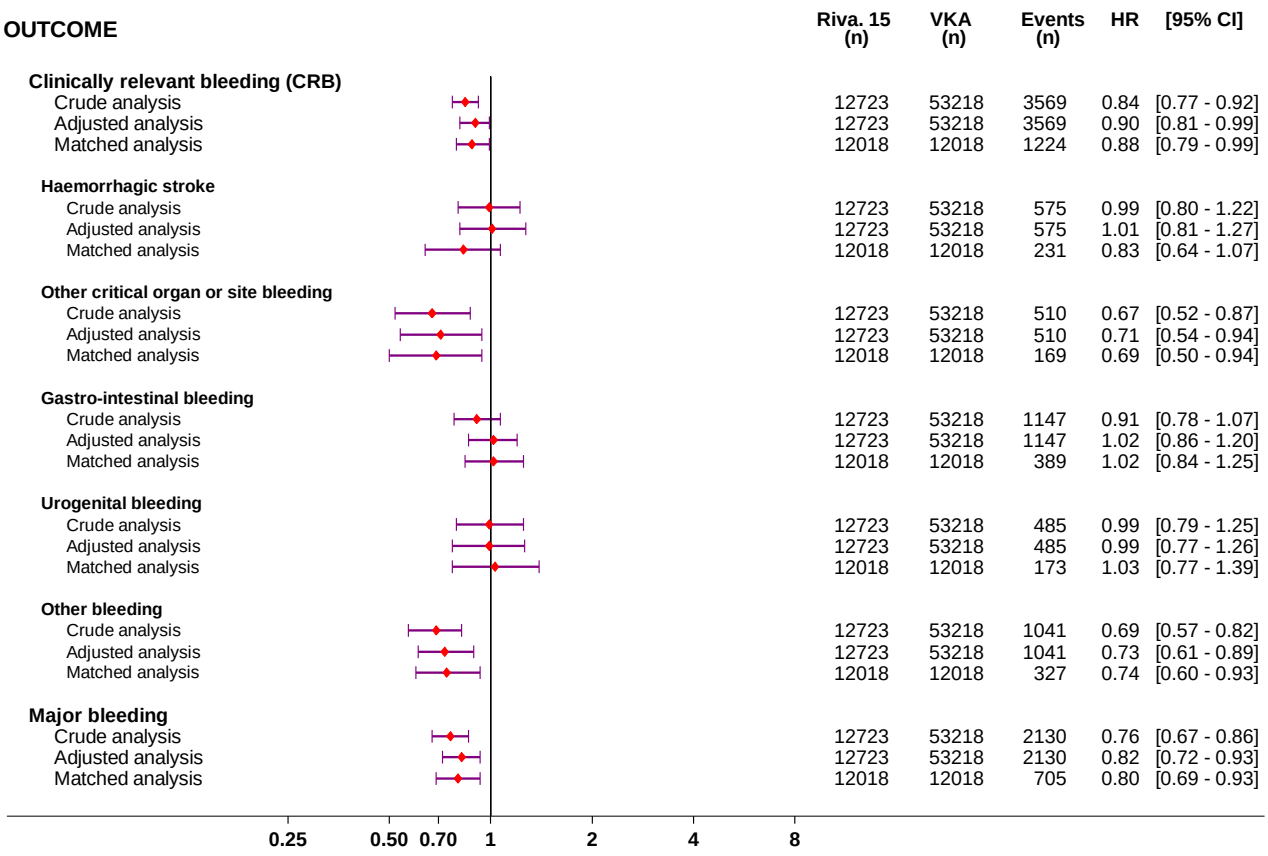
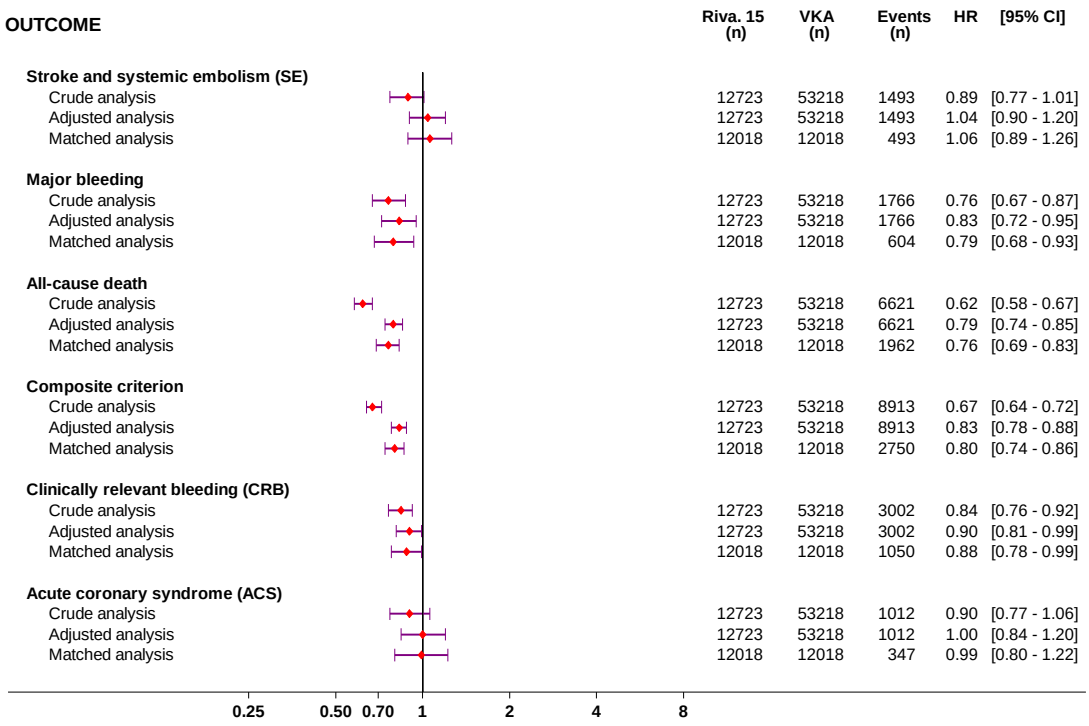


Figure 20. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95%CI of outcome details for the specific population and a 60-day grace period for drug discontinuation

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 (Appendix 1-11, 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



Sensitive population and a 60-day grace period

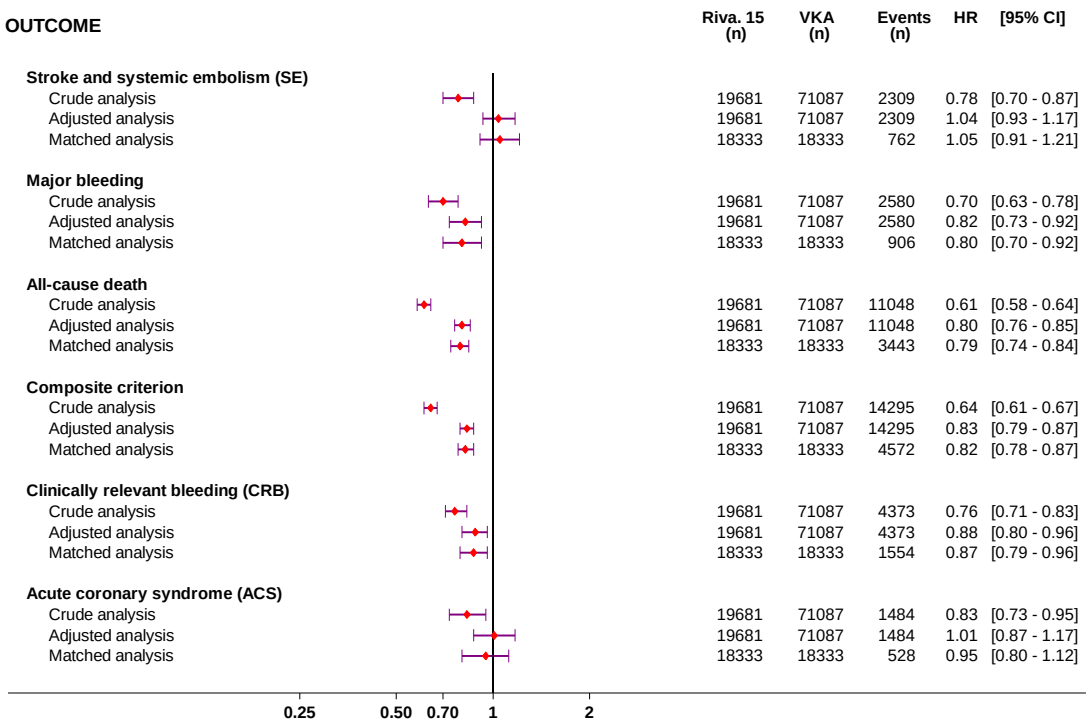


Figure 21. Rivaroxaban 15 mg versus VKA: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period

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

- **For stroke and systemic embolism,**
  - Between 10% and 24% non-significantly lower with rivaroxaban for 70-74 years old (17%), and the third quintile of logit hdPS (10%),
  - Similar with HR between 0.91 and 1.10 for female (1.06), < 65 years old (0.93), CHA_2DS_2-VASc score 2 (0.95), congestive heart failure (1.09), vascular disease history (1.05), and the second and fourth quintiles of logit hdPS (1.02 and 1.08, respectively),
  - Between 10% and 24% non-significantly lower with VKA for all matched patients (12%), male (19%), 75-79 and ≥ 80 years old (10% and 15%, respectively), CHA_2DS_2-VASc scores 3 and ≥ 4 (11% and 16%, respectively), hypertension (10%), diabetes mellitus (24%), stroke or TIA history (17%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (15% and 13%, respectively), HAS-BLED scores 2-3 and > 3 (12% for both), and the last quintile of logit hdPS (16%),
  - At least 25% significantly lower with VKA for the first quintile of logit hdPS (38%),
  - Without clear systematic variation;
- **For major bleeding,**
  - At least 25% lower with rivaroxaban for 65-69 and 70-74 years old (53% and 25%, respectively), CHA_2DS_2-VASc scores 0-1 and 2 (38% and 37%, respectively), age 65-74 years as CHA_2DS_2-VASc risk factor (35%), HAS-BLED scores > 3 (44%), the second quintile of logit hdPS (47%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Between 10% and 24% lower with rivaroxaban for all matched patients (20%), male and female (23% and 15%, respectively), ≥ 80 years old (22%), CHA_2DS_2-VASc scores 3 and ≥ 4 (15% for both), hypertension (21%), diabetes mellitus (19%), stroke or TIA history (15%), vascular disease history (12%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (17%), HAS-BLED scores 2-3 (19%), the fourth quintile of logit hdPS (22%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Similar with HR between 0.91 and 1.10 for < 65 and 75-79 years old (1.05 and 1.06, respectively), and the first, third and last quintiles of logit hdPS (0.95, 0.95 and 0.92, respectively),
  - Between 10% and 24% non-significantly lower with VKA for congestive heart failure (10%) and HAS-BLED scores 0-1 (12%),
  - With a gradient for HAS-BLED, from 0.56 to 1.14 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For clinically relevant bleeding,**
  - At least 25% lower with rivaroxaban for 65-69 years old (32%), CHA_2DS_2-VASc scores 0-1 (48%), HAS-BLED scores > 3 (25%), the second quintile of logit hdPS (26%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Between 10% and 24% non-significantly lower with rivaroxaban for all matched patients (12%), female (15%), < 65, 70-74 and ≥ 80 years old (18%, 18% and 11%, respectively), CHA_2DS_2-VASc scores 2 and 3 (23% and 15%, respectively), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (23% and 10%, respectively), HAS-BLED scores 0-1 (13%), and the two last quintiles of logit hdPS (16% and 10%, respectively),
  - Similar with HR between 0.91 and 1.10 for male (0.91), 75-79 years old (0.95), CHA_2DS_2-VASc scores ≥ 4 (0.96), hypertension (0.94), diabetes mellitus (0.95), stroke or TIA history (0.97), vascular disease history (0.91), HAS-BLED scores 2-3 (0.92), and the first and third quintiles of logit hdPS (0.94 and 1.01, respectively),
  - Between 10% and 24% non-significantly lower with VKA for congestive heart failure (17%),
  - With a gradient for CHA_2DS_2-VASc, from 0.52 to 0.96 for scores 0-1 to scores ≥ 4, and no clear systematic variation for the other factors;

- **For death,**
  - At least 25% significantly lower with rivaroxaban for diabetes mellitus (25%), and the two last quintiles of logit hdPS (25% and 33%, respectively),
  - Between 10% and 24% lower with rivaroxaban for all matched patients (21%), male and female (18% and 24%, respectively), 75-79 and ≥ 80 years old (14% and 23%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (16%, 23% and 22%, respectively), congestive heart failure (21%), hypertension (19%), stroke or TIA history (14%), vascular disease history (19%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (22%), all HAS-BLED scores (24%, 20% and 22%, respectively), the three first quintiles of logit hdPS (15%, 18% and 20%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Similar with HR between 0.91 and 1.10 for 65-69 and 70-74 years old (0.94 for both), and age 65-74 years as CHA_2DS_2-VASc risk factor (0.94),
  - Between 10% and 24% non-significantly lower with VKA for < 65 years old (13%),
  - At least 25% non-significantly lower with VKA for CHA_2DS_2-VASc scores 0-1 (33%),
  - With a gradient for quintiles of logit hdPS, from 0.67 to 0.85 for the last to the first quintile 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% lower with rivaroxaban for all matched patients (17%), male and female (16% and 19%, respectively), 70-74 and ≥ 80 years old (14% and 19%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (20%, 18% and 16%, respectively), congestive heart failure (15%), hypertension (15%), diabetes mellitus (17%), stroke or TIA history (10%), vascular disease history (13%), age 65-74 and ≥ 75 years as CHA_2DS_2-VASc risk factors (12% and 17%, respectively), all HAS-BLED scores (11%, 17% and 20%, respectively), the four last quintiles of logit hdPS (21%, 17%, 20% and 24%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Similar with HR between 0.91 and 1.10 for < 65, 65-69 and 75-79 years old (1.07, 0.92 and 0.93, respectively), and the first quintile (0.95),
  - Between 10% and 24% non-significantly lower with VKA for CHA_2DS_2-VASc scores 0-1 (15%),
  - With a weak gradient for HAS-BLED, from 0.80 to 0.89 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors;
- **For ACS,**
  - At least 25% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc score 3 (32%), HAS-BLED scores 0-1 and > 3 (30% and 32%, respectively),
  - Between 10% and 24% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc scores 0-1 (23%), stroke or TIA history (21%), and the third and last quintiles of logit hdPS (14% and 22%, respectively),
  - Similar with HR between 0.91 and 1.10 for all matched patients (1.03), male and female (1.09 and 0.96, respectively), 75-79 and ≥ 80 years old (1.0 and 0.93, respectively), CHA_2DS_2-VASc score 2 (1.08), age ≥ 75 years as CHA_2DS_2-VASc risk factor (0.95), and the second and fourth quintiles of logit hdPS (1.06 and 1.02, respectively),
  - Between 10% and 24% non-significantly lower with VKA for CHA_2DS_2-VASc scores ≥ 4 (22%), congestive heart failure (17%), hypertension (13%), and HAS-BLED scores 2-3 (16%),
  - At least 25% lower with VKA for < 65, 65-69 and 70-74 years old (35%, 35% and 25%, respectively), diabetes mellitus (25%), vascular disease history (38%), age 65-74 years as CHA_2DS_2-VASc risk factor (28%), the first quintile (35%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 51**),
  - Without clear systematic variation.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for SSE, death, as well as for major bleeding but with a non-significant 95%CI (HR: 0.90 [0.75 to 1.07]. It was also the same for the composite criterion, as well as for CRB but with a non-significant 95%CI (0.92 [0.81 to 1.05]), and somewhat different but yet not significant for ACS (0.92 [0.74 to 1.15]) (**Table 50**).

For the 2013-2014 matched patients at one-year, HR and 95%CI were in the same range for two of the three main outcomes (major bleeding and death), and a point estimate close to 1 for SSE. HR and 95%CI were also in the same range for CRB and the composite criterion, and a difference at the significant threshold for ACS in favour of rivaroxaban (HR: 0.85 [0.73 to 1.00]) (**Table 50**).

Table 50. Rivaroxaban 15 mg versus VKA, specific population, and a 60-day grace period for drug discontinuation: Hazard ratio (HR) and 95%CI of main and secondary outcomes at 1-year and at 2-year for the 2013 matched patients, and at 1-year for the 2013-2014 matched patients

	Matched patients of specific populations		
	New users in 2013		New users in 2013-2014
	Riva. 15 vs VKA at 1-year n = 12 077	Riva. 15 vs VKA at 2-year n = 12 018	Riva. 15 vs VKA at 1-year n = 23 314
	HR [95%CI]	HR [95%CI]	HR [95%CI]
Stroke and systemic embolism (SSE)	**1.18 [0.98; 1.42]**	**1.14 [0.97; 1.34]**	**1.05 [0.92; 1.21]**
Major bleeding	**0.90 [0.75; 1.07]**	**0.80 [0.69; 0.93]**	**0.84 [0.74; 0.96]**
Clinically relevant bleeding (CRB)	0.92 [0.81; 1.05]	0.88 [0.79; 0.99]	0.89 [0.81; 0.98]
Death (all causes)	**0.84 [0.77; 0.92]**	**0.79 [0.73; 0.85]**	**0.85 [0.79; 0.90]**
Composite criterion (SSE, major bleeding, and death)	**0.90 [0.83; 0.97]**	**0.83 [0.77; 0.88]**	**0.89 [0.84; 0.94]**
Acute coronary syndrome (ACS)	**0.92 [0.74; 1.15]**	**1.03 [0.85; 1.26]**	**0.85 [0.73; 1.00]**

Table 51. 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	12 018	12 018	1.14 [0.97 ; 1.34]	0.80 [0.69 ; 0.93]	0.88 [0.79 ; 0.99]	0.79 [0.73 - 0.85]	0.83 [0.77 - 0.88]	1.03 [0.85 ; 1.26]
Gender								
Male	5 687	5 687	1.23 [0.98 ; 1.55]	0.77 [0.63 ; 0.95]	0.91 [0.79 ; 1.06]	0.82 [0.73 - 0.91]	0.84 [0.77 - 0.93]	1.09 [0.85 ; 1.41]
Female	6 331	6 331	1.06 [0.84 ; 1.33]	0.85 [0.68 ; 1.05]	0.85 [0.72 ; 1.00]	0.76 [0.68 - 0.84]	0.81 [0.74 - 0.89]	0.96 [0.70 ; 1.30]
Age (years)								
<65	676	681	0.93 [0.35 ; 2.43]	1.05 [0.34 ; 3.18]	0.82 [0.39 ; 1.74]	1.15 [0.61 - 2.18]	1.07 [0.65 - 1.77]	1.55 [0.63 ; 3.80]
[65-70[	696	673	2.39 [0.99 ; 5.77]	0.47 [0.21 ; 1.04]	0.68 [0.39 ; 1.20]	0.94 [0.56 - 1.59]	0.92 [0.61 - 1.37]	1.55 [0.65 ; 3.73]
[70-75[	1 080	1 101	0.83 [0.47 ; 1.48]	0.75 [0.44 ; 1.28]	0.82 [0.55 ; 1.22]	0.94 [0.65 - 1.36]	0.86 [0.65 - 1.15]	1.33 [0.73 ; 2.44]
[75-80[	2 162	2 095	1.11 [0.75 ; 1.65]	1.06 [0.74 ; 1.51]	0.95 [0.73 ; 1.24]	0.86 [0.68 - 1.07]	0.93 [0.78 - 1.12]	1.00 [0.64 ; 1.54]
≥ 80	7 404	7 468	1.17 [0.96 ; 1.42]	0.78 [0.65 ; 0.93]	0.89 [0.78 ; 1.02]	0.77 [0.71 - 0.84]	0.81 [0.75 - 0.88]	0.93 [0.72 ; 1.20]
CHA_2DS_2-VASc score								
0-1	815	785	1.49 [0.61 ; 3.65]	0.62 [0.24 ; 1.59]	0.52 [0.26 ; 1.05]	1.49 [0.81 - 2.75]	1.17 [0.73 - 1.87]	0.77 [0.29 ; 2.10]
2	1 936	1 869	0.95 [0.56 ; 1.60]	0.63 [0.42 ; 0.95]	0.77 [0.58 ; 1.04]	0.84 [0.66 - 1.07]	0.80 [0.65 - 0.98]	1.08 [0.64 ; 1.81]
3	3 301	3 293	1.12 [0.79 ; 1.58]	0.85 [0.65 ; 1.12]	0.85 [0.69 ; 1.05]	0.77 [0.66 - 0.90]	0.82 [0.72 - 0.94]	0.68 [0.46 ; 1.00]
≥ 4	5 966	6 071	1.19 [0.97 ; 1.45]	0.85 [0.69 ; 1.04]	0.96 [0.83 ; 1.12]	0.78 [0.71 - 0.86]	0.84 [0.77 - 0.91]	1.28 [0.99 ; 1.68]
Risk factors								
Congestive heart failure	2 976	2 962	1.09 [0.79 ; 1.51]	1.11 [0.84 ; 1.48]	1.20 [0.96 ; 1.49]	0.79 [0.70 - 0.89]	0.85 [0.76 - 0.95]	1.21 [0.81 ; 1.80]
Hypertension	5 661	5 751	1.11 [0.89 ; 1.38]	0.79 [0.64 ; 0.97]	0.94 [0.81 ; 1.10]	0.81 [0.73 - 0.90]	0.85 [0.77 - 0.93]	1.15 [0.88 ; 1.50]
Diabetes mellitus	2 610	2 632	1.32 [0.98 ; 1.77]	0.81 [0.60 ; 1.10]	0.95 [0.76 ; 1.20]	0.75 [0.64 - 0.87]	0.83 [0.73 - 0.95]	1.33 [0.94 ; 1.89]
Stroke or TIA history	1 378	1 435	1.21 [0.83 ; 1.74]	0.85 [0.57 ; 1.26]	0.97 [0.72 ; 1.30]	0.86 [0.71 - 1.05]	0.90 [0.76 - 1.06]	0.79 [0.43 ; 1.46]
Vascular disease history	2 122	2 158	1.05 [0.79 ; 1.40]	0.88 [0.64 ; 1.21]	0.91 [0.71 ; 1.16]	0.81 [0.69 - 0.96]	0.87 [0.75 - 0.99]	1.62 [1.16 ; 2.26]
Age 65-74 years	1 776	1 774	1.17 [0.73 ; 1.87]	0.65 [0.42 ; 1.00]	0.77 [0.56 ; 1.06]	0.94 [0.70 - 1.27]	0.88 [0.69 - 1.10]	1.39 [0.85 ; 2.29]
Age ≥75 years	9 566	9 563	1.15 [0.97 ; 1.38]	0.83 [0.71 ; 0.97]	0.90 [0.80 ; 1.02]	0.78 [0.72 - 0.85]	0.83 [0.77 - 0.89]	0.95 [0.76 ; 1.18]
HAS-BLED score								
0-1	2 634	2 444	1.38 [0.85 ; 2.25]	1.14 [0.76 ; 1.70]	0.87 [0.65 ; 1.17]	0.76 [0.62 - 0.94]	0.89 [0.75 - 1.07]	0.70 [0.39 ; 1.23]
2-3	8 209	8 386	1.13 [0.94 ; 1.36]	0.81 [0.68 ; 0.97]	0.92 [0.80 ; 1.05]	0.80 [0.73 - 0.88]	0.83 [0.77 - 0.90]	1.19 [0.95 ; 1.50]
>3	1 175	1 188	1.13 [0.74 ; 1.74]	0.56 [0.37 ; 0.86]	0.75 [0.55 ; 1.03]	0.78 [0.63 - 0.96]	0.80 [0.67 - 0.96]	0.68 [0.39 ; 1.21]
Quintiles of logit (hdPS)								
Quintile 1	2 371	2 436	1.62 [1.14 ; 2.31]	0.95 [0.68 ; 1.32]	0.94 [0.74 ; 1.21]	0.85 [0.73 - 0.99]	0.95 [0.83 - 1.08]	1.54 [1.02 ; 2.34]
Quintile 2	2 374	2 433	1.02 [0.72 ; 1.44]	0.53 [0.38 ; 0.75]	0.74 [0.58 ; 0.95]	0.82 [0.69 - 0.96]	0.79 [0.68 - 0.91]	1.06 [0.68 ; 1.67]
Quintile 3	2 409	2 399	0.90 [0.63 ; 1.30]	0.95 [0.67 ; 1.34]	1.01 [0.78 ; 1.32]	0.80 [0.67 - 0.96]	0.83 [0.71 - 0.97]	0.86 [0.56 ; 1.34]
Quintile 4	2 369	2 438	1.08 [0.74 ; 1.56]	0.78 [0.57 ; 1.08]	0.84 [0.65 ; 1.08]	0.75 [0.62 - 0.91]	0.80 [0.68 - 0.93]	1.02 [0.63 ; 1.64]
Quintile 5	2 495	2 312	1.19 [0.80 ; 1.78]	0.92 [0.66 ; 1.29]	0.90 [0.70 ; 1.16]	0.67 [0.55 - 0.82]	0.76 [0.64 - 0.90]	0.78 [0.51 ; 1.20]

10.4.5. Rivaroxaban 15 mg versus dabigatran 110 mg comparison of the 2-year risk of outcomes during the exposure period (on treatment)

For matched patients, the risk at 2-year was significantly higher with rivaroxaban 15 mg than dabigatran 110 mg for two main outcomes: SSE (HR: 1.34 [1.10-1.64]), major bleeding (1.31 [1.08 to 1.59]), and not statistically different between the two groups for death (1.06 [0.96 to 1.17]). It was also significantly higher with rivaroxaban for CRB (1.34 [1.16 to 1.54]) and the composite criterion (1.14 [1.04 to 1.24]), and not statistically different for ACS (1.05 [0.84 to 1.32]) (**Table 52** and **Figure 22**; Appendix 1-7, Tables 49 to 53, 69 to 73, 89 to 93, 97 to 101, 105 to 109, 167 to 171).

The two-year hazard ratios were really similar when all patients were considered with adjusted analysis on gender, age and hdPS in deciles (**Figure 22**). The complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes of matched and all patients adjusted analyses (Appendix 1-7, Tables 196 to 201).

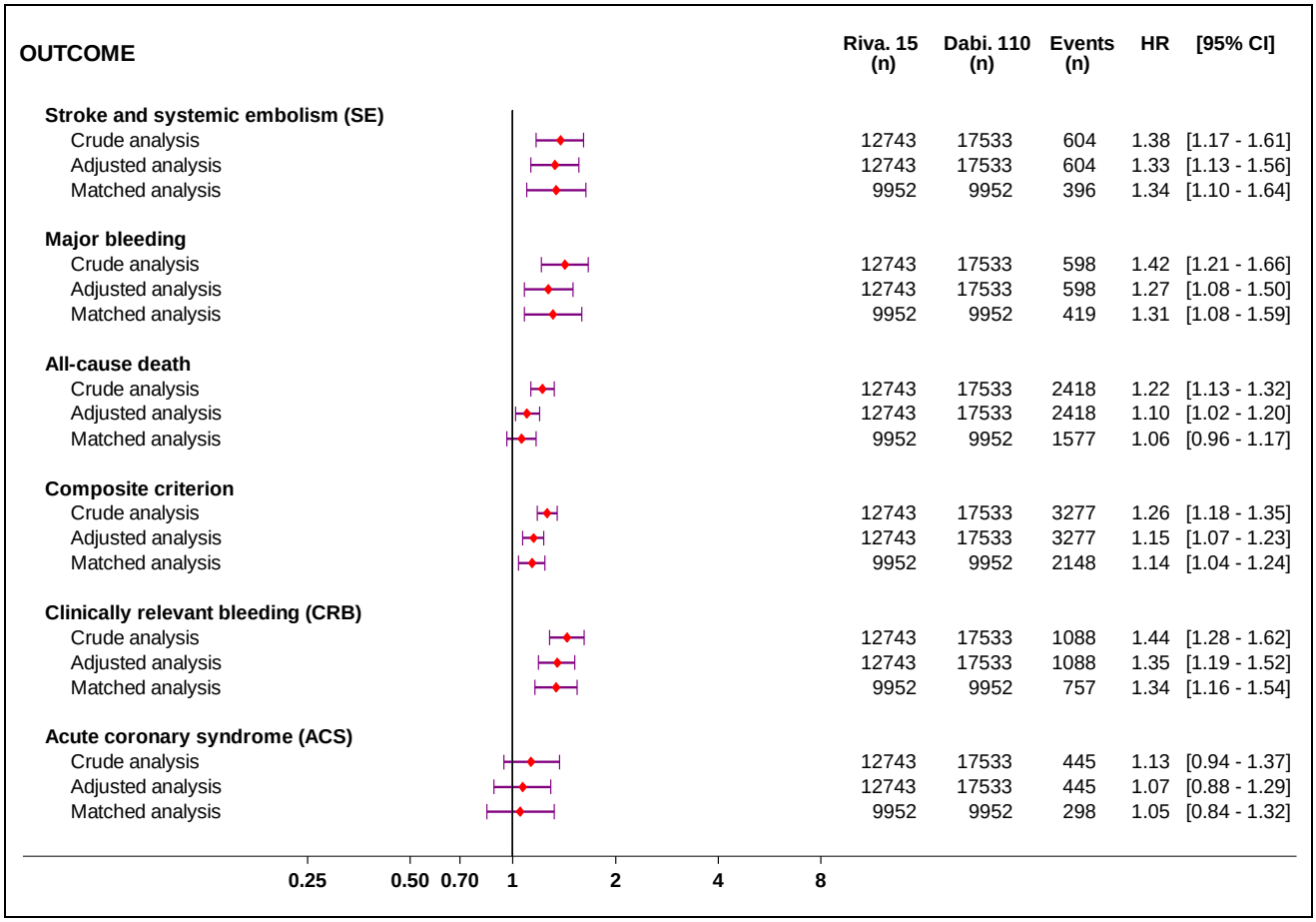
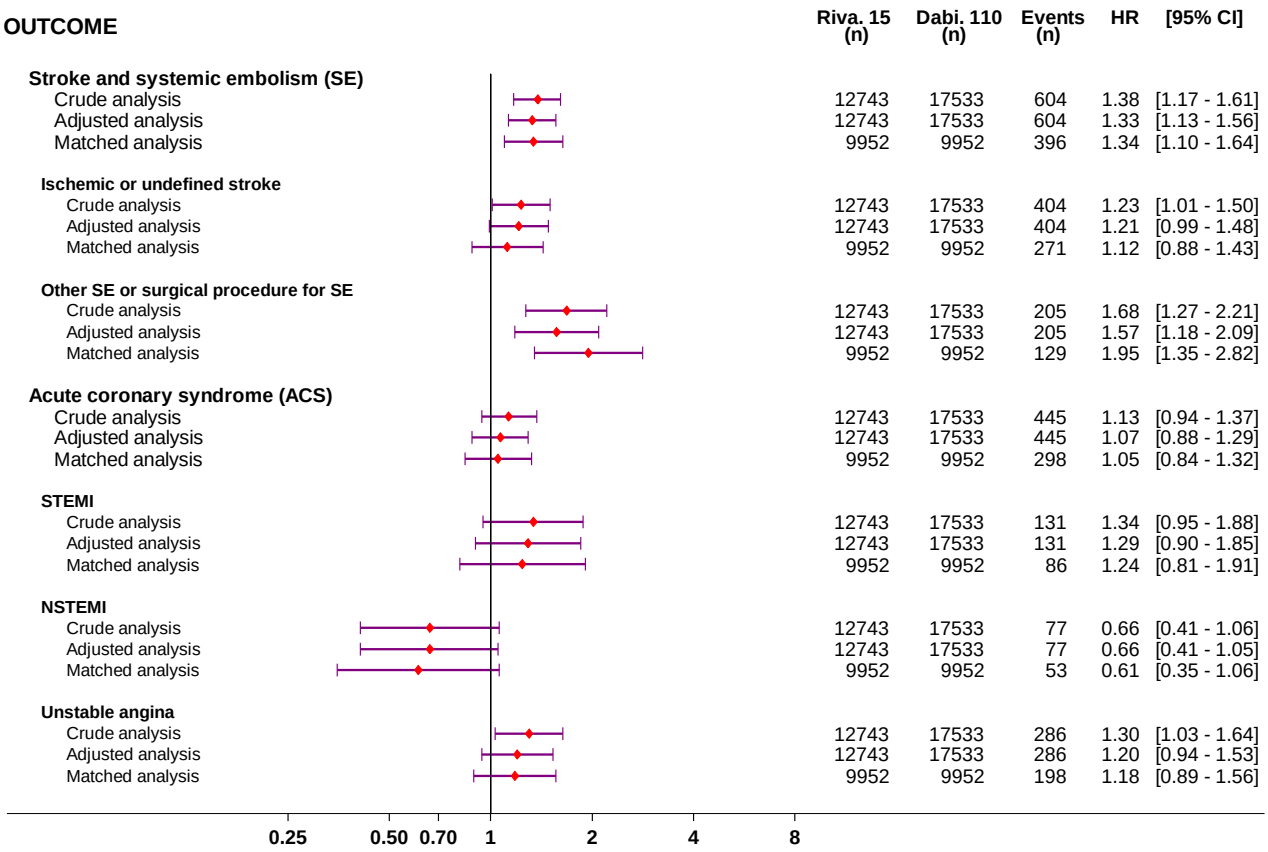


Figure 22. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population and a 60-day grace period for drug discontinuation

For other individual bleeding categories, the risk at 2-year was significantly higher with rivaroxaban 15 mg for haemorrhagic stroke (HR: 2.55 [1.67 to 3.91]), other critical organ or site bleeding (1.75 [1.12 to 2.73]), urogenital bleeding (1.52 [1.03 to 2.23]), and other bleeding (1.81 [1.31 to 2.50]), but not for GI bleeding (0.85 [0.69 to 1.06]). For other individual events of major outcomes, the risk was significantly higher with rivaroxaban for other SE or surgical procedure for SE (1.95 [1.35 to 2.82]), but not for ischemic or undefined stroke (1.12 [0.88 to 1.43]), STEMI (1.24 [0.81 to 1.91]), NSTEMI (0.61 [0.35 to 1.06]), and unstable angina (1.18 [0.89 to 1.56]) (**Figure 23**; Appendix 1-7, Tables 57 to 59, 63 to 65, 125 to 127, 143 to 145, 149 to 151, 155 to 157, 161 to 163, 181 to 183, 187 to 189, 193 to 195).



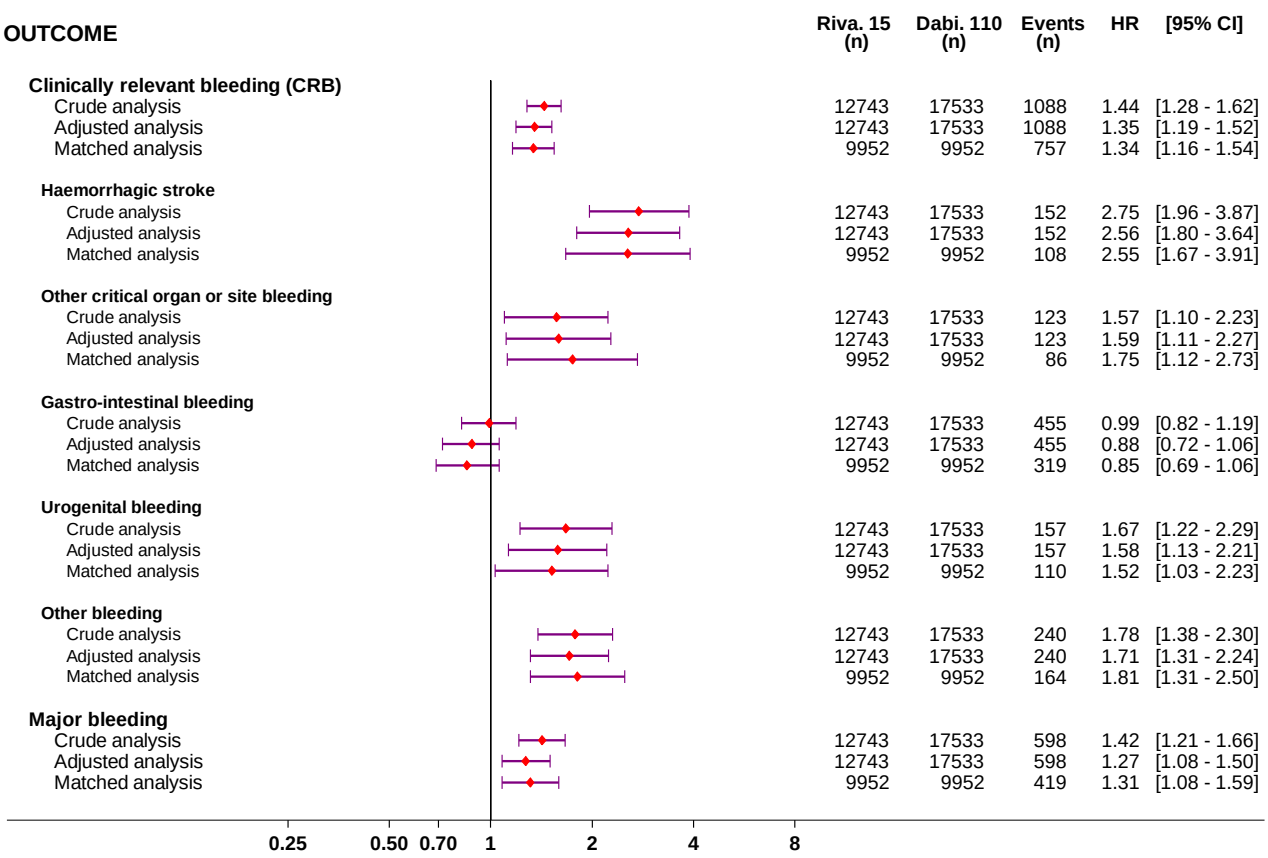
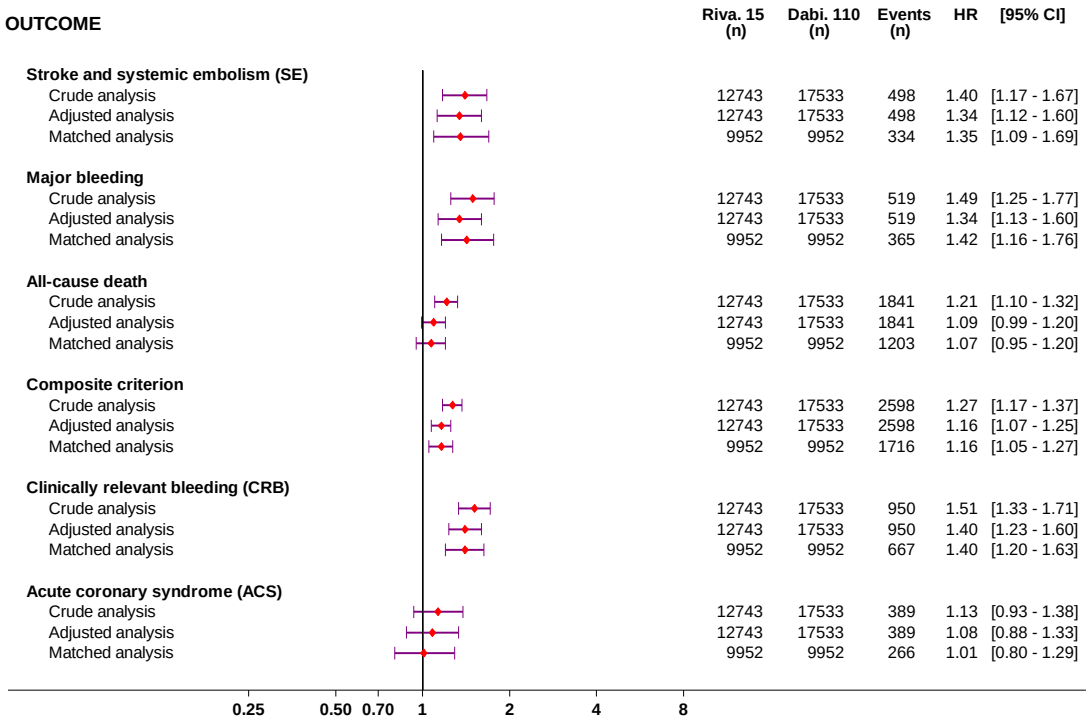


Figure 23. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95%CI of outcome details for the specific population and a 60-day grace period for drug discontinuation

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 (Appendix 1-12, 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



Sensitive population and a 60-day grace period

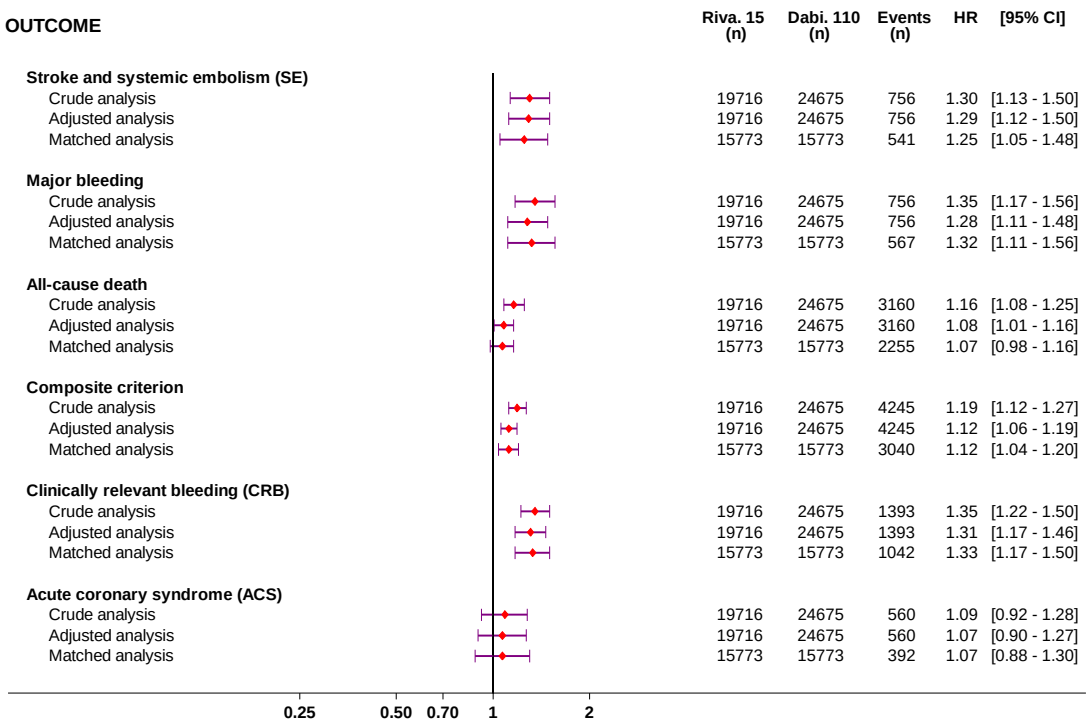


Figure 24. Rivaroxaban 15 mg versus dabigatran 110 mg: Hazard ratio (HR) and 95%CI of main and secondary outcomes for the specific population*30-day grace period and the sensitive population*60-day grace period

For the rivaroxaban 15 mg versus dabigatran 110 mg comparison, stratified analyses for the specific population and a 60-day grace period showed substantial variations of the HR point estimate according to the different subgroups (**Table 53**):

- **For stroke and systemic embolism,**
  - At least 25% non-significantly lower with rivaroxaban for < 65 years old (27%) with very few patients,
  - Relatively similar with HR between 0.91 and 1.10 for stroke or TIA history (1.06), and the first quintile of logit hdPS (1.10),
  - Between 10% and 24% lower with dabigatran for female (12%), 70-74, 75-79 and ≥ 80 years old (19%, 24% and 24%, respectively), CHA_2DS_2-VASc scores 2, 3 and ≥ 4 (19%, 18% and 24%, respectively), congestive heart failure (19%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (24%), HAS-BLED scores 0-1 and > 3 (19% and 24%, respectively), the two last quintiles of logit hdPS (21% and 24%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
  - At least 25% lower with dabigatran for all matched patients (25%), male (38%), 65-69 years old (73%), CHA_2DS_2-VASc scores 0-1 (88%), hypertension (27%), diabetes mellitus (27%), vascular disease history (42%), age 65-74 years as CHA_2DS_2-VASc risk factor (46%), HAS-BLED scores 2-3 (26%), the second and third quintiles (31% and 36%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
  - Without clear systematic variation;
- **For major bleeding,**
  - At least 25% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc scores 0-1 (47%) with very few patients,
  - Relatively similar with HR between 0.91 and 1.10 for < 65 and ≥ 80 years old (0.98 and 1.10, respectively), HAS-BLED scores 0-1 (1.08), and the last quintile of logit hdPS (0.91),
  - Between 10% and 24% lower with dabigatran for all matched patients (24%), female (19%), CHA_2DS_2-VASc scores ≥ 4 (19%), hypertension (22%), vascular disease history (22%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (22%), the second quintile (17%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
  - At least 25% lower with dabigatran for male (29%), 65-69, 70-74 and 75-79 years old (37%, 39% and 65%, respectively), CHA_2DS_2-VASc scores 2 and 3 (31% and 35%, respectively), congestive heart failure (25%), diabetes mellitus (35%), stroke or TIA history (38%), age 65-74 years as CHA_2DS_2-VASc risk factor (38%), HAS-BLED scores 2-3 and > 3 (27% and 26%, respectively), the first, third and fourth quintiles of logit hdPS (29%, 40% and 43%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
  - Without clear systematic variation;
- **For clinically relevant bleeding,**
  - At least 25% non-significantly lower with rivaroxaban for CHA_2DS_2-VASc scores 0-1 (39%) with very few patients,
  - Relatively similar with HR between 0.91 and 1.10 for the last quintile of logit hdPS (0.95),
  - Between 10% and 24% lower with dabigatran for female (21%), < 65 and ≥ 80 years old (18% and 15%, respectively), CHA_2DS_2-VASc scores ≥ 4 (21%), hypertension (23%), diabetes mellitus (17%), vascular disease history (19%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (24%), HAS-BLED scores 0-1 (12%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
  - At least 25% lower with dabigatran for all matched patients (25%), male (29%), 65-69, 70-74 and 75-79 years old (34%, 40% and 53% respectively), CHA_2DS_2-VASc scores 2 and 3 (41% and 30%, respectively), congestive heart failure (26%), stroke or TIA history (44%), age 65-74 years as CHA_2DS_2-VASc risk factor (39%), HAS-BLED scores 2-3 and > 3 (28% and 26%, respectively), the four first quintiles (40%, 32%, 32% and 31%, respectively), and

significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),

- With a gradient for quintiles of logit HdPS, from 0.95 to 1.67 for the last to the first quintile HR, and no clear systematic variation for the other factors;

– **For death,**
- At least 25% non-significantly lower with rivaroxaban for < 65 years old (38%),
- Between 10% and 24% non-significantly lower with rivaroxaban for the fourth quintile (14%),
- Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.06), male and female (1.09 and 1.04, respectively), ≥ 80 years old (1.0), CHA_2DS_2-VASc scores 0-1 and ≥ 4 (0.92 and 0.98, respectively), congestive heart failure (1.0), hypertension (1.01), diabetes mellitus (1.05), vascular disease history (1.07), age ≥ 75 years as CHA_2DS_2-VASc risk factor (1.04), all HAS-BLED scores (1.0, 1.08 and 0.97, respectively), and the last quintile (0.96),
- Between 10% and 24% non-significantly lower with dabigatran for 70-74 years old (19%), CHA_2DS_2-VASc scores 2 and 3 (23% and 14%, respectively), stroke or TIA history (17%), and the three first quintiles (15%, 17% and 15%, respectively),
- At least 25% significantly lower with dabigatran for 65-69 and 75-79 years old (60% and 26%, respectively), and age 65-74 years as CHA_2DS_2-VASc risk factor (33%),
- Without clear systematic variation;

– **For the composite criterion (stroke and systemic embolism, major bleeding and death),**
- At least 25% non-significantly lower with rivaroxaban for < 65 years old (30%),
- Relatively similar with HR between 0.91 and 1.10 for female (1.08), ≥ 80 years old (1.06), CHA_2DS_2-VASc scores ≥ 4 (1.05), congestive heart failure (1.05), hypertension (1.09), HAS-BLED scores > 3 (1.05), and the two last quintiles (1.02 and 1.00, respectively),
- Between 10% and 24% lower with dabigatran for all matched patients (12%), male (17%), 70-74 years old (21%), CHA_2DS_2-VASc scores 0-1 and 3 (14% and 19%, respectively), diabetes mellitus (14%), stroke or TIA history (17%), vascular disease history (18%), age ≥ 75 years as CHA_2DS_2-VASc risk factor (11%), HAS-BLED scores 0-1 and 2-3 (10% and 14%, respectively), the three first quintiles (18%, 22% and 19%, respectively), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
- At least 25% significantly lower with dabigatran for 65-69 and 75-79 years old (62% and 33%, respectively), CHA_2DS_2-VASc score 2 (28%), and age 65-74 years as CHA_2DS_2-VASc risk factor (36%),
- Without clear systematic variation;

– **For ACS,**
- At least 25% non-significantly lower with rivaroxaban for 65-69 years old (39%),
- Between 10% and 24% non-significantly lower with rivaroxaban for hypertension (10%), HAS-BLED scores > 3 (11%), and the two last quintiles (13% and 12%, respectively),
- Relatively similar with HR between 0.91 and 1.10 for all matched patients (1.05), female (0.95), 75-79 and ≥ 80 years old (0.96 and 0.94, respectively), CHA_2DS_2-VASc scores 3 and ≥ 4 (0.92 and 1.04, respectively), congestive heart failure (1.01), diabetes mellitus (1.04), stroke or TIA history (1.07), age ≥ 75 years as CHA_2DS_2-VASc risk factor (0.95), HAS-BLED scores 2-3 (1.03), and the third quintile of logit hdPS (0.91),
- Between 10% and 24% non-significantly lower with dabigatran for male (12%), CHA_2DS_2-VASc score 2 (13%), age 65-74 years as CHA_2DS_2-VASc risk factor (20%), HAS-BLED scores 0-1 (22%), and the first quintile (18%),
- At least 25% lower with dabigatran for < 65 and 70-74 years old (78% and 59%, respectively), CHA_2DS_2-VASc scores 0-1 (56%), vascular disease history (36%), the second quintile (37%), and significantly when there were enough patients and events to reach statistical power (underline in grey on the **Table 53**),
- With a gradient for HAS-BLED, from 0.89 to 1.29 for scores > 3 to scores 0-1 HR, and no clear systematic variation for the other factors.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion) with 95%CI just below the significant threshold for major bleeding (HR: 1.22 [0.98 to 1.51]) (**Table 52**).

For the 2013-2014 matched patients at one-year, HR and 95% CI were in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion) (**Table 52**).

Table 52. Rivaroxaban 15 mg versus dabigatran 110 mg, specific population, and a 60-day grace period for drug discontinuation: Hazard ratio (HR) and 95%CI of main and secondary outcomes at 1-year and at 2-year for the 2013 matched patients, and at 1-year for the 2013-2014 matched patients

	Matched patients of the specific populations		
	New users in 2013		New users in 2013-2014
	Riva. 15 vs Dabi. 110 at 1-year n = 10 017	Riva. 15 vs Dabi. 110 at 2-year n = 9 952	Riva. 15 vs Dabi. 110 at 1-year n = 15 131
	HR [95%CI]	HR [95%CI]	HR [95%CI]
Stroke and systemic embolism (SSE)	**1.40 [1.11; 1.77]**	**1.34 [1.10; 1.64]**	**1.27 [1.06; 1.53]**
Major bleeding	**1.22 [0.98; 1.51]**	**1.31 [1.08; 1.59]**	**1.28 [1.07; 1.53]**
Clinically relevant bleeding (CRB)	1.32 [1.13; 1.56]	1.34 [1.16; 1.54]	1.38 [1.20; 1.57]
Death (all causes)	**1.04 [0.93; 1.17]**	**1.06 [0.97; 1.17]**	**1.04 [0.95; 1.14]**
Composite criterion (SSE, major bleeding, and death)	**1.12 [1.02; 1.24]**	**1.14 [1.04; 1.24]**	**1.09 [1.01; 1.18]**
Acute coronary syndrome (ACS)	**1.13 [0.87; 1.46]**	**1.05 [0.84; 1.32]**	**0.97 [0.79; 1.19]**

Table 53. 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	Dabigatran 110 mg	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	9 952	9 952	1.34 [1.10 ; 1.64]	1.31 [1.08 ; 1.59]	1.34 [1.16 ; 1.54]	1.06 [0.96 - 1.17]	1.14 [1.04 - 1.24]	1.05 [0.84 ; 1.32]
Gender								
Male	4 702	4 702	1.61 [1.20 ; 2.15]	1.40 [1.06 ; 1.84]	1.40 [1.15 ; 1.70]	1.09 [0.95 - 1.25]	1.20 [1.06 - 1.35]	1.13 [0.84 ; 1.50]
Female	5 250	5 250	1.14 [0.86 ; 1.50]	1.24 [0.94 ; 1.62]	1.27 [1.02 ; 1.57]	1.04 [0.90 - 1.19]	1.08 [0.96 - 1.22]	0.95 [0.66 ; 1.37]
Age (years)								
<65	460	461	0.73 [0.16 ; 3.27]	0.98 [0.14 ; 6.73]	1.22 [0.33 ; 4.48]	0.62 [0.27 - 1.44]	0.70 [0.34 - 1.43]	4.52 [0.97 ; 21.03]
[65-70[	515	493	3.65 [1.03 ; 12.88]	1.58 [0.47 ; 5.35]	1.52 [0.67 ; 3.46]	2.51 [1.12 - 5.64]	2.63 [1.40 - 4.96]	0.61 [0.28 ; 1.35]
[70-75[	897	909	1.24 [0.53 ; 2.90]	1.63 [0.78 ; 3.40]	1.68 [0.96 ; 2.95]	1.24 [0.79 - 1.95]	1.26 [0.86 - 1.84]	2.45 [1.08 ; 5.56]
[75-80[	1 915	1 854	1.31 [0.83 ; 2.06]	2.85 [1.65 ; 4.93]	2.12 [1.47 ; 3.08]	1.36 [1.02 - 1.81]	1.50 [1.19 - 1.88]	0.96 [0.60 ; 1.54]
≥ 80	6 165	6 235	1.32 [1.04 ; 1.67]	1.10 [0.88 ; 1.38]	1.17 [0.99 ; 1.39]	1.00 [0.89 - 1.12]	1.06 [0.96 - 1.17]	0.94 [0.69 ; 1.28]
CHA_2DS_2-VASc score								
0-1	605	601	8.50 [1.09 ; 66.54]	0.53 [0.16 ; 1.81]	0.61 [0.25 ; 1.50]	0.92 [0.48 - 1.76]	1.16 [0.65 - 2.05]	2.28 [0.58 ; 9.04]
2	1 666	1 681	1.24 [0.67 ; 2.30]	1.45 [0.83 ; 2.56]	1.69 [1.15 ; 2.48]	1.30 [0.96 - 1.75]	1.38 [1.06 - 1.78]	1.15 [0.64 ; 2.06]
3	2 847	2 892	1.22 [0.80 ; 1.87]	1.55 [1.08 ; 2.24]	1.42 [1.08 ; 1.87]	1.16 [0.96 - 1.42]	1.23 [1.04 - 1.46]	0.92 [0.58 ; 1.45]
≥ 4	4 834	4 778	1.32 [1.03 ; 1.70]	1.23 [0.95 ; 1.59]	1.26 [1.04 ; 1.53]	0.98 [0.86 - 1.11]	1.05 [0.94 - 1.17]	1.04 [0.77 ; 1.40]
Risk factors								
Congestive heart failure	2 276	2 219	1.23 [0.81 ; 1.87]	1.33 [0.94 ; 1.89]	1.36 [1.03 ; 1.79]	1.00 [0.85 - 1.17]	1.05 [0.91 - 1.21]	1.01 [0.64 ; 1.61]
Hypertension	4 554	4 509	1.37 [1.03 ; 1.83]	1.28 [0.98 ; 1.68]	1.30 [1.07 ; 1.59]	1.01 [0.89 - 1.16]	1.09 [0.97 - 1.23]	0.90 [0.66 ; 1.23]
Diabetes mellitus	2 134	2 075	1.37 [0.96 ; 1.95]	1.55 [1.00 ; 2.41]	1.20 [0.89 ; 1.62]	1.05 [0.86 - 1.29]	1.16 [0.98 - 1.38]	1.04 [0.72 ; 1.51]
Stroke or TIA history	1 130	1 158	1.06 [0.69 ; 1.62]	1.61 [0.95 ; 2.74]	1.79 [1.19 ; 2.68]	1.20 [0.93 - 1.55]	1.21 [0.97 - 1.50]	1.07 [0.49 ; 2.33]
Vascular disease history	1 622	1 563	1.73 [1.17 ; 2.57]	1.29 [0.83 ; 2.01]	1.23 [0.88 ; 1.72]	1.07 [0.86 - 1.33]	1.22 [1.02 - 1.47]	1.57 [1.06 ; 2.34]
Age 65-74 years	1 412	1 402	1.84 [0.93 ; 3.67]	1.61 [0.86 ; 3.04]	1.63 [1.03 ; 2.59]	1.49 [1.01 - 2.21]	1.56 [1.13 - 2.15]	1.25 [0.73 ; 2.15]
Age ≥75 years	8 080	8 089	1.31 [1.06 ; 1.63]	1.29 [1.05 ; 1.58]	1.31 [1.12 ; 1.52]	1.04 [0.94 - 1.16]	1.12 [1.02 - 1.22]	0.95 [0.74 ; 1.23]
HAS-BLED score								
0-1	2 263	2 279	1.23 [0.70 ; 2.16]	1.08 [0.68 ; 1.71]	1.13 [0.80 ; 1.61]	1.00 [0.78 - 1.29]	1.11 [0.90 - 1.38]	1.29 [0.66 ; 2.53]
2-3	6 841	6 835	1.36 [1.08 ; 1.71]	1.37 [1.09 ; 1.72]	1.38 [1.17 ; 1.64]	1.08 [0.97 - 1.22]	1.16 [1.05 - 1.28]	1.03 [0.80 ; 1.34]
>3	848	838	1.31 [0.72 ; 2.36]	1.36 [0.73 ; 2.52]	1.35 [0.87 ; 2.10]	0.97 [0.72 - 1.31]	1.05 [0.81 - 1.35]	0.89 [0.42 ; 1.89]
Quintiles of logit (hdPS)								
Quintile 1	1 977	2 003	1.10 [0.68 ; 1.79]	1.41 [0.87 ; 2.29]	1.67 [1.18 ; 2.37]	1.18 [0.93 - 1.50]	1.22 [0.99 - 1.49]	1.22 [0.73 ; 2.04]
Quintile 2	1 976	2 005	1.44 [0.90 ; 2.28]	1.21 [0.76 ; 1.94]	1.46 [1.03 ; 2.06]	1.20 [0.95 - 1.52]	1.28 [1.05 - 1.57]	1.58 [0.91 ; 2.72]
Quintile 3	1 994	1 987	1.57 [1.01 ; 2.43]	1.66 [1.03 ; 2.66]	1.46 [1.05 ; 2.04]	1.17 [0.93 - 1.47]	1.24 [1.02 - 1.51]	0.91 [0.52 ; 1.60]
Quintile 4	1 983	1 998	1.27 [0.81 ; 2.00]	1.74 [1.13 ; 2.68]	1.44 [1.03 ; 2.00]	0.86 [0.68 - 1.07]	1.02 [0.84 - 1.23]	0.87 [0.55 ; 1.39]
Quintile 5	2 022	1 959	1.31 [0.86 ; 1.98]	0.91 [0.64 ; 1.31]	0.95 [0.72 ; 1.25]	0.96 [0.79 - 1.17]	1.00 [0.84 - 1.18]	0.88 [0.54 ; 1.45]

10.5. Other analyses

Not applicable.

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, death, CRB, 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 387 788 patients identified in the nationwide SNDS database with a first dispensing of DOAC (dabigatran or rivaroxaban) or VKA in 2013 and without history of prior DOAC (dabigatran, rivaroxaban or apixaban) or VKA dispensing in the 3 years, 118 048 had a NVAF diagnosis information without other probable indication and were included in the specific study population: 34 803 (29%) in the rivaroxaban group (17% with the 20 mg standard dose, 11% with the 15 mg reduced dose, and 1% with the 10 mg dose), 29 993 (25%) in the dabigatran group (10% with the 150 mg standard dose, 15% with the 110 mg reduced dose, and 1% with the 75 mg dose), and 53 252 (45%) in the VKA group. The 163 349 patients with a NVAF diagnosis or probabilistic information without other probable indication were included in the sensitive population included: 51 304 (31%) in the rivaroxaban group (18% with the 20 mg standard dose, 12% with the 15 mg reduced dose, and 1% with the 10 mg dose), 40 933 (25%) in the dabigatran group (9% with the 150 mg standard dose, 15% with the 110 mg reduced dose, and 1% with the 75 mg dose), and 71 112 (44%) in the VKA group. NVAF diagnosis information was defined as AF diagnosis from LTD or hospitalisation or procedure for AF before index date, without rheumatic valve disease or valve replacement. NVAF probabilistic information was defined as 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): 15 680 patients per group for rivaroxaban 20 mg versus VKA in the specific population and 21 963 per group in the sensitive population (77% and 75% of rivaroxaban patients), 10 342 per group for rivaroxaban 20 mg versus dabigatran 150 mg in the specific population and 13 893 per group in the sensitive population (89% and 92% of dabigatran patients), 12 018 per group for rivaroxaban 15 mg versus VKA in the specific population and 18 333 per group in the sensitive population (94% and 93% of rivaroxaban patients), and 9 952 per group for rivaroxaban 15 mg versus dabigatran 110 mg in the specific population and 15 773 per group in the sensitive population (57% and 64% 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 3.7 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 1.5 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 (41% and 39%, respectively), followed by hospital physicians (29% and 25%, respectively), and GP (21% and 25%, respectively). It was similar for dabigatran 150 mg and 110 mg: cardiologists (40% and 33%, respectively), hospital physicians (33% and 32%, respectively), and GP (16% and 22%, respectively), while VKA were mainly prescribed by hospital physicians (40%), followed by GP (27%), and a few by cardiologists (17%).

In this real-life study, the reduced dose of DOAC was frequently used and concerned 37% of patients for the rivaroxaban group and 59% 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 69.2 (± 11.1), 65.4 (± 10.1) and 78.0 (± 11.1) years, with 63%, 69% and 52% of men, 68%, 58% and 90% of CHA_2DS_2-VASc ≥ 2, 4%, 3% and 16% 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 80.2 (± 9.2) and 78.7 (± 9.4) years, 47% and 49% of men, 93% and 92% of CHA_2DS_2-VASc ≥ 2, 9% of HAS-BLED > 3 for both, respectively.

After matching, the mean age was 71.3 (± 10.1) 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, 66.3 and 66.2 (± 9.3) years with 69% of men, 59% of CHA_2DS_2-VASc ≥ 2, and 3% of HAS-BLED > 3 in both groups for rivaroxaban 20 mg and dabigatran 150 mg groups, 80.4 (± 8.6) years with 47% of men, 93% of CHA_2DS_2-VASc ≥ 2, 10% of HAS-BLED > 3 in both groups for rivaroxaban 15 mg and VKA groups, 80.5 and 80.4 (± 7.9) years with 47% 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.

Drug exposure

For matched patients, the 2-year cumulative incidence of discontinuation or switch, based on 60-day grace period, was 50.7% (34.7% of discontinuations and 24.6% of switches) and 56.7% (45.5% of discontinuations and 20.6% of switches) for rivaroxaban 20 mg and VKA groups, respectively. It was 51.5% (36.8% of discontinuations and 23.2% of switches) and 57.3% (38.4% of discontinuations and 30.6% of switches) for rivaroxaban 20 mg and dabigatran 150 mg groups, respectively; 55.1% (37.2% of discontinuations and 28.5% of switches) and 55.2% (46.9% of discontinuations and 15.7% of switches) for rivaroxaban 15 mg and VKA groups, respectively;

54.5% (36.5% of discontinuations and 28.3% of switches) and 61.4% (37.0% of discontinuations and 38.7% of switches) for rivaroxaban 15 mg and dabigatran 110 mg groups, respectively.

The number of person-years (PY) during the first drug exposure was 23 768, 12 698, and 59 588 PY, respectively for all rivaroxaban 20 mg, dabigatran 150 mg, and VKA patients, and 13 712 and 17 830 PY, respectively for all rivaroxaban 15 mg and dabigatran 110 mg patients. For matched patients, there were 18 524 and 18 489 PY, respectively for rivaroxaban 20 mg and VKA groups, 12 104 and 11 395 PY, respectively for rivaroxaban 20 mg and dabigatran 150 mg groups, 12 989 and 14 076 PY, respectively for rivaroxaban 15 mg and VKA groups, and 10 935 and 9 995 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 85% for all and matched patients.

Overall Incidence (all 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 1.3 [1.2 to 1.4], 1.1 [0.9 to 1.3] and 2.6 [2.5 to 2.7] for SSE, 1.2 [1.1 to 1.3], 0.5 [0.4 to 0.6], and 3.1 [3.1 to 3.2] for major bleeding, 3.0 [2.8 to 3.2], 1.7 [1.5 to 1.9] and 13.0 [12.7 to 13.3] for death, 5.1 [4.8 to 5.4], 3.1 [2.8 to 3.4] and 17.0 [16.7 to 17.3] 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 2.3 [2.0 to 2.6] and 1.7 [1.5 to 1.9] for SSE, 2.3 [2.3 to 2.6] and 1.6 [1.4 to 1.8] for major bleeding, 8.5 [8.0 to 9.0] and 7.0 [6.6 to 7.4] for death, 11.8 [11.3 to 12.3] and 9.5 [9.1 to 9.9] for the composite.

Two-year cumulative incidence and risk comparison *(main analysis:* matched patients of the specific population with a 60-day grace period for the drug discontinuation)

Rivaroxaban 20 mg versus VKA

The 2-year cumulative incidence was significantly lower with rivaroxaban 20 mg than VKA for two main outcomes: 2.4% [2.1 to 2.7] vs. 3.5% [3.2 to 3.9] (HR: 0.69 [0.59 to 0.81]) for major bleeding, 6.5% [6.0 to 7.0] vs. 9.7% [9.1 to 10.3] (HR: 0.67 [0.61 to 0.74]) for death, while the risk was similar between the two groups for SSE (2.6% [2.3 to 2.9] vs. 2.7% [2.4 to 3.0] (HR: 0.99 [0.84 to 1.16]). It was also significantly lower with rivaroxaban for the three secondary outcomes: 5.5% [5.0 to 5.9] vs. 6.4% [5.9 to 6.9] (HR: 0.86 [0.77 to 0.97]) for CRB, 1.6% [1.4 to 1.9] vs. 2.2% [1.9 to 2.5] (HR: 0.75 [0.62 to 0.91]) for ACS, and 10.2% [9.6 to 10.8] vs. 14.0% [13.3 to14.7] (HR: 0.73 [0.68 to 0.79]) for the composite criterion.

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban for other critical organ or site bleeding (HR: 0.38 [0.26 to 0.56]) and other bleeding (0.75 [0.60 to 0.93]), but not statistically different for haemorrhagic stroke, GI bleeding, and urogenital bleeding (0.84 [0.63 to 1.12], 1.02 [0.84 to 1.22], 1.12 [0.86 to 1.46], respectively). For other individual events of major outcomes, the risk was significantly lower with rivaroxaban for STEMI (0.51 [0.34 to 0.76]), but not for ischemic or undefined stroke (0.97 [0.79 to 1.19]), other SE or surgical procedure for SE (1.02 [0.78 to 1.34]), NSTEMI (0.64 [0.39 to 1.05]), and unstable angina (0.87 [0.69 to 1.09]).

Stratified analyses were performed for main and secondary outcomes, according to 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: 0.67 (fourth quintile) to 1.24 (diabetes mellitus) for SSE, 0.44 (65-69 years old) to 0.94 (vascular disease history) for major bleeding, 0.47 (last quintile) to 0.82 (HAS BLED scores > 3) for death, 0.61 (65-69 years old) to 0.89 (70-74 years old) for the composite criterion, with a HAS-BLED HR gradient for all main outcomes from > 3 to 0-1 scores for SSE (0.86 to 1.15), from 0-1 to > 3 scores for major bleeding (0.59 to 0.89), death (0.59 to 0.82), composite criterion (0.70 to 0.83), a CHA_2DS_2-VASc HR gradient from 0-1 to ≥ 4 scores for major bleeding (0.55 to 0.86), and a quintile HR gradient from the last to the first quintile of logit hdPS for major bleeding (0.54 to 0.86), and no clear systematic variation for the other factors and outcomes.

The HR point estimate after one year of follow-up for the 2013 matched patients was quite the same for two of the three main outcomes (major bleeding and death) with some variations of the 95%CI, and a little better HR with rivaroxaban but also not significant for SSE (0.90 [0.74 to 1.08]). It was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with some variations of the 95%CI, including a non-significant 95%CI for CRB. It was quite the same for the 2013-2014 matched patients at one-year presented in the previous report, with twice more patients: similar HR for two of the three main outcomes (major bleeding and death) with narrower 95%CI due to larger population, but a significant lower risk for SSE with rivaroxaban compared to VKA (HR: 0.79 [0.69 to 0.90] for 2013 and 2014 matched patients, and 0.68 [0.56 to 0.83] for the only 2014 matched patients). Result was quite the same for the three secondary outcomes (CRB, ACS, composite criterion) with narrower 95%CI due to larger population.

Rivaroxaban 20 mg versus dabigatran 150 mg

The 2-year cumulative incidence was significantly higher with rivaroxaban 20 mg than dabigatran 150 mg for two main outcomes: major bleeding (1.7% [1.4 to 2.1] vs. 0.8% [0.6 to 1.1], HR: 2.13 [1.53 to 2.95]), death (3.9% [3.5 to 4.4] vs. 3.0% [2.6 to 3.5], HR: 1.30 [1.08 to 1.57]), and almost the same for SSE (2.0% [1.7 to 2.4] vs. 2.0% [1.6 to 2.3], HR: 1.03 [0.81 to 1.31]). It was also significantly higher with rivaroxaban for CRB (4.5% [4.0 to 5.0] vs. 2.3% [1.9 to 2.7], HR: 2.0 [1.64 to 2.44]), the composite criterion (7.0% [6.4 to 7.6] vs. 5.6% [5.0 to 6.2], HR: 1.26 [1.10 to 1.45]), and almost the same for ACS (1.5% [1.2 to 1.8] vs. 1.4% [1.2 to 1.8], HR: 1.07 [0.81 to 1.42]).

The 2-year risk of other individual events was significantly higher with rivaroxaban 20 mg for haemorrhagic stroke (HR: 4.46 [2.18 to 9.15]), GI bleeding (1.73 [1.26 to 2.35]), urogenital bleeding (2.24 [1.46 to 3.44]), other bleeding (1.91 [1.25 to 2.92]), but not for other critical organ or site bleeding (1.13 [0.59 to 2.15]), ischemic or undefined stroke (1.16 [0.86 to 1.57]), other SE or surgical procedure for SE (0.85 [0.57 to 1.26]), STEMI (0.57 [0.32 to 1.01]), NSTEMI (2.01 [0.94 to 4.27]), and unstable angina (1.17 [0.83 to 1.65]).

Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.66 (second quintile) to 2.12 (fourth quintile), with a HAS-BLED gradient from 0.88 to 1.33 for scores 0-1 to > 3, and only one significant HR. For the three other outcomes, the risk was in favour of dabigatran for almost all subgroups, with a HR from 1.59 (HAS-BLED scores > 3) to 3.73 (< 65 years old) for major bleeding, with a HAS-BLED gradient, from 1.59 to 2.21 for scores > 3 to 0-1, 1.11 (first and fourth quintiles) to 2.02 (HAS-BLED scores > 3) for death, with a HAS-BLED gradient, from 1.19 to 2.02 for scores 0-1 to > 3, and 0.95 (second quintile) to 1.90 (70-74 years old) for composite criterion, with a HAS-BLED gradient, from 1.18 to 1.59 for scores 0-1 to > 3, without clear systematic variation for the other factors and outcomes.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main outcomes (SSE, major bleeding, death) and two of the three secondary outcomes (CRB and composite criterion) with some variations of the 95%CI, while the risk of ACS was significantly lower with dabigatran (HR: 1.57 [1.15 to 2.14]). For the 2013-2014 matched patients at one-year, HR was similar with some variations of the 95%CI for death, a little better with rivaroxaban but also not significant for SSE, and with a lower difference for major bleeding but always in favour of dabigatran. It was similar with some variations of the 95%CI for CRB, and the composite criterion, and also with a lower difference for ACS with dabigatran (HR: 1.35 [1.05 to 1.75]).

Rivaroxaban 15 mg versus VKA

The 2-year cumulative incidence was significantly lower with rivaroxaban 15 mg than VKA for two main outcomes: major bleeding (3.7% [3.3 to 4.1] vs. 4.6% [4.2 to 5.1], HR: 0.80 [0.69 to 0.93]), death (14.1% [13.3 to 14.9] vs. 18.3% [17.5 to 19.2], HR: 0.79 [0.73 to 0.85]), and not statistically different between the two groups for SSE (3.7% [3.3 to 4.1] vs. 3.2% [2.9 to 3.6], HR: 1.14 [0.97 to 1.34]). It was also significantly lower with rivaroxaban for CRB (6.7% [6.2 to 7.3] vs. 7.6% [7.1 to 8.2], HR: 0.88 [0.79 to 0.99]) and the composite criterion (18.9% [18.0 to 19.8] vs. 23.2% [22.3 to 24.1], HR: 0.83 [0.77 to 0.88]), and almost the same for ACS (2.4% [2.0 to 2.7] vs. 2.3% [2.0 to 2.7], HR: 1.03 [0.85 to 1.26]).

For other individual bleeding categories, the risk at 2-year was significantly lower with rivaroxaban 15 mg for other critical organ or site bleeding (HR: 0.69 [0.50 to 0.94]) and other bleeding (0.74 [0.60 to 0.93]), but not for haemorrhagic stroke, GI bleeding and urogenital bleeding (0.83 [0.64 to 1.07], 1.02 [0.84 to 1.25] and 1.03 [0.77 to 1.39], respectively). For other individual events of major outcomes, the risk was not different between groups: ischemic or undefined stroke (1.13 [0.92 to 1.38]), other SE or surgical procedure for SE (1.15 [0.88 to 1.49]), STEMI (0.98 [0.69 to 1.37]), NSTEMI (1.09 [0.63 to 1.86]) and unstable angina (1.16 [0.91 to 1.48]).

Stratified analyses for main and secondary outcomes showed substantial HR variations for SSE from 0.83 (70-74 years old) to 2.39 (65-69 years old), and one significant HR. For the three other outcomes, the risk was in favour of rivaroxaban for almost all subgroups, with a HR from 0.53 (second quintile) to 1.14 (HAS-BLED scores 0-1) for major bleeding, with a HAS-BLED gradient, from 0.56 to 1.14 for scores > 3 to 0-1, 0.67 (last quintile) to 1.49 (CHA_2DS_2-VASc scores 0-1) for death, with a quintile gradient from 0.67 to 0.85 for the last to the first quintile, and 0.76 (last quintile) to 1.17 (CHA_2DS_2-VASc scores 0-1) for composite criterion, with a weak HAS-BLED gradient, from 0.80 to 0.89 for scores > 3 to 0-1.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for SSE, death as well as for major bleeding but with a non-significant 95%CI (HR: 0.90 [0.75 to 1.07]. It was also the same for the composite criterion, as well as for CRB but with a non-significant 95%CI (0.92 [0.81 to 1.05]), and somewhat different but yet not significant for ACS (0.92 [0.74 to 1.15]). For the 2013-2014 matched patients at one-year, HR and 95%CI were in the same range for two of the three main outcomes (major bleeding and death), and a point estimate close to 1 for SSE. HR and 95%CI were also in the same range for CRB and the composite criterion, and a difference at the significant threshold for ACS in favour of rivaroxaban (HR: 0.85 [0.73 to 1.00]).

Rivaroxaban 15 mg versus dabigatran 110 mg

The 2-year cumulative incidence was significantly higher with rivaroxaban 15 mg than dabigatran 110 mg for two main outcomes: SSE (3.5% [3.0; 3.9] vs. 2.7% [2.3; 3.1], HR: 1.34 [1.10-1.64]), and major bleeding (3.6% [3.2; 4.1] vs. 2.7% [2.3; 3.1], HR: 1.31 [1.08 to 1.59]), and not statistically different between the two groups for death (12.9% [12.1; 13.8] vs. 12.3% [11.4; 13.2], HR: 1.06 [0.96 to 1.17]). It was also significantly higher with rivaroxaban for CRB (6.6% [6.0; 7.2] vs. 4.9% [4.3; 5.4], HR: 1.34 [1.16 to 1.54]) and the composite criterion (17.5% [16.6; 18.5] vs. 15.7% [14.8; 16.7], HR: 1.14 [1.04 to 1.24]), and not statistically different for ACS (2.3% [1.9; 2.6] vs. 2.2% [1.9; 2.6], HR: 1.05 [0.84 to 1.32]).

For other individual events, the risk at 2-year was significantly higher with rivaroxaban 15 mg for other SE or surgical procedure for SE (HR: 1.95 [1.35 to 2.82]), haemorrhagic stroke (2.55 [1.67 to 3.91]), other critical organ or site bleeding (1.75 [1.12 to 2.73]), urogenital bleeding (1.52 [1.03 to 2.23]), other bleeding (1.81 [1.31 to 2.50]), but not for ischemic or undefined stroke (1.12 [0.88 to 1.43]), STEMI (1.24 [0.81 to 1.91]), NSTEMI (0.61 [0.35 to 1.06]), unstable angina (1.18 [0.89 to 1.56]), and GI bleeding (0.85 [0.69 to 1.06]).

Stratified analyses for main and secondary outcomes showed non-systematic substantial variations across sub-groups, mainly in favour of dabigatran, from a HR of 0.73 (< 65 years old) to 8.50 (CHA_2DS_2-VASc scores 0-1) for SSE, 0.53 (CHA_2DS_2-VASc scores 0-1) to 2.85 (75-79 years old) for major bleeding, 0.62 (< 65 years old) to 2.51 (65-69 years old) for death, 0.70 (< 65 years old) to 2.63 (65-69 years old) for the composite criterion.

The HR point estimate after one year of follow-up for the 2013 matched patients was in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion) with 95%CI just below the significant threshold for major bleeding (HR: 1.22 [0.98 to 1.51]). For the 2013-2014 matched patients at one-year, HR and 95% CI were in the same range for the three main and secondary outcomes (SSE, major bleeding, death, CRB, ACS, and composite criterion).

Sensitivity analyses

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 complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS, did not change the previous results for main outcomes for both matched and all patients adjusted analyses.

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, 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 patients' 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 2-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 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 120 000 first users of anticoagulant for NVAF with a specific AF definition in 2013 in France, nearly half (45.1%) starting a VKA, 29.5% rivaroxaban, 17.3% with the 20 mg standard dose, 10.8% with the 15 mg reduced dose and 1.3% with the 10 mg dose and 25.4% dabigatran, 9.9% with the 150 mg standard dose, 14.9% with the 110 mg reduced dose and 0.6% with the 75 mg dose. From them, patients were individually 1:1 matched for each comparison, 15 680 patients per group for rivaroxaban 20 mg versus VKA, 12 018 for rivaroxaban 15 mg versus VKA, 10 342 for rivaroxaban 20 mg versus dabigatran 150 mg, and 9 952 for rivaroxaban 15 mg versus dabigatran 110 mg. This represents a high rate of matching for the smaller group of each comparison: 76.6% for rivaroxaban 20 mg versus VKA, 93.9% for rivaroxaban 15 mg versus VKA, 88.5% for rivaroxaban 20 mg versus dabigatran 150 mg and 56.7% for rivaroxaban 15 mg versus dabigatran 110 mg.

Compared to the ROCKET-AF randomized control trial, our study included 2.2 times more patients for the comparison rivaroxaban 20 mg versus VKA, allowing a higher statistical power (**Table 68**; Patel 2011). In the ROCKET-AF trial, the risk of SSE was 21% significantly lower with rivaroxaban 20 mg than VKA, without difference for CRB and major bleeding (HR: 1.03 [0.96-1.11] and 1.04 [0.90-1.20], respectively), 3.2% versus 2.2% for GI bleeding, and non-significant difference for MI and death (0.81 [0.63-1.06] and 0.85 [0.70-1.02], respectively). While in this study, no difference was observed for SSE (0.99 [0.84-1.16]), but a lower risk of CRB and major bleeding with rivaroxaban 20 mg (0.86 [0.77-0.97] and 0.69 [0.59-0.81], respectively) without difference for GI bleeding (1.02 [0.84-1.22]), and a similar point estimate for ACS and death, but reaching in this study the significant threshold (0.75 [0.62-0.91] and 0.67 [0.61-0.74], respectively). 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 54**), 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 stroke and SE, or ischemic stroke, transient ischemic attack and SE was different in our study compared to 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 stroke and SE, 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 in favour of VKA in our study in the French study (HR: 1.14 [0.97-1.34]). 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 many 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.

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 major bleeding, death, and the composite of three main outcomes (SSE, major bleeding, death), for all patients and certain subgroups analyses, as well as for several of secondary outcomes, especially CRB and ACS, but not for SSE and GI bleeding risk. The benefit-risk was also in favour of the rivaroxaban 15 mg compared to VKA with no difference for SSE, and a significant lower risk of major bleeding and death for all patients and certain subgroups analyses, as well as several secondary outcomes, especially CRB, and still without significant GI bleeding increase risk.

These results were strengthens with really similar HR when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses according to a more sensitive population definition, a 30-day grace period for drug discontinuation definition, and a complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS. Results were also almost the same for most subgroups from stratified analyses (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); with however some substantial variations of the HR point estimate. It means that the global result of the whole population treated relied of the characteristics of this population; and could be an explanation for HR variations at one year between 2013 and 2013 + 2014 matched patients, especially a somewhat better SSE HR with rivaroxaban 20 mg for the 2014 matched patients (0.68 [0.56 to 0.83] than for the 2013 matched patients (0.90 [0.74 to 1.08]). Indeed, the trend of DOAC initiation from 2013 to 2014 showed an increase of rivaroxaban, a drop of dabigatran and start of apixaban prescriptions in 2014 (Huiart 2018).

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 and ACS risks, 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, and GI bleeding, 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, but not for death, ACS, and GI bleeding, still with substantial variations across subgroups analysed. These results were strengthens with really similar HR when all patients were considered with adjusted analysis on gender, age and hdPS in deciles, as well as for sensitivity analyses according to a more sensitive population definition, a 30-day grace period for drug discontinuation definition, and a complementary adjustment using the Charlson comorbidity index score, a major prognostic factor of death in the SNDS. Results were also almost the same for most subgroups from stratified analyses (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), with also some substantial variations of the HR point estimate.

Table 54. Results of pre-registration randomized trial and observational studies of new rivaroxaban/VKA users, HR [95%CI]

Main author (Country year)	N	Stroke and SE HR [95%CI]	Major bleeding HR [95%CI]	CRB HR [95%CI]	GI bleeding HR [95%CI]	MI HR [95%CI]	Death (all-cause) 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%) & 20 mg (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 are 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

This nationwide cohort study shows that from the conditions of use in 2013 in France, rivaroxaban and VKA were prescribed preferentially to rather different patients, while differences between the two DOAC were smaller. Patients receiving reduce doses were older with more stroke and bleeding risk factors than those receiving standard doses.

Compared to VKA, the rivaroxaban 20 mg had a lower risk of major bleeding, CRB, ACS and death, but not for SSE, with an overall better benefit-risk for the composite criterion (SSE, major bleeding, and death). The overall benefit-risk was also better with rivaroxaban 15 mg than VKA, but a little less marked than for 20 mg, with a lower risk of major bleeding, CRB, and death, and no difference for SSE and ACS. For the two DOAC comparisons, the risk was higher with rivaroxaban 20 mg than dabigatran 150 mg for major bleeding, CRB, and death, and not different for SSE and ACS. For reduced dose, the risk was higher with rivaroxaban 15 mg than dabigatran 110 mg for SSE, major bleeding, CRB, but not for ACS and death. For the four comparisons, some substantial variations were observed across stratification subgroups.

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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 1.0	16 November 2018	Results Rivaroxaban 20 mg vs VKA Specific NVAF population, grace period of 60 days, two years of follow-up
1-5	Version 1.0	16 November 2018	Results Rivaroxaban 20 mg vs dabigatran 150 mg Specific NVAF population, grace period of 60 days, two years of follow-up
1-6	Version 1.0	16 November 2018	Results Rivaroxaban 15 mg vs VKA Specific NVAF population, grace period of 60 days, two years of follow-up
1-7	Version 1.0	16 November 2018	Results Rivaroxaban 15 mg vs dabigatran 110 mg Specific NVAF population, grace period of 60 days, two years of follow-up
1-8	Version 1.0	11 October 2018	Additional results Specific NVAF population, grace period of 60 days, two-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, two years 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, two years 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, two years 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, two years 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, two years 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, two years 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, two years 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, two years of follow-up
1-17			Signature pages

Appendix 2. Additional information

Not applicable.