

# Effectiveness and Safety of Rivaroxaban 15 or 20 mg Versus Vitamin K Antagonists in Nonvalvular Atrial Fibrillation

## A Population-Based New Users High-Dimensional Propensity Score Matched Cohorts Study

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**Background and Purpose**—We compared the 1-year safety and effectiveness of rivaroxaban 15 mg (R15) or rivaroxaban 20 mg (R20) to vitamin K antagonists (VKAs) in patients with nonvalvular atrial fibrillation.

**Methods**—New user cohort study of patients dispensed R15 or R20 versus VKA in 2013 or 2014 for nonvalvular atrial fibrillation, followed 1 year in the French *Système National des Données de Santé* (66 million people). R15 and R20 users were matched 1:1 with VKA users on sex, age, date of first drug dispensing, and high-dimensional propensity score. Hazard ratios (95% CIs) for stroke and systemic embolism, major bleeding, and death were computed using Cox proportional hazards or models by Fine and Gray during exposure.

**Results**—In 31 171 matched R20 and VKA, mean age, 71; 62% men; 76% with  $CHA_2DS_2-VASc \geq 2$ ; 5% HAS-BLED  $>3$  (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol); incidence rates for stroke and systemic embolism were 1.5% and 1.9% (hazard ratio, 0.79 [0.69–0.90]); major bleeding, 1.5% and 2.2% (0.67 [0.59–0.77]); death, 3.9% and 5.8% (0.67 [0.61–0.73]). In 23 314 matched R15 and VKA patients, mean age, 80; 47% men; 93% with  $CHA_2DS_2-VASc \geq 2$  and 9% with HAS-BLED  $>3$ ; incidence rates of stroke and systemic embolism were 2.3% and 2.1% (1.05 [0.92–1.21]); major bleeding, 2.4% and 2.9% (0.84 [0.74–0.96]); death, 9.1% and 10.8% (0.85 [0.79–0.90]). Numbers needed to treat to observe one fewer death (NNT) were 46 for R15 and 61 for R20.

**Conclusions**—In real life in France over 2013 to 2015, R15 and R20 were at least as effective and safer than VKA.

**Clinical Trial Registration**—URL: <http://www.encepp.eu>. Unique identifier: EUPAS14567. (*Stroke*. 2019;50:2469-2476. DOI: 10.1161/STROKEAHA.119.025824.)

**Key Words:** atrial fibrillation ■ France ■ humans ■ pharmacoepidemiology ■ rivaroxaban

Atrial fibrillation increases 5-fold the risk of ischemic stroke.<sup>1</sup> Vitamin K antagonists (VKAs) have long been the reference treatment for stroke prevention, with a risk of serious bleeding.<sup>2–5</sup> The direct-acting oral anticoagulant rivaroxaban was approved for stroke prevention in nonvalvular atrial fibrillation (NVAf) in 2012.<sup>6</sup> In the ROCKET-AF pivotal trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), patients were randomized to rivaroxaban 20 mg (R20) daily or 15 mg in patients with a low creatinine clearance (about 20% of the participants).<sup>7</sup> Patients randomized to rivaroxaban had fewer

stroke and systemic embolisms (SSEs) than patients randomized to warfarin without significant difference in clinically relevant bleeding (CRB) or major bleeding (MB).<sup>7</sup> There was no separate description of rivaroxaban 15 mg (R15) or R20 patients or results.

The translation of clinical trial results to actual practice is uncertain because physicians, patients, drug prescriptions, and usage may not be the same.<sup>8–10</sup> Few observational studies have compared standard and reduced doses of rivaroxaban versus VKA.<sup>11</sup> Studies in Asian patients concerned lower doses.<sup>12,13</sup>

When rivaroxaban was first marketed in France in 2012, regulatory authorities requested a comparative effectiveness

Received February 25, 2019; final revision received June 6, 2019; accepted June 14, 2019.

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The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.025824>.

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DOI: 10.1161/STROKEAHA.119.025824

and safety study of R20 or R15 in NVAf, compared with VKA. To this end, we performed the study reported herein

## Research Question and Objectives

To compare the 1-year event rates of SSE, MB, and all-cause death in new users of R15 or R20 versus VKA for NVAf.

## Methods

The data used in this study are public, provided by the French National Healthcare System (Système National des Données de Santé [SNDS]).<sup>14</sup> The data can be accessed in our department. Alternatively, readers may request the same dataset from SNDS at <https://www.indesante.fr>.

## Study Design

High-dimensional propensity score (hdPS)-matched cohorts study of new users of R20 versus VKA and R15 versus VKA for NVAf in SNDS in 2013 or 2014, followed for 1 year.

The full study protocol, as approved by the regulatory authorities, which requested the study, can be found at <http://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/26842>.

## Setting

SNDS is the national healthcare data system in France. It links the mandatory public health insurance system claims database to the hospital discharge database and the death registry.<sup>14</sup> It includes >99% of the French population (66 million people) from birth (or immigration) to death (or emigration), irrespective of socioeconomic status even if a person changes occupation or retires. SNDS contains individual anonymized information on all medical and paramedical encounters, drug claims, hospital admission diagnoses and procedures, and date of death, which are linked to create a longitudinal record of health encounters (inpatient or outpatient) from private or public hospitals and from private practice.<sup>14</sup>

SNDS has been used to perform real-life studies comparing direct-acting oral anticoagulant to warfarin or to each other.<sup>15–18</sup> It is described elsewhere.<sup>14</sup>

In brief, all prescribed drug dispensings are recorded with the drug's Anatomical Chemical Therapeutic Classification code, the strength, the number of tablets per pack, and the number of packs. All medical and paramedical encounters are recorded, as are all laboratory tests. Chronic diseases that warrant full coverage are recorded (*International Classification of Diseases, Tenth Revision*). Hospital admissions are recorded including main and secondary diagnoses (*International Classification of Diseases, Tenth Revision*), in-hospital procedures, and expensive drugs.

Regular internal and external quality assurance processes verify the validity of the diagnostic coding.<sup>19</sup> For instance, the positive predictive values of codes for stroke, myocardial infarction, or heart failure are above 80% to 90%.<sup>20–22</sup>

## Subjects

All adults with a dispensing of any oral anticoagulant in 2013 or 2014, with a diagnosis of definite NVAf as described previously,<sup>4,15,16</sup> and with no dispensing of any oral anticoagulant in the previous 3 years were identified (Figure 1).

Only the results concerning definite NVAf are presented. Results in probable NVAf were not different and are not shown.

Patients with rheumatic valvular heart disease or valve replacement, patients with another indication for anticoagulation (deep vein thrombosis or pulmonary embolism, orthopedic surgery), or without a definite diagnosis of atrial fibrillation were excluded.

Only patients with definite NVAf, and complete datasets (3-year history, 1-year follow-up in the absence of death) were retained in the cohort study (Figure 1).

Index date was first anticoagulant dispensing between January 1, 2013, and December 31, 2014.

## Baseline Covariates

All chronic conditions, cardiovascular risk factors, previous and concomitant drug dispensing, and hospital admission diagnoses were collected over the 3 years previous to the index date. The elements composing the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol) are reported in Table 1.<sup>4,18</sup> Codes used for these scores are indicated in Appendix II in the [online-only Data Supplement](#). Further baseline covariates are described in Table I in the [online-only Data Supplement](#) for all and matched populations. They include a modified Charlson index predictive of mortality in this database.<sup>23</sup>

## Exposure

The drug exposure period started at index date and ended 30 days after the last dispensing or at dispensing of a different anticoagulant (switch). Last dispensing was defined as a dispensing that was not followed by another dispensing of the same drug within 60 days.<sup>4</sup>

## Follow-Up

Follow-up began on index date and continued until patient death, treatment discontinuation, occurrence of an outcome of interest (for that outcome), or end of study (1 year after index date), whichever came first. There was no loss to follow-up.

## Study Outcomes

The 3 primary outcomes were hospitalization for ischemic stroke or systemic embolism (SSE), hospitalization for MB, and all-cause death.

Secondary outcomes included acute coronary syndrome (myocardial infarction or unstable angina), CRB, and specific bleeding sites.

## Composite Outcome of SSE, MB, and Death Was Also Studied

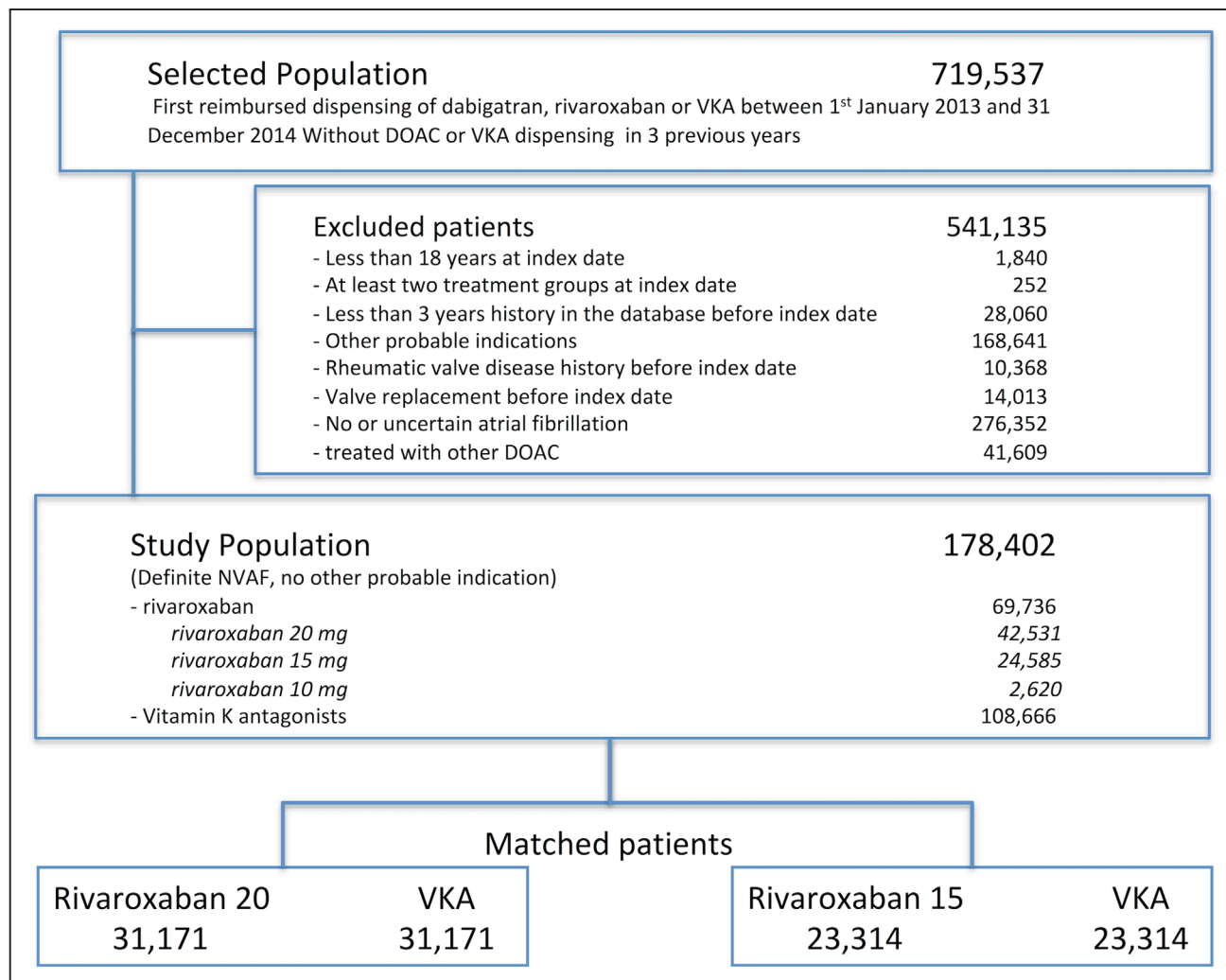
MB was hospital diagnosis of intracerebral hemorrhage, critical organ bleeding, any CRB with blood transfusion or acute posthemorrhagic anemia, or death during hospital stay for bleeding event (International Society for Thrombosis and Hemostasis definition).<sup>24</sup> CRBs were all hospitalizations with a main diagnosis of bleeding. Specific bleeding sites were intracerebral hemorrhage, gastrointestinal bleeding, urogenital bleeding, other critical organ or site bleeding, and other bleeding.

The *International Classification of Diseases, Tenth Revision*, codes used to identify these outcomes are provided in Appendix III in the [online-only Data Supplement](#). The same codes were used for other studies of anticoagulant users.<sup>4,15,16,18</sup>

## Statistical Methods

All analyses were prespecified and described in a statistical analysis plan. The protocol was registered with the European Medicines Agency EUPAS (European Union Post-Authorization Study) database before start of study and is available at <http://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/26842>.

In brief, to reduce confounding because of imbalance in study covariates, hdPS matching was used.<sup>25</sup> Unconditional binary logistic regression was used to estimate separately the predicted probability of patients initiating R15 or R20 rather than VKA,<sup>26,27</sup> taking into account all the information in the database, with multiple data dimensions from patient data and healthcare reimbursements during the 3-year period before index date (see Appendix IV in the [online-only Data Supplement](#)). Variables were chosen for their association with outcomes, among other criteria including demographic variables at inclusion (age and sex), individual stroke and bleeding risk factors from the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores, hospitalization (other than cardioversion or catheter ablation) in the month before index date, chronic obstructive pulmonary disease, coronary heart



**Figure 1.** Patient disposition. DOAC indicates direct-acting oral anticoagulant; NVAf, nonvalvular atrial fibrillation; and VKA, vitamin K antagonist.

disease, diabetes mellitus, hospital and nonhospital costs during the year and the month before index date, and 500 other variables<sup>26-29</sup> selected from 4 dimensions. The codes and variables concerned are listed in Appendix IV in the [online-only Data Supplement](#).

R15 versus VKA and R20 versus VKA patients were matched separately on the hdPS score, using greedy nearest neighbor matching. Goodness of match was assessed by the hdPS distributions in unmatched and matched populations (Figures I and II in the [online-only Data Supplement](#)) and by standardized mean differences.<sup>30</sup> An absolute standardized mean difference of  $\leq 0.1$  (10%) indicates a negligible difference between groups.<sup>30</sup>

The main analysis was performed in the matched patients during exposure (on treatment). Incidence rates were measured using event counts and exposed patient time and represented with Kaplan-Meier plots. Hazard ratio and 95% CIs of R15 versus VKA and R20 versus VKA were estimated using Cox proportional hazards model for death and the model by Fine and Gray<sup>31</sup> for competing risks for nonfatal events. The number needed to observe one fewer event in one group compared with the other (NNO) is  $1/(p[A]-p[B]) \times 100$  where  $p(A)$  and  $p(B)$  are event rates with treatment A and B.

Sensitivity analyses were performed on the whole population using adjustment on sex, age at index date, and hdPS (in deciles; Figures 2 and 3).

Statistical analysis was done by Bordeaux PharmacoEpi—a research platform of University of Bordeaux—using SAS software (version 9.4; SAS Institute, NC) and the Harvard routines for hdPS (SAS pharmacoepi toolbox, [www.drugapi.org](http://www.drugapi.org)).<sup>32</sup>

### Ethics and Registration

This study was requested by the National Healthcare authorities. It was authorized by the Institut National des Données de Santé on February 1, 2016, and by the National Commission on Informatics and Liberties on April 8, 2016. It is registered with the EUPAS registry as EUPAS14567 (<http://www.encepp.eu>). Study data were received on November 4, 2016. Bordeaux PharmacoEpi is ISO 9001:2015-certified for pharmacoepidemiological research.

### Results

Of 719 537 new anticoagulant users in 2013 and 2014, 220 011 had a diagnosis of NVAf; 108 666 had been dispensed VKA and 69 736 rivaroxaban, of whom 24 585 were dispensed R15 and 42 531 R20 (Figure 1). Before matching, R20 patients were younger and at lower risk than VKA or R15 patients (Table 1).

Thirty-one thousand one hundred seventy-one R20 patients (73% of all R20 patients) and 23 314 R15 patients (95% of all R15 patients) were individually matched to the same numbers of VKA patients (Table 1). hdPSs were identically distributed in matched R15 and VKA or R20 and VKA patients (Appendix V in the [online-only Data Supplement](#); Figures I and II in the [online-only Data Supplement](#)). Standardized mean differences in matched patients were always  $< 5\%$  for

Table 1. Baseline Characteristics of Patients Using R20, R15, or VKAs in All and Matched Patients

	All Patients			Crude Standardized Differences, %		Matched Patients		Matched Patients		Matched Standardized Differences, %	
	R20, n=42 480	R15, n=24 529	VKA, n=108 656	R20 vs VKA	R15 vs VKA	R20, n=31 171	VKA, n=31 171	R15, n=23 314	VKA, n=23 314	R20 vs VKA	R15 vs VKA
Sex, male; n (%)	27 352 (64.4)	11 574 (47.2)	56 349 (51.9)	-25.6	9.4	19 329 (62.0)	19 329 (62.0)	11 070 (47.5)	11 070 (47.5)	0.0	0.0
Mean age at index date, y	68.6 (11.1)	79.8 (9.4)	78.4 (11.0)	-88.2	14.2	71.2 (10.0)	71.2 (10.0)	80.1 (8.7)	80.1 (8.7)	-0.2	0.0
Minimum–maximum	18.0–104.0	19.0–105.0	18.0–108.0			22.0–101.0	22.0–101.0	24.0–103.0	23.0–103.0		
Age at index date (in categories), y; n (%)											
<65	13 331 (31.4)	1648 (6.7)	12 892 (11.9)			7305 (23.4)	7278 (23.3)	1369 (5.9)	1380 (5.9)		
65–80	22 544 (53.1)	8145 (33.2)	36 631 (33.7)			17 326 (55.6)	17 550 (56.3)	7851 (33.7)	7768 (33.3)		
≥80	6605 (15.5)	14 736 (60.1)	59 133 (54.4)			6540 (21.0)	6343 (20.3)	14 094 (60.5)	14 166 (60.8)		
Stroke risk factors (score), n (%)											
Congestive heart failure	5282 (12.4)	5580 (22.7)	38 534 (35.5)	-56.0	-28.3	4853 (15.6)	4949 (15.9)	5467 (23.4)	5393 (23.1)	-0.8	0.8
Hypertension	14 284 (33.6)	11 084 (45.2)	60 473 (55.7)	-45.4	-21.0	11 908 (38.2)	12 354 (39.6)	10 694 (45.9)	10 710 (45.9)	-2.9	-0.1
Age ≥75 y	13 678 (32.2)	19 172 (78.2)	75 405 (69.4)	-80.2	20.0	12 824 (41.1)	12 930 (41.5)	18 344 (78.7)	18 325 (78.6)	-0.7	0.2
Diabetes mellitus	8713 (20.5)	5186 (21.1)	29 335 (27.0)	-15.3	-13.7	7016 (22.5)	7285 (23.4)	4997 (21.4)	5088 (21.8)	-2.1	-0.9
Stroke or TIA history	3735 (8.8)	2683 (10.9)	16 225 (14.9)	-19.1	-11.9	3329 (10.7)	3521 (11.3)	2619 (11.2)	2654 (11.4)	-2.0	-0.5
Vascular disease history	4645 (10.9)	4051 (16.5)	24 993 (23.0)	-32.6	-16.3	4098 (13.1)	4315 (13.8)	3922 (16.8)	3989 (17.1)	-2.0	-0.8
Age, 65–74 y	15 471 (36.4)	3709 (15.1)	20 359 (18.7)	40.4	-9.7	11 042 (35.4)	10 963 (35.2)	3601 (15.4)	3609 (15.5)	0.5	-0.1
Women	15 128 (35.6)	12 955 (52.8)	52 307 (48.1)	-25.6	9.4	11 842 (38.0)	11 842 (38.0)	12 244 (52.5)	12 244 (52.5)	0.0	0.0
CHA <sub>2</sub> DS <sub>2</sub> -VASC score (in categories), n (%)											
0	5565 (13.1)	539 (2.2)	3101 (2.9)			2546 (8.2)	2522 (8.1)	455 (2.0)	470 (2.0)		
1	8805 (20.7)	1342 (5.5)	6957 (6.4)			5072 (16.3)	4901 (15.7)	1202 (5.2)	1195 (5.1)		
≥2	28 110 (66.2)	22 648 (92.3)	98 598 (90.7)			23 553 (75.6)	23 748 (76.2)	21 657 (92.9)	21 649 (92.9)		
Bleeding risk factors (score), n (%)											
Hypertension	14 284 (33.6)	11 084 (45.2)	60 473 (55.7)	-45.4	-21.0	11 908 (38.2)	12 354 (39.6)	10 694 (45.9)	10 710 (45.9)	-2.9	-0.1
Abnormal renal function	891 (2.1)	1660 (6.8)	19 538 (18.0)	-54.8	-34.6	852 (2.7)	1043 (3.3)	1625 (7.0)	1651 (7.1)	-3.6	-0.4
Abnormal liver function	579 (1.4)	397 (1.6)	3531 (3.2)	-12.6	-10.6	526 (1.7)	558 (1.8)	382 (1.6)	377 (1.6)	-0.8	0.2
Stroke history	3107 (7.3)	2240 (9.1)	14 124 (13.0)	-18.9	-12.4	2825 (9.1)	3014 (9.7)	2191 (9.4)	2214 (9.5)	-2.1	-0.3
Bleeding history	647 (1.5)	588 (2.4)	3658 (3.4)	-12.0	-5.8	554 (1.8)	627 (2.0)	565 (2.4)	586 (2.5)	-1.7	-0.6
Age >65 y	27 590 (64.9)	22 625 (92.2)	93 976 (86.5)	-51.9	18.8	22 846 (73.3)	22 890 (73.4)	21 694 (93.1)	21 717 (93.2)	-0.3	-0.4
Medication use predisposing to bleeding	22 611 (53.2)	15 249 (62.2)	72 275 (66.5)	-27.4	-9.1	18 476 (59.3)	18 899 (60.6)	14 641 (62.8)	14 727 (63.2)	-2.8	-0.8
HAS-BLED score (in categories), n (%)											
0	6106 (14.4)	630 (2.6)	2825 (2.6)			2610 (8.4)	2266 (7.3)	489 (2.1)	446 (1.9)		
1	13 470 (31.7)	5309 (21.6)	17 231 (15.9)			8843 (28.4)	8555 (27.4)	4912 (21.1)	4628 (19.9)		

(Continued)

Table 1. Continued

	All Patients			Crude Standardized Differences, %		Matched Patients		Matched Patients		Matched Standardized Differences, %	
2	14 266 (33.6)	9710 (39.6)	36 637 (33.7)			11 742 (37.7)	11 985 (38.4)	9280 (39.8)	9663 (41.4)		
3	6998 (16.5)	6722 (27.4)	33 943 (31.2)			6395 (20.5)	6746 (21.6)	6519 (28.0)	6536 (28.0)		
>3	1640 (3.9)	2158 (8.8)	18 020 (16.6)			1581 (5.1)	1619 (5.2)	2114 (9.1)	2041 (8.8)		

More data on baseline characteristics are shown in the [online-only Data Supplement](#). HAS-BLED indicates hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; R15, rivaroxaban 15 mg; R20, rivaroxaban 20 mg; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

all parameters and <2% for most (Table 1; Appendix V in the [online-only Data Supplement](#)).

Mean drug possession ratio (percentage days covered during exposure period) was above 80% in 93% and 94.9% of R15 and R20 patients, respectively. This cannot be calculated for VKAs, which do not have a fixed daily dose.

**Outcomes**

R20 patients had significantly better results for all primary outcomes than VKA (Table 2). Among secondary outcomes, CRB including intracerebral hemorrhage, and gastrointestinal bleeding, and acute coronary syndrome were less common in R20 users than in matched VKA users (Table 2; Figures 2 and 3).

Number needed to observe one fewer death with R20 than with VKA was 61 and 43 to observe one fewer of any primary event.

There was no difference between R15 and VKA for SSE, but MB and all-cause death were significantly less common with R15 (Table 2). Among secondary outcomes, CRB including intracerebral hemorrhage were less common with R15 (Figure 3).

Number needed to observe one fewer death with R15 than VKA was 46 and 42 to observe one fewer of any primary event.

Results were similar when analyses were done in the whole population, adjusted on the same parameters used for matching (Figures 2 and 3).

Events accrued regularly throughout the study (Appendix V in the [online-only Data Supplement](#); Figures III and IV in the [online-only Data Supplement](#)).

**Discussion**

In this countrywide new user cohort study of real-life experience with standard (20 mg) or reduced (15 mg) doses of

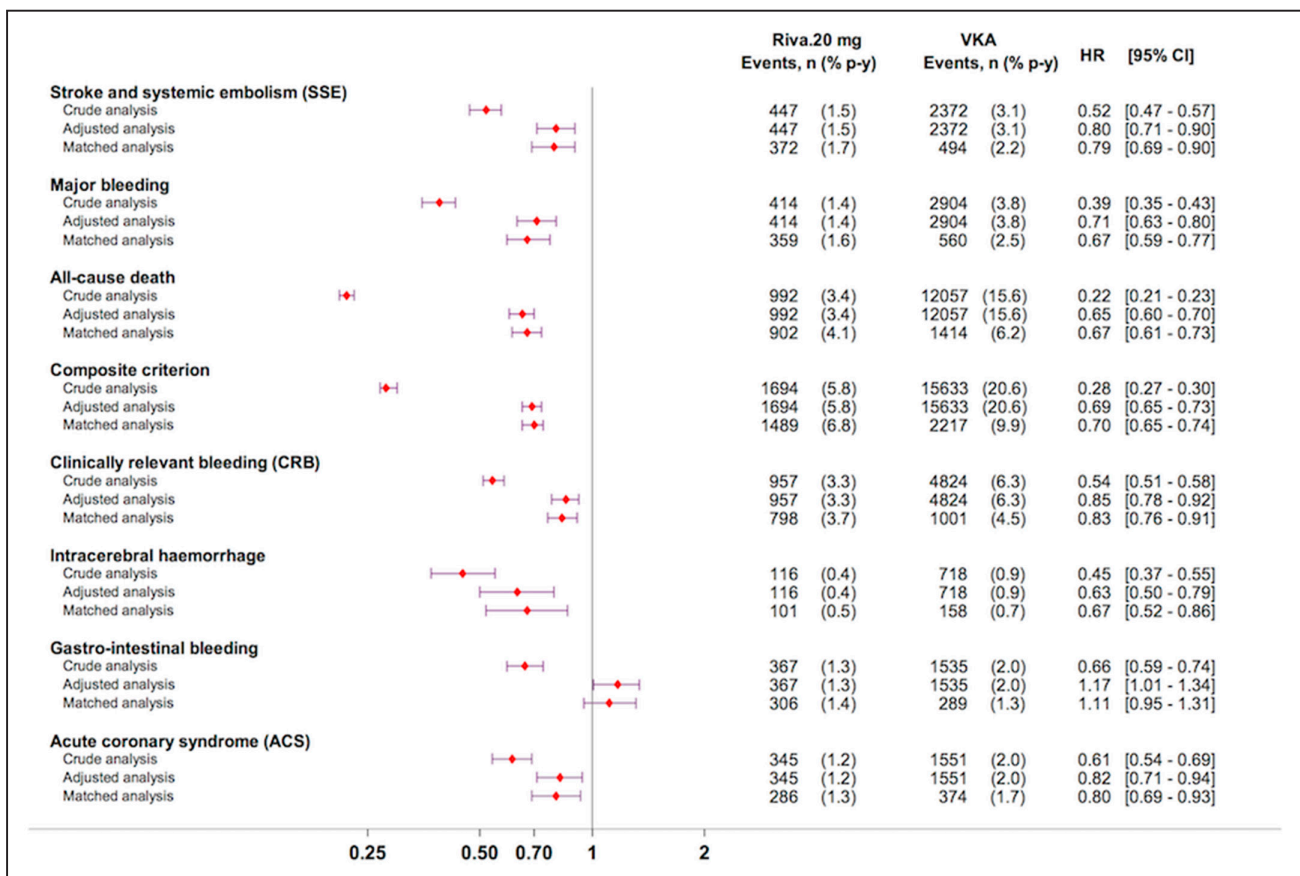


Figure 2. Effectiveness and safety outcomes in rivaroxaban 20 mg (R20) vs vitamin K antagonist (VKA) patients: forest plots. HR indicates hazard ratio.

**Table 2. Cumulative Incidence of Main Outcomes (Kaplan-Meier Estimate) During Drug Exposure in Matched R20 and VKA and Matched R15 and VKA Patients**

	R20, n=31 171		VKA, n=31 171		HR (95% CI)	R15, n=23 314		VKA, n=23 314		HR (95% CI)
	n	% (95% CI)	n	% (95% CI)		n	% (95% CI)	n	% (95% CI)	
SSE	372	1.5 (1.4–1.7)	494	1.9 (1.8–2.1)	0.79 (0.69–0.90)	399	2.3 (2.0–2.5)	419	2.1 (1.9–2.3)	1.05 (0.92–1.21)
MB	359	1.5 (1.4–1.7)	560	2.2 (2.1–2.4)	0.67 (0.59–0.77)	426	2.4 (2.2–2.6)	560	2.9 (2.6–3.1)	0.84 (0.74–0.96)
CRB	798	3.3 (3.1–3.6)	1001	4.0 (3.7–4.2)	0.83 (0.76–0.91)	787	4.4 (4.1–4.7)	975	4.9 (4.6–5.3)	0.89 (0.81–0.98)
Death (all causes)	902	3.9 (3.7–4.2)	1414	5.8 (5.5–6.1)	0.67 (0.61–0.73)	1565	9.1 (8.6–9.5)	2069	10.8 (10.3–11.2)	0.85 (0.79–0.90)
Composite criterion (SSE, MB, and death)	1489	6.3 (6.0–6.6)	2217	8.9 (8.5–9.2)	0.70 (0.65–0.74)	2189	12.5 (12.0–13.0)	2738	14.0 (13.5–14.5)	0.89 (0.84–0.94)
Acute coronary syndrome	286	1.2 (1.0–1.3)	374	1.4 (1.3–1.6)	0.80 (0.69–0.93)	270	1.5 (1.3–1.7)	347	1.7 (1.6–1.9)	0.85 (0.73–1.00)

CRB indicates clinically relevant bleeding; HR, hazard ratio; MB, major bleeding; R15, rivaroxaban 15 mg; R20, rivaroxaban 20 mg; SSE, stroke and systemic embolism; and VKA, vitamin K antagonist.

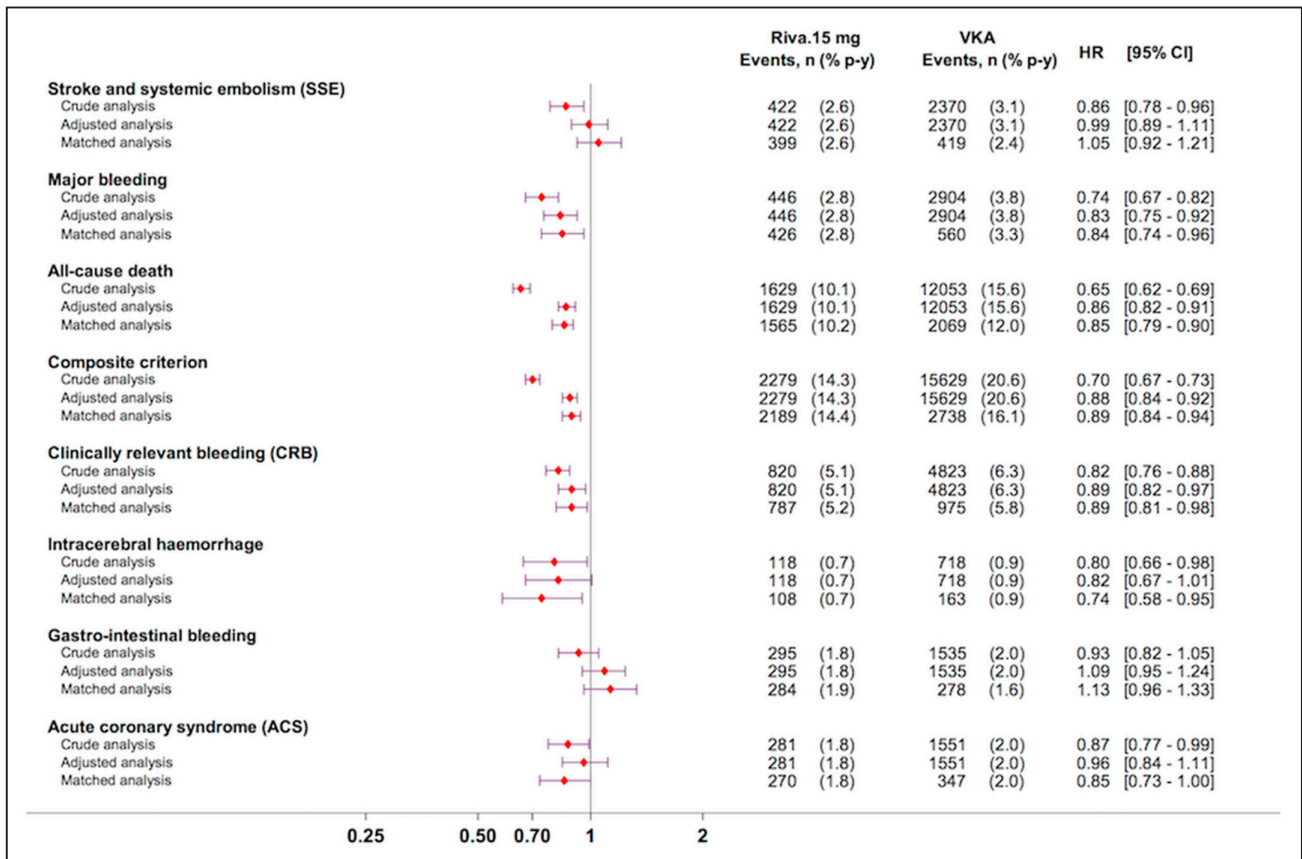
rivaroxaban compared with matched VKA patients with definite NVAF, rivaroxaban at either dose was associated with better indicators of effectiveness or safety and with lower mortality.

The pivotal trial that compared rivaroxaban to warfarin, ROCKET-AF,<sup>7</sup> did not differentiate the 2 dosages. Patients were randomized to R20 or R15 if they had renal disease. About 20% of the trial patients were on the reduced dose, 35% here. SSEs were less common on treatment in rivaroxaban patients than in patients randomized to VKA. Deaths were also less common but not significantly so (hazard ratio, 0.85 [0.70–1.02]), with overall death rates at 1.9% to 2.2% per year, compared with 3.9% and 5.8% in our R20 versus

VKA cohorts, that is, a real-life death rate about double that in the clinical trial.

Death rates in the older and sicker R15 and matched VKA patients were higher (R15, 8.1%; VKA, 10.9%). Higher death rates in real-life patients than in apparently similar patients from pivotal clinical trials<sup>33</sup> are commonly attributed to exclusion from clinical trials of patients with poor short-term prognosis. Signals of increased gastrointestinal bleeding in ROCKET-AF were not duplicated.

Our results are of the drugs as they were used, not in a randomized clinical trial. The results despite our best efforts might suffer from residual unmeasured confounding, and we cannot affirm causality. However, the matched cohorts were



**Figure 3.** Effectiveness and safety outcomes in rivaroxaban 15 mg (R15) vs vitamin K antagonist (VKA) patients: forest plots. HR indicates hazard ratio.

identical to within <5% of standardized mean differences in all variables, including all measurable bleeding and embolism risk factors, as well as common fatality risks, medical history, and drug dispensings. The differences between crude and matched results indicate the degree to which biases were corrected. The hdPS distribution curves overlapped over the whole population range, so that results in the matched population could be safely extrapolated to the whole population, as indicated by the similar results in matched and adjusted populations.

hdPS matching has been used in many pharmacoepidemiology studies. Unmeasured confounders such as smoking and obesity may be captured by various combinations of claims such as visits, prescriptions, procedures, tests, and hospitalizations, which may collectively be a proxy for risk factors that are not present as such in the database.<sup>27,28</sup>

The data in SNDS are collected prospectively and independently for healthcare insurance purposes, excluding information bias. Data are present for the whole population, with no selection according to social status, employer, age, or pre-existing conditions.<sup>14</sup> There are no sampling issues because the whole population is captured. All outpatient use of anticoagulants is identified. Drugs are dispensed as fixed preparations (eg, rivaroxaban, 20 mg per capsule, 30 capsules) that are individually identified, providing the exact quantity and dosage dispensed.

Diagnoses are based on hospital discharge summaries and on registration for chronic diseases and any other available data such as drug dispensings or procedures. The same methods and diagnostic algorithms were used in other studies of VKA and direct-acting oral anticoagulant for NVAf.<sup>4,15,16,18,34</sup> The identification of all-cause death is exhaustive.

Our results are generally consistent with other epidemiological studies done in different settings, and different medical environments, generally showing fewer SSEs, bleeding, and deaths than VKA. However, a Danish nationwide analysis by Larsen et al<sup>35</sup> found a markedly higher risk of death with R15 compared with matched VKA (hazard ratio, 1.52).<sup>36</sup> Our results obtained in a larger study show a lower risk of death with R15 than matched VKA.

In Taiwan, where lower doses of rivaroxaban are used (15 mg, 10 mg), both doses were associated with lower event rates of SSE, bleeding, and all-cause death than VKA—a finding shared with other studies.<sup>13,37–40</sup>

Other population-based studies did not compare rivaroxaban to VKA or differentiate doses.<sup>11,41–43</sup> The populations were relatively small, with 2000 to fewer than 6000 patients included, resulting in large CIs. However, point estimates for hazard ratio were not different from those found here.

Whether differences between studies are related to a different approach to the use of VKA,<sup>44</sup> to different healthcare systems, different sets of patients treated, or to a different statistical approach may be debated.

We did not directly compare R15 with R20, which were used in different populations.

## Conclusions

In this real-life countrywide hdPS-matched new users cohort study, rivaroxaban appears to be at least as effective (R15) or

more effective (R20) and for both doses safer than VKA for the prevention of thromboembolic events in NVAf.

## Acknowledgments

We thank ADERA for the administrative, legal, and human resources support without which this project could not have been done.

## Sources of Funding

This study was funded by Bayer Healthcare. The company had an observer role and had no part in study design, implementation or analysis, in the decision to publish this paper, or its content (see <http://www.encepp.eu>).

## Disclosures

Dr Moore declares the present study was funded by Bayer Healthcare (see funding, above). A parallel study on the same topic was funded by Boehringer Ingelheim. All funds were managed by University of Bordeaux and ADERA. Dr Sacher declares consulting fees from Bayer Healthcare and Boston Scientific and speaking honoraria from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Medtronic, Abbott, Microport, and Biosense Webster. Dr Fauchier reports consulting or speaker fees for Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Livanova, Medtronic, and Novartis. Dr Dallongeville reports scientific consulting with Bayer Healthcare, MSD, Biogen, and AstraZeneca. All Bordeaux PharmacoEpi employees of ADERA may have derived part of their salaries indirectly from the funding from Bayer Healthcare and other companies. The other authors report no conflicts.

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