ORIGINAL ARTICLE

Effectiveness and safety of 110 or 150 mg dabigatran *vs.* vitamin K antagonists in nonvalvular atrial fibrillation

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AIMS

We compared the 1-year safety and effectiveness of dabigatran 110 mg (D110) or 150 mg (D150) twice daily to vitamin K antagonists (VKA) in patients with nonvalvular atrial fibrillation.

METHODS

New user cohort study of patients dispensed D110 or D150 *vs.* VKA in 2013 for nonvalvular atrial fibrillation, followed 1 year in the French *Système National des Données de Santé* (66 million persons). D110 and D150 users were matched 1:1 with VKA users on sex, age, date of first drug dispensing and high-dimensional propensity score. Hazard ratios [HR (95% confidence intervals)] for stroke and systemic embolism (SSE), major bleeding (MB) and death were computed using Cox proportional hazards or Fine and Gray models during exposure.

RESULTS

In 14 442 matched D110 and VKA patients, mean age 79, 49% male, 91% with CHA_2DS_2-VASc $\geq$2 and 8% with HAS-BLED score >3, incidence rates of SSE were 1.9% and 2.6% person-years [HR 0.69 (0.56–0.84)], MB 1.8% and 2.9% [0.62 (0.51–0.76)], death 7.2% and 8.6% [0.84 (0.76–0.94)]. In 8389 matched D150 and VKA patients, mean age 67, 67% male, 65% with CHA_2DS_2-VASC $\geq$2; < 5% HAS-BLED >3, incidence rates were for SSE 1.4% and 1.9% [0.76 (0.56–1.04)], MB 0.6% and 1.9% [0.30 (0.20–0.46)], death 1.6% and 3.6% [0.46 (0.35–0.59)]. Numbers needed to treat to observe one fewer death were 78 for D110, 88 for D150.

CONCLUSION

In real life D110 and D150 were at least as effective, and safer than VKA.

Introduction

Atrial fibrillation (AF) is associated with a 5-fold increased risk of ischaemic stroke [1]. Vitamin K antagonists (VKA) such as **warfarin** have long been the reference treatment for stroke prevention, at the cost of a risk of serious bleeding [2–6]. Among the direct oral anticoagulants (DOAC), **dabigatran** was approved for stroke prevention in nonvalvular AF (NVAF) in 2012 [7]. In the open-label RE-LY pivotal trial, compared to patients randomized to VKA, patients randomized to dabigatran 150 mg twice daily (D150) had fewer strokes and systemic embolisms (SSE) without significant difference in clinically relevant bleeding (CRB) or major bleeding (MB). Patients randomized to dabigatran 110 mg twice daily (D110) had the same rate of SSE but fewer bleeds. In addition, there was an excess of acute coronary syndrome (ACS) and upper gastrointestinal bleeding (UGIB) with D150 *vs*. VKA.

The translation of clinical trial results to actual practice is uncertain, since physicians, patients, drug prescriptions and usage may not be the same [8–11]. These differences may be especially relevant here for dose related effects. In the clinical trial, D110 and D150 were randomized in the same patient population. In contrast, in real life, D150 is the standard dose and D110 is a reduced dose indicated in patients with renal impairment, a higher risk of bleeding, or in older patient, i.e. in different patient populations. To estimate the real-life benefits and risks of D110 and D150 as used in the French population, a high-dimensional propensity score (hdPS)-matched cohort study of D110 or D150 compared to VKA was undertaken, using the *Systeme National des Données de Santé* (SNDS) nationwide claims and hospitalization database [12].

Research question and objectives

To compare the 1-year event rates of SSE, MB and all-cause death, as well as CRB, ACS and UGIB (and other bleeding sites), in new users of D110 or D150 *vs*. VKA for NVAF.

Methods

Study design

This was an hdPS-matched cohort study of all new users of D110 or D150 *vs*. VKA for NVAF in 2013, followed for one year.

Further information on methods can be found in supplementary data Appendix S1.

Setting

SNDS is the national healthcare data system in France. It links the nationwide mandatory public health insurance system claims database SNIIRAM to the national hospital discharge database PMSI and to the national death registry *CépiDC*. It includes more than 99% of the French population (66 million persons in 2013) from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires, and irrespective of socioeconomic status. The SNDS contains individual anonymized information on all medical and paramedical encounters, drugs claims, hospital admissions and procedures, and date of death, which are linked to create a longitudinal record of outpatient health encounters, hospital diagnoses and drug dispensing [12].

SNDS includes the hospital discharge summaries database, which includes all hospital discharge summaries from all private or public hospitals with main, associated and secondary diagnoses. Procedures are also recorded, as are the more expensive drugs or implantable devices.

Diagnoses may be identified from:

- Registration for long-term diseases [LTD, >4000 International Classification of Diseases (ICD)-10 codes] that warrant full healthcare coverage with no copayment. This registration is requested by the patient's physicians (outpatient or hospital), and diagnoses are verified by the healthcare insurance system. Registration is not mandatory. It may be missing for instance if the medical expenses are already covered by another chronic disease or the treatment is not expensive. LTD concern background diseases and are not directly related to any individual medical encounter. They are therefore not used for outcomes, only for baseline patient description parameters.
- Hospital discharge diagnoses (main, associated, secondary), which will inform on the reason for admission (main), and on background risk modifiers (e.g., diabetes, renal failure, coronary heart disease) that modify the hospital costs. Associate diagnoses inform on reasons for procedures as main diagnosis.
- Drug, laboratory, imaging or other outpatient or inpatient procedures, combinations of which may be diagnostic [13]. A patient with regular cardiology consultations, Holter recordings, use of rate-limiting anti-arrhythmic drugs and anticoagulants might be suspect of AF [4].

A patient with a registration for LTD for AF, or a hospital diagnosis of AF, would be considered as definite AF. Patients without definite AF but with a combination of specialist visit, procedure and medication would be suspected of having probable AF. Only definite AF patients were included in this study.

Subjects

All adults with a first dispensing of any oral anticoagulant in 2013 (cohort entry date, or index date) were identified. Patients had to have a 3-year database history without any dispensing of an anticoagulant before index date. Patients with valvular heart disease, valve replacement or repair, patients with another indication for anticoagulation (deep vein thrombosis or pulmonary embolism, orthopaedic surgery), as well as patients with erroneous or incomplete data were excluded (Table 1). Only patients with definite NVAF, and complete datasets (3-year look-back, 1-year follow-up were retained in the cohort study (103 101 patients). Of these, 44 653 patients had been prescribed VKA and 27 060 dabigatran, of whom 15 532 received D110 and 10 847 D150. New D110 and D150 users were separately 1:1 matched with new VKA users on sex, age at cohort entry date (± 1 year), cohort entry date (± 2 weeks), CHA_2DS_2-VASc and HAS-BLED scores, and a 500 variable hdPS using the Greedy method with a calliper of 0.05.

Table 1

Patient disposition

	Study populations N
Selection criteria	**371 539**
- **First dispensing of DOAC or VKA between 1st January 2013 and 31st December 2013**	
- **With a 3-year history without DOAC or VKA dispensing**	
Exclusion criteria	**227 319**
- **Missing or incorrect data (age, death date)**	701
- **Younger than 18 years at index date**	888
- **At least two treatment groups at index date**	151
- **Death at index date**	98
- **Uncertain identification (several beneficiaries, e.g., twins)**	732
- **Less than 3 years history in the SNDS before index date**	12 610
- **Alive at 1 year with incomplete data after index date**	284
- **Other probable indications**	86 857
- **Valvular disease history before index date**	25 509
- **No definite atrial fibrillation identified**	99 489
Possible NVAF without other probable indication	41 119
Study population	**103 101**
Definite NVAF without other probable indication	
- **Dabigatran**	27 060
D110	15 532
D150	10 847
- **VKA**	44 653
- **Other anticoagulants**	31 388
Matched populations	
- **D110 vs. VKA (per group)**	14 442 (93% of D110)
- **D150 vs. VKA (per group)**	8389 (77% of D150)

DOAC, direct acting anticoagulants; VKA, vitamin K antagonists; NVAF, nonvalvular atrial fibrillation; D110, dabigatran 110 mg twice daily; D150, dabigatran 150 mg twice daily

Variables

The index date or cohort entry date was the date of first dispensing of the anticoagulant, between 1 January 2013 and 31 December 2013, the first full year of marketing of dabigatran for NVAF in France.

Baseline covariates

Chronic medical conditions, cardiovascular risk factors, previous and concomitant drug dispensings, and hospital admission diagnoses were collected over the 3 years prior to the index date. From these, the CHA_2DS_2-VASc and HAS-BLED scores were calculated, indicative of the stroke risk in AF, and the bleeding risk in patients treated with VKA [4, 14]. HAS-BLED was adapted to the database information and, for example, labile INR, which is not relevant to patients without previous anticoagulant use or to DOAC, was not included. We found this score predictive of bleeding in a previous study [4].

The Charlson comorbidity score, adapted to the data source [15], was computed and used for further adjustment. We also included the total medical expenses over the previous year and the previous month as an indicator of overall disease burden [16].

The ICD-10 codes used to identify the elements of the CHA_2DS_2-VASc and HAS-BLED scores are indicated in Appendix S2 in supplementary data.

Exposure

The drug exposure period started at the 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 [4].

Follow-up

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

Study outcomes

The primary outcomes were hospitalizations with a main diagnosis of ischaemic stroke or systemic embolism, major bleeding, or all-cause death, individually and combined.

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

Major bleeding was intracerebral haemorrhage, critical organ bleeding, any CRB with blood transfusion or acute posthaemorrhagic anaemia, or death during hospital stay (ISTH definition) [17]. CRB were all hospitalizations with a main diagnosis of bleeding. Specific bleeding sites were intracerebral haemorrhage, gastrointestinal (GI) bleeding, urogenital bleeding, other critical organ or site bleeding, and other bleeding.

The ICD-10 codes used to identify these outcomes are given in supplementary material Appendix S3. The same codes have been used for other studies of outcomes in anticoagulant users and NVAF [4, 14] and for studies of outcomes after myocardial infarction. [11, 18] Stroke has been validated in a specific study, with a PPV >90% [19].

Statistical methods

To reduce confounding due to imbalance in study covariates, hdPS matching was used [20]. The hdPS is a measure

of the probability of being treated by one of the anticoagulants studied related to the outcome (D110 *vs*. VKA, D150 *vs*. VKA). Unconditional binary logistic regression was used to estimate the association of the available variables with the outcomes, deriving separately predicted probability of patients initiating D110 or D150 rather than VKA [21, 22]. HdPS considered all the information in the database, with multiple data dimensions from patient data and healthcare reimbursements during the 3-year period before index date. The variables included demographic variables at inclusion (age, sex), individual stroke and bleeding risk factors from the CHA$_2$DS$_2$-VASc and HAS-BLED scores, hospitalization other than cardioversion or catheter ablation in the month before index date, chronic obstructive pulmonary disease, coronary heart disease, diabetes, and 500 other variables [21–24] selected from four dimensions:

• Chronic disease registration ICD-10 codes;
• ICD-10 hospitalization codes during the 3 years before index date;
• Medical and paramedical visits and laboratory tests;
• Drugs dispensed during the previous year.

The codes and variables concerned are listed in appendix S4.

D110 *vs*. VKA and D150 *vs*. VKA patients were matched separately on the hdPS score.

HdPS calculation used the routines developed within the Division of Pharmacoepidemiology and Pharmacoeconomics and Brigham and Women's Hospital and Harvard Medical School (www.drugepi.org) [25].

Standardized mean differences were used to measure goodness of matching. An absolute standardized mean difference of 0.1 (10%) or less indicates a negligible difference between groups [26] (see supplementary data Figures S2B and S3B).

The main analysis was performed in the matched patients during exposure as defined above (on treatment). A complementary analysis added further adjustment on Charlson's index and medical costs during the year and during the month previous to index date (Supplementary Table S7).

Incidence rates were measured using event counts and exposed patient-time, and represented with Kaplan–Meier plots. Hazard ratio and 95% confidence intervals (CI) of D110 *vs*. VKA and D150 *vs*. VKA were estimated using Cox proportional hazards model for death, and Fine and Gray's model for competing risks for nonfatal events [27].

In addition, the number needed to observe one fewer event in one group compared to the other (NNT) was computed using $1/[p(A) - p(B)] \times 100$ where p(A) and p(B) are event rates with treatment A or B.

Sensitivity analyses were performed on the whole population using adjustment on sex, age at index date and hdPS (in deciles), rather than matching, to check the generalizability of the matched results to the full populations. (See Supplementary Figure S4A,B).

Statistical analysis was conducted by Bordeaux PharmacoEpi, a research platform of University of Bordeaux, using SAS® software (SAS Institute, Version 9.4, Cary, NC,

USA) and the Harvard routines for hdPS (SAS pharmacoepi toolbox, www.drugepi.org).

Ethics and registration

This study was done in an anonymized claims database. For such secondary use of previously collected data, individual patient consent was not required by law. This study was requested by national healthcare authorities. It was authorized by the National Consultative Committee for the treatment of healthcare data (CCTIRS), and by the National Commission on Informatics and Liberties (CNIL) on 22 October 2015 under N°1 858 904. It is registered with the EUPAS registry as EUPAS13017 (www.encepp.eu), and in Clinicaltrials.gov as NCT02785354.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [28].

Results

Of 371 539 incident anticoagulant users in 2013, 103 101 had NVAF; 44 653 received VKA and 27 060 dabigatran, of whom 15 532 were dispensed D110 and 10 847 D150 (Table 1). Overall, D110 patients were older and at higher risk of stroke and bleeding than D150 patients (see Supplementary Tables S1 and S2).

In total, 14 442 D110 patients (93% of D110 patients) were matched to the same number of VKA patients, and 8389 D150 patients (77% of D150 patients) were matched to the same numbers of VKA patients. (Tables 1 and 2). VKA patients had the same characteristics as their respective matched dabigatran populations. HdPS were identically distributed in matched D110 and VKA or D150 and VKA patients (Supplementary Figure S1A,B). Standardized mean differences in matched patients were < 5% for all parameters, and generally <2%. (Supplementary Figure S2A,B for D110 *vs*. VKA, supplementary Figure S3A,B for D150 *vs*. VKA).

Median duration of treatment exposure was 205 days for D110 *vs*. 251 days for matched VKA, and 246 days for D150 *vs*. 206 days for their matched VKA.

Outcomes

In the D110 population, all primary outcomes: SSE, MB and all-cause death were significantly less common than in their matched VKA population (Figure 1). Among secondary outcomes, CRB, including intracerebral haemorrhage and other critical organ or site bleeding were also less common in D110 users. There was no difference between D110 and VKA for ACS or UGIB.

The NNT with D110 compared to matched VKA users was 78 patients to observe one fewer death and 33 for any one of the primary endpoints (composite endpoint).

Compared to matched VKA patients, D150 patients had significantly fewer MB and deaths. The hazard ratio for SSE (0.75 [0.56–1.04]) did not quite reach statistical significance, due to the small number of events (Figure 2).

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Table 2

Baseline patient characteristics of the patients on dabigatran 110 mg twice daily (D110) or dabigatran 150 mg twice daily (D150), matched to vitamin K antagonists (VKA). All standardized differences were < 5% (see Supplementary Figures 2B and 3B for distribution of standardized differences)

|	Matched populations			
	D110 *n* = 14 442	Matched VKA *n* = 14 442	D150 *n* = 8389	Matched VKA *n* = 8389
Sex, *n* (%)				
Male	7077 (49.0)	7077 (49.0)	5634 (67.2)	5634 (67.2)
Age at index date (in years)				
Mean (± SD)	78.6 (9.1)	78.6 (9.1)	67.3 (9.0)	67.3 (9.1)
Age at index date (in categories), *n* (%)				
<60 years	553 (3.8)	545 (3.8)	1509 (18.0)	1502 (17.9)
60–69 years	1672 (11.6)	1710 (11.8)	3239 (38.6)	3229 (38.5)
70–79 years	4420 (30.6)	4425 (30.6)	3173 (37.8)	3168 (37.8)
≥ 80 years	7797 (54.0)	7762 (53.7)	468 (5.6)	490 (5.8)
Stroke risk factors (score), *n* (%)				
Congestive heart failure	2966 (20.5)	3030 (21.0)	1083 (12.9)	1132 (13.5)
Hypertension	6651 (46.1)	6681 (46.3)	2793 (33.3)	2962 (35.3)
Age > 65 years	13 056 (90.4)	13 048 (90.3)	5123 (61.1)	5147 (61.4)
Age 65–74 years	2635 (18.2)	2636 (18.3)	3611 (43.0)	3583 (42.7)
Age ≥ 75 years	10 622 (73.5)	10 609 (73.5)	1881 (22.4)	1903 (22.7)
Diabetes mellitus	3016 (20.9)	3171 (22.0)	1811 (21.6)	2001 (23.9)
Stroke or transient ischaemic attack	1980 (13.7)	1969 (13.6)	801 (9.5)	865 (10.3)
Stroke	1691 (11.7)	1702 (11.8)	676 (8.1)	762 (9.1)
Vascular disease	2165 (15.0)	2022 (14.0)	843 (10.0)	1028 (12.3)
Abnormal renal function	705 (4.9)	776 (5.4)	137 (1.6)	175 (2.1)
Abnormal liver function	245 (1.7)	207 (1.4)	115 (1.4)	166 (2.0)
Bleeding history	342 (2.4)	328 (2.3)	104 (1.2)	163 (1.9)
Medication usage predisposing to bleeding	8596 (59.5)	8413 (58.3)	4479 (53.4)	4821 (57.5)
CHA$_2$DS$_2$-VASc score, *n* (%)				
0–1	1290 (8.9)	1331 (9.2))	3024 (36.0)	2882 (34.3)
2	2562 (17.7)	2472 (17.1)	2196 (26.2)	2120 (25.3)
>2	10 590 (73.4)	10 639 (73.7)	3169 (37.8)	3387 (40.4)
HAS-BLED score, *n* (%)				
0	442 (3.0)	426 (3.0)	1187 (14.1)	987 (11.8)
1	3172 (22.0)	3165 (21.9)	2842 (33.9)	2681 (32.0)
2	5727 (39.7)	5856 (40.5)	2786 (33.2)	2996 (35.7)
3	3894 (27.0)	3832 (26.5)	1299 (15.5)	1406 (16.8)
>3	1207 (8.3)	1163 (8.1)	275 (3.3)	319 (3,8)
First drug exposure duration per patient (in days)				
Median	205.0	251.0	246.0	206.0
Interquartile range	66.0–365.0	110.0–365.0	87.0–365.0	90.0–365.0
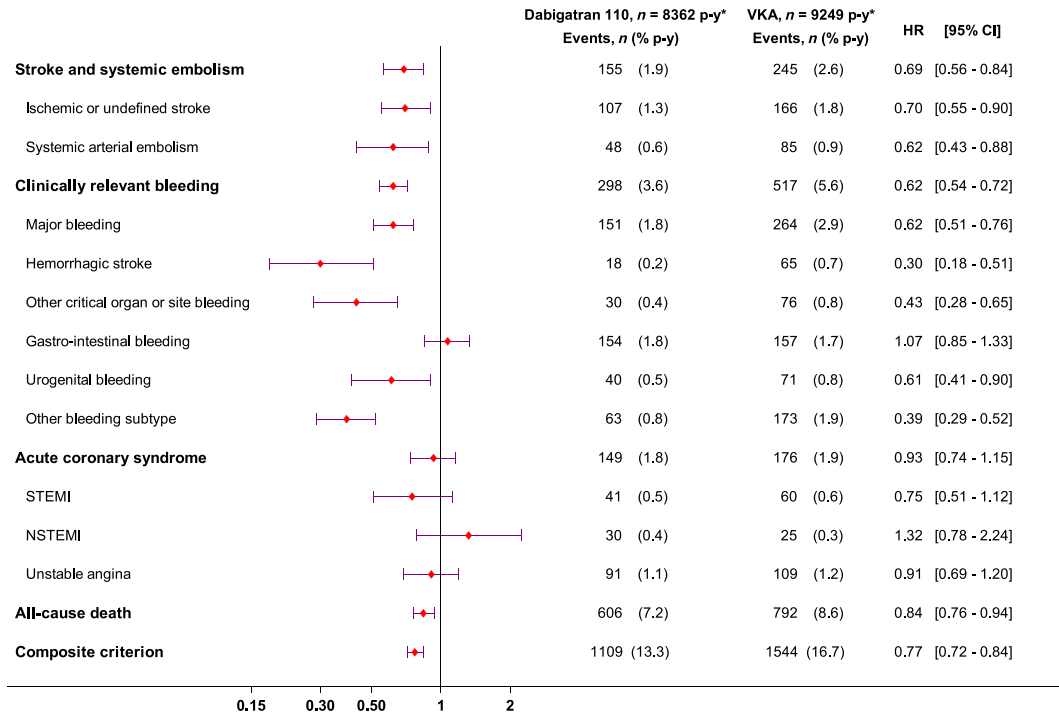
Figure 1

Effectiveness and safety outcomes in dabigatran 110 mg twice daily *vs.* vitamin K antagonist (VKA) patients: forest plots. STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction
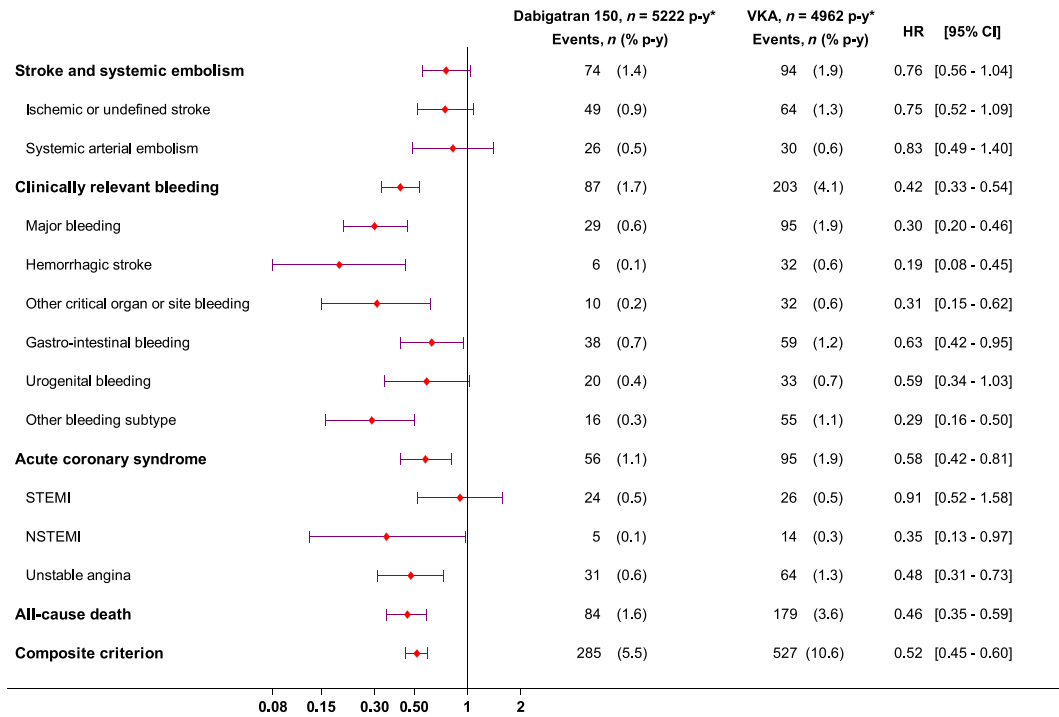

Figure 2

Effectiveness and safety outcomes in dabigatran 150 mg twice daily *vs.* vitamin K antagonist (VKA) patients: forest plots. STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

Among secondary outcomes, CRB, including intracerebral haemorrhage, other critical organ or site bleeding, UGIB and ACS were less common in D150 users than in matched VKA users (Figure 2). The relevant NNT were 88 patients treated with D150 rather than VKA to observe one fewer death, and 35 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 (Supplementary Figures S4 and S5), with similar NNT.

Adding the Charlson comorbidity index as adapted to SNDS, a predictor of 1-year mortality, did not modify the results (Supplementary Table S7).

Events occurred regularly throughout the study period (Supplementary Figures S6 and S7).

Discussion

In this countrywide new users cohort study of the real-life experience with dabigatran 110 mg or 150 mg twice daily compared to hdPS-matched VKA-treated patients with definite NVAF, dabigatran at either dose was associated with better safety than VKA, and lower mortality. D110 also showed better effectiveness. We did not find the excess UGIB and ACS reported in the RE-LY clinical trial [29–31].

The populations were different from those included in RE-LY (Supplementary Tables S3 and S4), with lower overall bleeding and death in RE-LY (Supplementary Tables S5 and S6). In RE-LY, the attribution of the drugs in the three treatment groups was random, so that the patient characteristics for D110, D150 and VKA were identical. In real life, D110 is indicated in older patients at higher risk of stroke or bleeding than D150. In our populations, D110 was indeed used in older patients than D150, with more previous history of or concomitant diseases, with higher $CHAD_2VA_2SC$ and HAS-BLED scores, and correspondingly higher event rates (Supplementary Tables S5 and S6). In addition, in RE-LY over 50% of the patients had had an experience of VKA use before randomization, whereas all our patients were new users. Previous experience of VKA might select a population of users at lower risk of events. For these reasons and because of the usual exclusion of patients with poor prognosis from clinical trials [11] it was not unexpected to find real life results different from RE-LY.

Differences in bleeding rates between D110 and D150 relate to the choice of the drug dosage in real life, adapted to the patients' individual bleeding risk as perceived by the prescriber. Since D110 is indicated in patients with a higher risk of bleeding, old age or organ failures, it is unsurprising that D110 patients would have higher bleeding rates than the younger, lower-risk D150 patients. This was not found in RE-LY, where the choice of dosage was imposed by randomization. This difference in event rates was also noted between VKA patients matched to D110 or D150, compared to the RE-LY VKA arm (Figure S4A,B).

The lower risk of bleeding with D110 or D150 than matched VKA was not at the expense of effectiveness. The signals of increased GI bleeding and increased coronary artery events with D150 in RE-LY were not confirmed (Supplementary Table S6) [32, 33].

Our results are globally consistent with other epidemiological studies done in different settings [33] with some differences: we did not find more GI bleeding compared to VKA with either dose, and in fact less GI bleeding with D150 than VKA, in contrast for instance with RE-LY, Graham [31] or Hernandez [30]. This might be related to excess GI bleeding in France with VKA, maybe because of environmental or sociocultural factors, poorer control of bleeding risks with warfarin or other regional differences as shown with Rocket-AF [34]. It might also be due to higher relative VKA dosing, which would fit with the combination of no difference for SSE and more bleeding, relative to D150 instead of more SSE and less bleeding with VKA in these other studies.

For D110 (Supplementary Table S6), event rates were much higher here than in RE-LY, as expected from the age and risk differences. In this elderly high-risk population, SSE, bleeding and death rates were lower with D110 than with VKA. This cannot be compared to the RE-LY trial, where the patients on D110 were irrelevant to real-life use, or to the pharmacoepidemiological studies done in the USA, where D110 is not marketed [35, 36].

In Denmark (in a healthcare system similar to ours), Larsen *et al*. [37] included only D150, with a median age of 67 *vs*. 72 years for warfarin. They also found lower rates of all bleeding with dabigatran compared to warfarin but did not specifically study GI bleeding or D110 [37].

Staerk *et al*.'s study did not include warfarin [38].

In Taiwan, Chan *et al*. [39] found an HR for GI bleeding of 0.77 [0.59–1.02], dabigatran *vs*. warfarin. These results were reasonably similar to ours (HR < 1, but wide confidence intervals because of fewer patients and events), for both doses of dabigatran [39].

These studies provide globally coherent results [33]. Results could differ in other populations, depending on healthcare systems, or social and cultural differences. We did not directly compare D110 with D150, which were used in very different populations. Our results are observations of the drugs as they were used during the timeframe of the study. We cannot presume what the results might be if patients on VKA were switched to dabigatran, although there are indications that the results might be the same [40].

Study limits and biases

This was not a randomized clinical trial, so that the results, despite our best efforts, might still suffer from unmeasured confounding.

The matched cohorts were identical to within <5% of standardized mean differences in 500 variables in four dimensions, including all measurable bleeding and embolism risk factors as well as common fatality risks, and all previous medical history and drug dispensings in the previous 3 years. The differences between crude and matched results indicate the degree to which biases were corrected. Adding the Charlson comorbidity index, a predictor of 1-year mortality in the database [15], did not change the results, especially on mortality. The hdPS distribution curves overlapped over the whole population range, so that results in the matched population might safely be extrapolated to the whole population, as indicated by the similarity between results in matched populations and adjusted results in whole populations.

HdPS matching has already been used in many studies in the field of pharmacoepidemiology and drug safety. Unmeasured confounders such as smoking, obesity etc. may be approached 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 [22, 23].

The data in the national claims database are collected prospectively for healthcare insurance purposes, independently from this or any other study, *a priori* excluding information bias [12]. Data are present for the whole population, and there is no selection of patients according to social status, employer, age or pre-existing conditions as might exist in other population databases [12, 31]. All outpatients dispensed an anticoagulant during the study inclusion period were identified. Drugs started in hospital would be rapidly relayed by an outpatient prescription, which is captured. There are no sampling issues, since essentially the whole population is captured.

There is little or no unrecorded use (e.g. internet pharmacies) of these expensive reimbursed drugs. Drugs are dispensed as fixed quantity preparations (e.g. dabigatran, 150 mg per capsule, 60 capsules) that are individually identified in the system, providing the exact quantity and dosage dispensed over time.

Diagnoses were based on hospital discharge summaries and on registration for chronic diseases, and any other available data such as drug dispensing or procedures. The same methods and diagnostic algorithms were used in similar studies of VKA and DOAC in NVAF, [4, 14, 40] or of the same outcomes in other circumstances [11, 18]. The identification of all-cause death is exhaustive.

Undocumented bleeding resulting in death before the patient reaches the hospital would have been captured in the overall all-cause death rates, which was also lower with dabigatran at both dosages.

Conclusions

This countrywide hdPS-matched new users cohort study found in real-life that dabigatran as used appears to be at either dose at least as effective and safer than VKA for the prevention of thromboembolic events in NVAF, with a lower overall mortality and an NNT around 80 for death. Considering the annual number of users of anticoagulants for NVAF, these results could translate into hundreds fewer deaths and thousands fewer events yearly in a country such as France.

Competing Interests

N.M. declares fees from Sanofi, Merck-Serono, Merck & Co, IPSEN, Novartis, Vifor Pharma and Servier for training, data safety monitoring boards, and consulting activities, none in the field of this study. Y.C. declares consulting fees from Bayer, Servier, Astra-Zeneca, Boehringer, Vifor Pharma. P.M. declares consulting fees with Bristol-Myers Squibb, Pfizer and Bayer. The other authors have no competing interests to declare.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13815/suppinfo

Table S1
Description of dabigatran 110 mg twice daily, dabigatran 150 mg twice daily and vitamin K antagonist populations before matching

Table S2 Crude event rates during drug exposure

Table S3 Baseline patient characteristics in dabigatran 110 mg twice daily users: comparison with RE-LY

Table S4 Baseline patient characteristics in dabigatran 150 mg twice daily users: comparison with RE-LY

Table S5 Outcomes in matched dabigatran 110 mg twice daily users: comparison with RE-LY

Table S6 Outcomes in matched dabigatran 150 mg twice daily users: comparison with RE-LY

Table S7 matched analyses of main outcomes with Charlson score and cost before index date as additional adjustment variables

Figure S1 High-dimensional propensity score distributions for unmatched (left panels) and matched (right panels) cohorts, of dabigatran 110 mg twice daily *vs*. vitamin K antagonist (A) and dabigatran 150 mg twice daily *vs*. vitamin K antagonist (B)

Figure S2 (A) Standardized mean differences in characteristics included in the high-dimensional propensity score, before matching, dabigatran 110 twice daily *vs*. vitamin K antagonist. Each line is a different parameter (490 shown). (B) Standardized mean differences in characteristics included in the high-dimensional propensity score, after matching, dabigatran 110 *vs*. vitamin K antagonist. Each line is a different parameter (490 shown)

Figure S3 (B) Standardized mean differences in characteristics included in the high-dimensional propensity score, before matching, dabigatran 150 twice daily *vs*. vitamin K antagonist. Each line is a different parameter (490 shown). (B) Standardized mean differences in characteristics included in the high-dimensional propensity score, after matching, dabigatran 150 *vs*. vitamin K antagonist. Each line is a different parameter (490 shown)

Figure S4 Forest plots for crude, adjusted and matched analyses of main outcomes, dabigatran 110 mg twice daily *vs*. vitamin K antagonist

Figure S5 Forest plots for crude, adjusted and matched analyses of main outcomes, dabigatran 150 mg twice daily *vs*. vitamin K antagonist

Figure S6 One-year cumulative incidence (Kaplan–Meier estimate) of outcomes during the first drug exposure period for matched dabigatran 110 mg twice daily and vitamin K antagonist patients. Upper panels, from left to right: acute thrombotic events, clinically relevant bleeding, major bleeding. Lower panels, from left to right acute coronary syndromes, death, composite outcomes

Figure S7 One-year cumulative incidence (Kaplan–Meier estimate) of outcomes during the first drug exposure period for matched dabigatran 150 mg twice daily and vitamin K antagonist patients. Upper panels, from left to right: acute thrombotic events, clinically relevant bleeding, major bleeding. Lower panels, from left to right acute coronary syndromes, death, composite outcomes

Appendix S1 Methods

Appendix S2 Codes used for CHA2DS2-VASc and HAS-BLED scores

Appendix S3 International Classification of Diseases codes for outcomes

Appendix S4 Variables included in the high-dimensional propensity score