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Safety and effectiveness of appropriately and inappropriately dosed rivaroxaban or apixaban versus warfarin in patients with atrial fibrillation: a cohort study with nested case–control analyses from UK primary care

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ABSTRACT

Objectives To investigate effects of appropriately and inappropriately dosed apixaban/rivaroxaban versus warfarin on effectiveness and safety outcomes in patients with non-valvular atrial fibrillation (NVAF).

Design Cohort study with nested case–control analyses using primary care electronic health records (IQVIA Medical Research Data UK database).

Setting UK primary care.

Participants Patients aged ≥18 years with NVAF newly prescribed apixaban (N=14 701), rivaroxaban (N=14 288) or warfarin (N=16 175) between 1 January 2012 and 30 June 2018, and followed up to 31 December 2018.

Primary and secondary outcome measures Incident cases of ischaemic stroke/systemic embolism (IS/SE) and intracranial bleeding (ICB). Cases were matched to controls on age, sex and OAC naïve status. Using logistic regression, adjusted ORs with 95% CIs were calculated for the outcomes comparing apixaban/rivaroxaban use (appropriate or inappropriate dosing based on the product label criteria) and warfarin.

Results For IS/SE, ORs (95% CIs) for apixaban versus warfarin were 1.19 (0.92–1.52) for appropriate dose and 1.01 (0.67–1.51) for inappropriate dose; for rivaroxaban versus warfarin, estimates were 1.07 (0.83–1.37) for appropriate dose and 1.21 (0.78–1.88) for inappropriate dose. For ICB, ORs (95% CIs) for apixaban versus warfarin were 0.67 (0.44–1.00) for appropriate dose and 0.45 (0.21–0.95) for inappropriate dose; for rivaroxaban versus warfarin, estimates were 0.81 (0.55–1.20) for appropriate dose and 1.14 (0.56–2.31) for inappropriate dose.

Conclusions Dosing appropriateness in NVAF was not associated with a significant difference in IS/SE risk or increase in ICB risk versus warfarin. These findings may reflect residual confounding and biases that were difficult to control, as also seen in other observational studies. They should, therefore, be interpreted with caution, and prescribers should adhere to the dosing instructions in the respective Summary of Product Characteristics. Further studies on this topic from real-world populations are needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our findings have external validity because the IQVIA Medical Research Data UK database is representative of the UK general population demographic.
⇒ The availability of data on age, bodyweight and renal function enabled an accurate categorisation of inappropriate/appropriate direct oral anticoagulant (DOAC) dosing.
⇒ DOAC dosing appropriateness was assessed at the time of the event date in the nested case–control analyses to minimise exposure misclassification that can occur over a lengthy follow-up duration.
⇒ The classification of dosing appropriateness could not incorporate the individual clinical judgements made in the decision to prescribe standard/reduced DOAC doses.
⇒ Residual confounding, bias (favouring warfarin) from preferential prescribing of DOACs to higher risk patients, and differential exposure misclassification (potentially higher for warfarin), cannot be excluded.

INTRODUCTION

Direct oral anticoagulants (DOACs) have largely replaced vitamin K antagonists such as warfarin as the standard of care for patients with atrial fibrillation (AF) at high risk of stroke.[1 2] An important aspect of DOAC treatment is dose adjustment in accordance with the approved drug label. This requires consideration of age, bodyweight and renal function, although the specific requirements differ between individual DOACs.[3 4] In a recently published meta-analysis of 23 studies totalling 162 474 patients with AF,[5] the pooled

prevalence of off-label DOAC dosing was 24%, although not all the included studies had information on all DOAC dose-reduction criteria to calculate their estimate. In our previous research of patients with AF,[6] underdosing was seen in 22% of patients initiated on apixaban and 9% initiated on rivaroxaban, based on evaluating all DOAC dose-reduction criteria. A study of elderly patients with AF in the US found that 23% received an inappropriate dose of a DOAC,[7] while a study in Israel[8] reported that 39% of patients with AF and initiated on DOAC therapy received an off-label dose reduction—estimates that were also calculated using all DOAC dose-reduction criteria.

Arbel *et al*[8] showed that, in patients with AF, use of off-label reduced dose DOACs versus per-label reduced dose DOACs was associated with a significant increased risk of stroke, myocardial infarction (MI) and death as a composite outcome, as well as an increased risk of severe bleeding. However, we are unaware of any study that has evaluated outcomes in association with inappropriate dosing in terms of individual DOACs versus warfarin, based on DOAC dose-reduction criteria in the European product label. It is important to note that physicians make individual clinical judgements whether to prescribe a standard/reduced DOAC dose based on the specific clinical characteristics of the patient, and this may not always align with the instructions on the product label. Notwithstanding this, we performed a large population-based cohort study with nested case–control analyses that aimed to investigate the effect of appropriately and inappropriately dosed apixaban/rivaroxaban versus warfarin on the risk of major effectiveness and safety outcomes in patients with non-valvular atrial fibrillation (NVAF) in the UK. Warfarin was chosen as the comparator in order to better understand the real-world performance of apixaban and rivaroxaban in different dosing scenarios relative to the comparator used in their respective pivotal clinical trials.

METHODS

Data sources

We used data from the IQVIA Medical Research Data UK (IMRD-UK) database (formerly The Health Improvement Network), a population-based longitudinal database of anonymised primary care records from participating UK practices and covering approximately 6% of the UK population.[9] The database captures demographic and clinical information entered by general practitioners during routine patient care and records all prescriptions issued in the primary care setting. Clinical data are predominantly entered using Read codes,[10] the standard clinical coding system used by the UK's National Health Service, with additional details able to be entered manually as free text. Information received from secondary care is entered into a patient's primary care record retrospectively. The IMRD-UK is representative of the UK with regards to age, sex and geographic distribution.[11] The study protocol was approved by an Independent Scientific Research Committee (reference SRC-19THIN006).

Patient and public involvement

There was no patient or public involvement in the design, conduct, reporting or dissemination plans of our research.

Study population and OAC cohorts

Identification of the study cohorts is depicted in online supplemental figure 1. The study population included individuals aged ≥18 years with a first prescription for apixaban, rivaroxaban or warfarin between 1 January 2012 and 30 June 2018 (see online supplemental methods for further inclusion/exclusion criteria). We categorised patients into three mutually exclusive cohorts: new-users of (a) apixaban, (b) rivaroxaban and (c) warfarin. We restricted the study cohorts to patients with a code for AF any time before the first prescription for the study drug or in the 2 weeks after, and who had no code for valvular replacement or mitral stenosis during these time periods. Patients were considered to be non-naïve if they had a prescription for an OAC other than the study drug before the start date, otherwise they were considered to be OAC naïve.

Dosing recommendations

Apixaban, rivaroxaban and warfarin tablet strengths were derived from the description of the prescribed product, and daily dosing frequency/posology was derived from instructions in the free text. For DOACs, a posology of three or more doses per day was considered invalid. We categorised new users of apixaban/rivaroxaban as eligible for standard or reduced dose DOAC therapy based on the information provided in the respective European Union label, as described previously.[6] Patients eligible for standard dose DOAC who were prescribed an inappropriate reduced dose DOAC were considered potentially underdosed, and patients eligible for reduced dose DOAC who were prescribed an inappropriate standard dose were considered potentially overdosed. We were unable to do this for the warfarin cohort due to the difficulty in later assessing whether these patients were appropriately/inappropriately dosed—dose adjustment for warfarin is very variable and it would have been too complex to determine appropriate dose adjustment using the data recorded.

Outcome identification

Separate follow-ups of the study cohorts were conducted to identify incident cases of each study outcome. Primary outcomes were ischaemic stroke/systemic embolism (IS/SE) for effectiveness, and intracranial bleeding (ICB, comprising intracerebral haemorrhage, subarachnoid haemorrhage, subdural and epidural hematoma) for safety. Secondary outcomes included MI, haemorrhagic stroke (intracerebral haemorrhage and subarachnoid haemorrhage) and all-cause mortality. Patients were followed from the start date until the earliest of the following: a diagnostic code for the outcome of interest, death or the last date of data collection (31 December

2018). To confirm incident case status, we manually reviewed the computerised clinical profiles (with free text when available) of all potential cases, excluding those where event onset was deemed to precede the start of follow-up, or when the event did not involve a hospital visit/admission. The number of confirmed cases was as follows: IS (n=1474), SE (n=13), MI (n=631) and ICB (n=286, consisting of 130 intracerebral haemorrhage, 36 subarachnoid haemorrhage and 120 subdural/epidural hematoma).

Nested case–control analyses

Individual nested case–control analyses were performed for each outcome. The event date for confirmed cases was the date of the outcome. Controls for each case were randomly sampled from the case risk set, which included all individuals from the study cohorts at risk of the outcome on the event date and were matched on age, sex and OAC naïve status. The case:control ratio was based on the number of available controls: 1:3 for effectiveness outcomes, 1:4 for safety outcomes and 1:1 for mortality. Sampling was performed sequentially without replacement. The event date for controls was the same as their matched case. Current use of apixaban/rivaroxaban/warfarin was determined using prescription records and defined as use that lasted until/over the event date or ended in the previous 30 days (individuals exposed to more than one OAC at the event date were not deemed to be current users).

Covariates

We obtained patient information during two time periods: before the start of follow-up (baseline characteristics) and before the event date (for the nested case–control analyses). We extracted information on demographics (age and sex) and on bodyweight and renal function for which we used the most recently recorded measurement. For renal function, we used the most recent valid serum creatinine value in the previous year to calculate the estimated glomerular filtration rate (eGFR) expressed as mL/min/1.73[2] using the Chronic Kidney Disease Epidemiology Collaboration equation[12] but excluding ethnicity as this was not routinely recorded. Individuals with no valid serum creatinine measurement were assigned to a category 'unknown'. We also collected data on lifestyle variables (body mass index (BMI), alcohol consumption and smoking), health service use in the previous year (ie, hospitalisations, referrals, primary care visits), CHA_2DS_2Vasc score for stroke risk, HAS-BLED score for major bleeding risk, frailty (based on an algorithm for studies using primary care EHRs),[13] history of cardiovascular/gastrointestinal disease, other comorbidities, and comedications (in the previous year), details of which have been published previously.[6]

Statistical analysis

Baseline characteristics of each study cohort were described using counts and percentages for categorical variables and means with SD for continuous variables. Incidence rates of each outcome were calculated by dividing the number of confirmed cases by the total person-time, with 95% CIs, assuming a Poisson distribution. Incidence rates were also stratified by age and sex. For the nested case–control analyses, we used unconditional logistic regression to calculate ORs with 95% CIs as estimates of the relative risk of the study outcome with apixaban/rivaroxaban use (current use) versus warfarin (current use) as the reference group, adjusted for confounders. Covariates included in the final models were selected using a stepwise automated approach (p value threshold 0.1). We explored associations according to any dose of apixaban/rivaroxaban, standard/reduced dose and appropriate/inappropriate use, which was assessed at the event date. Subgroup analyses were performed among individuals with (a) chronic kidney disease (CKD), (b) diabetes, (c) CHA_2DS_2VASc score >4, (d) HAS-BLED score >2, (d) severe frailty and (e) no missing data on eGFR and BMI. Analyses were performed using Stata V.12.1.

RESULTS

Patient characteristics

We identified 45 164 patients with NVAF: 14 701 started on apixaban, 14 288 on rivaroxaban and 16 175 on warfarin (online supplemental figure 1). Baseline characteristics are described in table 1, with the apixaban/rivaroxaban cohorts stratified by whether the first prescription was standard or reduced dose. Compared with patients prescribed standard dose apixaban/rivaroxaban, those prescribed reduced dose apixaban/rivaroxaban were, on average, older, more severely frail and underweight. They were also more likely to have a higher CHA_2DS_2VASc score, higher HAS-BLED score, reduced renal function and a history of cardiovascular disease. Approximately 82% of the rivaroxaban cohort and 70% of the apixaban cohort received the standard dose. Mean age was similar in patients prescribed warfarin (73.7 years) and those prescribed standard dose apixaban/rivaroxaban (73.2/72.0 years). Among patients prescribed standard dose apixaban, this was appropriate in 96.8%; for reduced dose apixaban, this was appropriate in 42.7% (online supplemental table 1). Among patients prescribed standard dose rivaroxaban, this was appropriate in 93.1%; for reduced dose rivaroxaban, this was appropriate in 65.7% (online supplemental table 1). The distribution of patients eligible for standard/reduced DOAC dose according to the product label is shown in online supplemental table 2. Mean follow-up in the study cohorts was 1.9 years for rivaroxaban, 1.7 years for apixaban and 3.0 years for warfarin.

Primary outcomes

Ischaemic stroke and systemic embolism

The crude incidence rate of IS/SE per 1000 person-years was 8.33 (95% CI 7.24 to 9.54) for the apixaban cohort, 8.91 (95% CI 7.84 to 10.09) for the rivaroxaban cohort

Table 1 Baseline characteristics of the cohort of 45 164 patients with NVAF (and no other recent OAC indication) newly prescribed an OAC, stratified by standard or reduced dose*

	Apixaban (N=14 701)		Rivaroxaban (N=14 288)		Warfarin (N=16 175)
	Standard dose (n=10 237; 69.6%)	Reduced dose (n=4464; 30.4%)	Standard dose (n=11 689; 81.8%)	Reduced dose (n=2599; 18.2%)	NA (n=16 175)
Sex					
Male	6267 (61.2)	1806 (40.5)	7018 (60.0)	1078 (41.5)	9061 (56.0)
Female	3970 (38.8)	2658 (59.5)	4671 (40.0)	1521 (58.5)	7114 (44.0)
Age (years)					
<60	1119 (10.9)	71 (1.6)	1220 (10.4)	34 (1.3)	1375 (8.5)
60–69	2625 (25.6)	216 (4.8)	2669 (22.8)	132 (5.1)	3619 (22.4)
70–79	4158 (40.6)	744 (16.7)	4362 (37.3)	610 (23.5)	6295 (38.9)
80–89	2115 (20.7)	2626 (58.8)	2990 (25.6)	1342 (51.6)	4384 (27.1)
≥90	220 (2.1)	807 (18.1)	448 (3.8)	481 (18.5)	502 (3.1)
Mean age (SD)	72.0 (10.1)	83.0 (7.8)	73.2 (10.5)	82.5 (7.9)	73.7 (10.1)
OAC naïve status					
Naïve	7397 (72.3)	2838 (63.6)	7640 (65.4)	1482 (57.0)	16 060 (99.3)
Non-naïve	2840 (27.7)	1626 (36.4)	4049 (34.6)	1117 (43.0)	115 (0.7)
BMI					
10–19 (underweight)	172 (1.7)	413 (9.3)	371 (3.2)	155 (6.0)	446 (2.8)
20–24 (healthy weight)	1857 (18.1)	1454 (32.6)	2454 (21.0)	713 (27.4)	3357 (20.8)
25–29 (overweight)	3774 (36.9)	1420 (31.8)	4140 (35.4)	901 (34.7)	5801 (35.9)
≥30 (obese)	4007 (39.1)	965 (21.6)	4243 (36.3)	717 (27.6)	5894 (36.4)
Missing	427 (4.2)	212 (4.7)	481 (4.1)	113 (4.3)	677 (4.2)
Smoking					
Non-smoker	4107 (40.1)	1984 (44.4)	4701 (40.2)	1123 (43.2)	6604 (40.8)
Smoker	915 (8.9)	274 (6.1)	994 (8.5)	135 (5.2)	1368 (8.5)
Ex-smoker	5196 (50.8)	2198 (49.2)	5978 (51.1)	1339 (51.5)	8185 (50.6)
Unknown	19 (0.2)	8 (0.2)	16 (0.1)	2 (0.1)	18 (0.1)
Alcohol (units/week)					
None	1961 (19.2)	1344 (30.1)	2074 (17.7)	743 (28.6)	2982 (18.4)
1–9	4379 (42.8)	1902 (42.6)	5329 (45.6)	1197 (46.1)	7523 (46.5)
10–20	1895 (18.5)	531 (11.9)	1963 (16.8)	252 (9.7)	2734 (16.9)
21–41	646 (6.3)	125 (2.8)	790 (6.8)	74 (2.8)	941 (5.8)
≥42	358 (3.5)	56 (1.3)	378 (3.2)	40 (1.5)	391 (2.4)
Unknown	998 (9.7)	506 (11.3)	1155 (9.9)	293 (11.3)	1604 (9.9)
History of CVD					
IHD	2685 (26.2)	1541 (34.5)	2838 (24.3)	952 (36.6)	4070 (25.2)
Heart failure	1598 (15.6)	1011 (22.6)	1588 (13.6)	667 (25.7)	2025 (12.5)
Hypertension	6576 (64.2)	3293 (73.8)	7518 (64.3)	2009 (77.3)	10 818 (66.9)
Ischaemic stroke	1335 (13.0)	814 (18.2)	1351 (11.6)	427 (16.4)	1585 (9.8)
History of bleeding disorders					
Intracranial bleeding	96 (0.9)	74 (1.7)	95 (0.8)	29 (1.1)	93 (0.6)
GI bleeding	1301 (12.7)	655 (14.7)	1464 (12.5)	366 (14.1)	1835 (11.3)
Urogenital bleeding	1264 (12.3)	613 (13.7)	1516 (13.0)	383 (14.7)	1864 (11.5)

Continued

Table 1 Continued

	Apixaban (N=14 701)		Rivaroxaban (N=14 288)		Warfarin (N=16 175)
	Standard dose (n=10 237; 69.6%)	Reduced dose (n=4464; 30.4%)	Standard dose (n=11 689; 81.8%)	Reduced dose (n=2599; 18.2%)	NA (n=16 175)
eGFR (CKD-EPI)/min/1.73 m^2					
≥60	6521 (63.7)	1643 (36.8)	7787 (66.6)	497 (19.1)	9402 (58.1)
50–59	1234 (12.1)	657 (14.7)	1494 (12.8)	391 (15.0)	2096 (13.0)
30–49	1013 (9.9)	1305 (29.2)	759 (6.5)	1268 (48.8)	2091 (12.9)
15–29	43 (0.4)	340 (7.6)	47 (0.4)	218 (8.4)	389 (2.4)
<15	6 (0.1)	15 (0.3)	1 (0.0)	3 (0.1)	69 (0.4)
Missing	1420 (13.9)	504 (11.3)	1601 (13.7)	222 (8.5)	2128 (13.2)
Frailty index†					
Fit	1954 (19.1)	238 (5.3)	2256 (19.3)	83 (3.2)	3193 (19.7)
Mild frailty	4197 (41.0)	1142 (25.6)	4656 (39.8)	587 (22.6)	6896 (42.6)
Moderate frailty	2793 (27.3)	1652 (37.0)	3246 (27.8)	1022 (39.3)	4411 (27.3)
Severe frailty	1293 (12.6)	1432 (32.1)	1531 (13.1)	907 (34.9)	1675 (10.4)
CHA_2DS_2VASc score					
0	679 (6.6)	33 (0.7)	704 (6.0)	11 (0.4)	891 (5.5)
1	971 (9.5)	60 (1.3)	1146 (9.8)	37 (1.4)	1280 (7.9)
2	2046 (20.0)	307 (6.9)	2291 (19.6)	154 (5.9)	3088 (19.1)
3	2354 (23.0)	803 (18.0)	2768 (23.7)	443 (17.0)	3932 (24.3)
≥4	4187 (40.9)	3261 (73.1)	4780 (40.9)	1954 (75.2)	6984 (43.2)
Mean (SD)	3.2 (1.7)	4.4 (1.5)	3.2 (1.7)	4.4 (1.5)	3.2 (1.6)
HAS-BLED score					
0	1122 (11.0)	56 (1.3)	1226 (10.5)	27 (1.0)	1109 (6.9)
1	3671 (35.9)	1390 (31.1)	4371 (37.4)	793 (30.5)	4752 (29.4)
2	3681 (36.0)	1778 (39.8)	4286 (36.7)	1086 (41.8)	6891 (42.6)
3	1485 (14.5)	943 (21.1)	1503 (12.9)	534 (20.5)	2780 (17.2)
≥4	278 (2.7)	297 (6.7)	303 (2.6)	159 (6.1)	643 (4.0)
Mean (SD)	1.6 (1.0)	2.0 (0.9)	1.6 (0.9)	2.0 (0.9)	1.8 (0.9)
Medications‡					
Antiplatelets	4603 (45.0)	2219 (49.7)	5184 (44.3)	1331 (51.2)	10 222 (63.2)
Antiarrhythmics	2247 (21.9)	710 (15.9)	2422 (20.7)	414 (15.9)	3426 (21.2)
Antihypertensives	9780 (95.5)	4262 (95.5)	11 061 (94.6)	2510 (96.6)	15 486 (95.7)

Data are n (%) unless otherwise specified.
*Standard or reduced dose refers to the dose of the patient's first OAC prescription.
†Frailty was determined using an adaptation of a frailty index developed from data recorded in primary care databases, and categorised patients as fit, mildly frail, moderately frail or severely frail.
‡Prescription within 1 year before/after the first DOAC prescription.
BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology; CVD, cardiovascular disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; IHD, ischaemic heart disease; NA, not applicable; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant.;

and 7.93 (95% CI 7.16 to 8.76) for the warfarin cohort. Incidence rates of IS/SE increased with age in both sexes in each cohort (online supplemental figure 2). Risk estimates for IS/SE are shown in figure 1 and online supplemental table 3. There was no significant difference in IS/SE risk between patients prescribed an appropriate dose of apixaban and those prescribed warfarin (OR 1.19, 95% CI 0.92 to 1.52) or between patients prescribed an inappropriate dose of apixaban and those prescribed warfarin (OR 1.01, 95% CI 0.67 to 1.51); the OR for any dose apixaban was 1.14 (95% CI 0.90 to 1.45). Similarly, there was no significant difference in IS/SE risk between

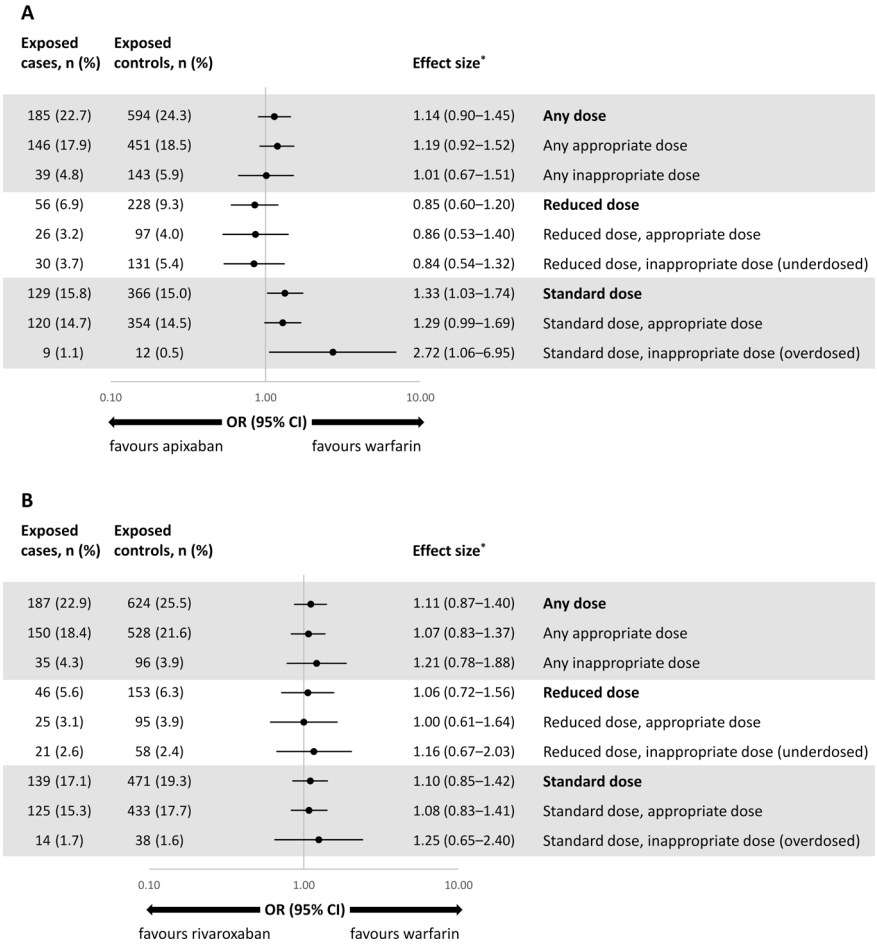

Figure 1 ORs (95% CI) for the risk of IS/SE associated with (A) apixaban versus warfarin and (B) rivaroxaban versus warfarin, according to dose classification. *ORs were adjusted for the matching factors (OAC naive at start date, sex, and year of birth), frailty, health services utilisation (hospitalisations, referrals), BMI, alcohol abuse, polymedication, history of ischaemic stroke, myocardial infarction, peripheral artery disease, tachycardia, hyperlipidaemia, gastrointestinal diseases, osteoarthritis, asthma, obesity, and use of gastroprotective drugs, antiplatelets, other anticoagulants, oral antidiabetics, anti-infectives, and antipsychotics. BMI, body mass index; IS/SE, ischaemic stroke/systemic embolism.

patients prescribed an appropriate dose of rivaroxaban and those prescribed warfarin (OR 1.07, 95% CI 0.83 to 1.37) or between patients prescribed an inappropriate dose of rivaroxaban and those prescribed warfarin (OR 1.21, 95% CI 0.78 to 1.88); the OR for any dose rivaroxaban was 1.11 (95% CI 0.87 to 1.40). For standard dose apixaban, the risk of IS/SE was possibly increased among patients prescribed an appropriate standard dose of apixaban (OR 1.29, 95% CI 0.99 to 1.69) or an inappropriate standard dose (OR 2.72, 95% CI 1.06 to 6.95 [potentially overdosed]; although based on only 9 cases); the overall OR for standard dose apixaban was 1.33 (95% CI 1.03 to 1.74). For standard dose rivaroxaban, no clear difference in IS/SE risk was seen among patients prescribed an appropriate standard dose (OR 1.08, 95% CI 0.83 to 1.41) or an inappropriate standard dose (potentially overdosed, OR 1.25, 95% CI 0.65 to 2.40); the overall OR for standard dose rivaroxaban was 1.10, 95% CI 0.85 to 1.42). For reduced dose apixaban, no difference in IS/SE risk was seen between patients prescribed an appropriate reduced dose (OR 0.86, 95% CI 0.53 to 1.40) or an inappropriate reduced dose (potentially underdosed, OR 0.84, 95% CI 0.54 to 1.32); the overall OR for reduced dose apixaban was 0.85 (95% CI 0.60 to 1.20). Similarly, for reduced dose rivaroxaban, no differences in IS/SE risk were seem among patients prescribed an appropriate reduced dose (potentially underdosed, OR 1.00, 95% CI 0.61 to 1.64) or those prescribed an inappropriate reduced dose (OR 1.16, 95% CI 0.67 to 2.03); the overall OR for reduced dose rivaroxaban was 1.06 (95% CI 0.72 to 1.56).

Intracranial bleeding

The crude incidence of ICB per 1000 person-years overall was 2.55 (95% CI 1.96 to 3.26) for the apixaban cohort, 2.62 (95% CI 2.06 to 3.30) for the rivaroxaban cohort and 3.06 (95% CI 2.59 to 3.59) for the warfarin cohort. Incidence rates increased with age in both sexes in each cohort (online supplemental figure 3). Risk estimates for ICB are shown in figure 2 and online supplemental table 3. Compared with users of warfarin, users of appropriately dosed apixaban had a reduced risk of ICB (OR 0.67, 95% CI 0.44 to 1.00) as did users of inappropriately

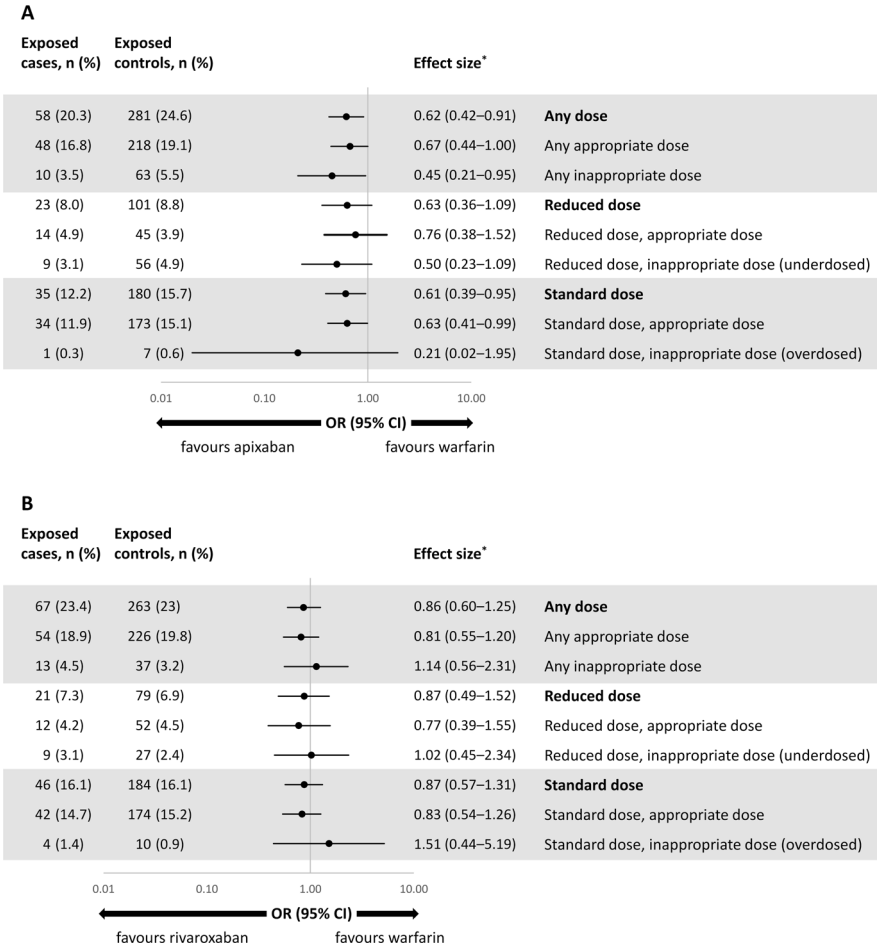

Figure 2 ORs (95% CI) for the risk of ICB associated with (A) apixaban versus warfarin and (B) rivaroxaban versus warfarin, according to dose classification. *ORs were adjusted for frailty, hospitalisations in the year before the index date, BMI, history of haemorrhagic stroke, osteoarthritis, asthma, Parkinson's disease, dementia/psychosis, and use of gastroprotective drugs, antidepressants, injectable steroids, and digoxin. BMI, body mass index; ICB, intracranial bleeding.

dosed apixaban (OR 0.45, 95% CI 0.21 to 0.95); the OR for any dose apixaban was 0.62 (95% CI 0.42 to 0.91). For rivaroxaban, ORs were 0.81 (95% CI 0.55 to 1.20) for an appropriate dose and 1.14 (95% CI 0.56 to 2.31) for an inappropriate dose. The same direction of effect was seen for patients prescribed an appropriate or inappropriate dose of apixaban/rivaroxaban in the respective standard and reduced dose strata.

Secondary outcomes

Risk estimates for the secondary study outcomes are shown in online supplemental table 4.

Hemorrhagic stroke

No significant differences in risk of haemorrhagic stroke were seen between patients prescribed apixaban/rivaroxaban and those prescribed warfarin in any dosing strata, although it should be noted that the number of exposed case and controls was low in some categories.

Myocardial infarction

A significant increase in risk of MI was seen in patients prescribed an inappropriate dose of apixaban compared with those prescribed warfarin (OR 1.73, 95% CI 1.12 to 2.67); for appropriately dosed apixaban, the OR was 1.29 (95% CI 0.96 to 1.73), and for any dose apixaban, it was 1.37 (95% CI 1.04 to 1.81). Similar estimates were seen between patients prescribed rivaroxaban and those prescribed warfarin; ORs were 1.68 (95% CI 1.04 to 2.70) for inappropriately dosed rivaroxaban, 1.21 (95% CI 0.89 to 1.64) for appropriately dosed rivaroxaban and 1.30 (95% CI 0.98 to 1.73) for any dose rivaroxaban. Reduced dose apixaban/rivaroxaban was generally associated with higher point estimates than for standard dose apixaban/rivaroxaban.

All-cause mortality

Compared with warfarin users, the risk of all-cause mortality was higher in patients prescribed an inappropriate dose of apixaban (OR 1.41, 95% CI 1.20 to 1.66), no difference in patients prescribed an appropriate dose of apixaban (OR 1.08, 95% CI 0.95 to 1.22) and increased in those prescribed an inappropriate dose of rivaroxaban (OR 1.58, 95% CI 1.33 to 1.89) and in those prescribed an appropriate dose of rivaroxaban (OR 1.25, 95% CI 1.11 to 1.41). The higher point estimates in the inappropriate dosing strata were also seen in the reduced and standard dose categories.

Subgroup analyses

In the subgroup analyses, most risks of IS/SE, ICB, haemorrhagic stroke, MI and all-cause mortality were not significantly different between patients prescribed an appropriate/inappropriate dose of apixaban/rivaroxaban and those prescribed warfarin (online supplemental tables 5–10). Among patients with high CHA_2DS_2VASc score, the risk of MI was higher among patients prescribed any appropriate dose of apixaban versus warfarin (OR 1.91, 95% CI 1.11 to 3.30), and among patients with severe frailty the risk of MI was higher among patients prescribed any appropriate dose of apixaban versus warfarin (OR 2.68, 95% CI 1.29 to 5.59). Finally, among patients with HAS-BLED score >2, the risk of ICB was lower among patients prescribed any appropriate dose of apixaban (OR 0.38, 95% CI 0.16 to 0.90) or any appropriate dose of rivaroxaban (OR 0.30, 95% CI 0.11 to 0.79) vs warfarin; this effect was not observed in patients receiving any inappropriate dose of either apixaban or rivaroxaban, although the numbers of patients in these strata were small.

DISCUSSION

In this large population-based study among patients with NVAF, we found no significant difference in the risk of IS/SE between users of appropriately/inappropriately dosed apixaban/rivaroxaban and users of warfarin. Risk of ICB was significantly reduced in patients prescribed an appropriate/inappropriate dose of apixaban, and not significantly different in patients prescribed an appropriate/inappropriate dose of rivaroxaban, when compared with those prescribed warfarin. However, a trend towards a reduced risk in ICB was observed among patients prescribed an appropriate dose of rivaroxaban but not among those prescribed an inappropriate dose. Few differences in IS/SE or ICB risk were seen between comparison groups in patients with impaired renal function, diabetes, high CHA_2DS_2VASc score or severe frailty. A reduced risk of ICB was observed among patients with high HAS-BLED score that were prescribed appropriate doses of either DOAC, but not among those prescribed inappropriate doses (although based on a limited number of cases).

Our study compared outcomes between patients appropriately/inappropriately prescribed a DOAC based on all main dose reduction criteria on the drug label, and those prescribed warfarin in routine clinical practice. A recent meta-analysis of 10 studies, involving 148 909 patients with AF from Europe, the USA and Asia, found that DOAC underdosing was associated with a significant difference in the risk of mortality, but not thromboembolic events, when compared with on-label dosing.[14] Slightly different dose-reduction criteria for rivaroxaban are used in Asian populations, where recent studies have shown increased risks of ischaemic events associated with off-label underdosing without a significant decrease in major bleeding.[15–18] Other observational studies on this topic from Europe have presented results for DOACs either as a class[19–21] and/or by standard/reduced dose.[19] Results from our analyses of 'any DOAC dose' are mostly consistent with these previous studies for IS/SE and ICB from Europe, particularly the study by Vinogradavo *et al*,[19] which also used UK primary care EHRs. The exception was that, along with Vinogradavo *et al*, we did not observe the significantly reduced risk of ICB with rivaroxaban versus warfarin seen in the studies from Scandinavia,[20 21] although the point estimates indicated the same direction of effect. These differences could be explained by issues of residual confounding and bias that exist in all observational studies. One may expect that apixaban/rivaroxaban potential underdosing would lead to reduced IS/SE protection, and potential overdosing would lead to an increased risk of ICB. However, we did not observe this in our study, although the size of some of the relevant strata was small, limiting the power to detect such effects. For ICB, the point estimates appeared to favour rivaroxaban over warfarin when used at an appropriate standard/reduced dose and to favour apixaban over warfarin when used at an inappropriate standard/reduced dose. Despite the substantial overlapping CIs of the inappropriate and appropriate dosing estimates, this finding is interesting. One explanation for the favourable ICB point estimates with inappropriate standard/reduced dose apixaban is that most inappropriate use derives from incorrect reduced dose prescribing (5 mg; half the standard 10 mg dose),[6] which in turn drives the observed lower ICB rates. Previously, we have found that inappropriate prescribing of reduced dose rivaroxaban (15 mg dose) is less frequent[6] and, therefore unlikely to favour rivaroxaban over warfarin in terms of ICB risk.

In marked contrast to the phase III ARISTOTLE[22] and ROCKET-AF trials,[23] yet consistent with the observational study by Vinogradova *et al*,[19] we found the risk of all-cause mortality to be higher in patients prescribed apixaban/rivaroxaban than in those prescribed warfarin, particularly among those receiving an inappropriate DOAC dose (with similar findings seen for MI). This was seen in patients prescribed either standard/reduced dose rivaroxaban or reduced dose apixaban. Similarly, we did not find standard dose apixaban to be associated with a significantly different risk of IS/SE versus warfarin, whereas, in ARISTOTLE, 10 mg/day apixaban was associated with a significantly reduced risk of all-cause mortality and IS/SE when compared with warfarin. Our results were broadly similar to those in the ROCKET AF trial for IS/SE but differed for ICB as we did not observe a reduced risk with rivaroxaban. Residual confounding or other biases not fully addressed in this study and characteristic of observational studies could account for these differences as discussed hereafter and by others.[24] It is highly plausible that DOACs are preferentially prescribed to patients perceived to be at higher risk of adverse outcomes. In our cohort of patients with NVAF, those prescribed apixaban/rivaroxaban were on average older, had a higher prevalence of cardiovascular disease and were more frequently

classified as moderately/severely frail. Additionally, withdrawal of OAC therapy in patients in the final stage of life might have been more common among warfarin users—who required close monitoring of blood international normalised ratio (INR) levels——than DOAC users, which would lead to results spuriously favouring warfarin over DOAC in terms of mortality. There may also have been some differential exposure misclassification, being higher for warfarin due to a combination of its INR-based dosing, large pack size prescriptions and our assumed one-per-day posology. Previous reports have suggested that exposure duration could be particularly underestimated among individuals with labile INRs, who are also inherently at higher risk of experiencing adverse events such as ICB, stroke or death.[25] In turn, the limited ability to accurately capture warfarin exposure in some patients could underestimate associations between warfarin and these clinical events. Another consideration is that while our nested case–control analyses analysed 'current use', any patient could have switched OAC in the recent past (>30 days before the index date). In our study, this was more common for warfarin-to-DOAC switching than vice versa (15% of current DOAC user cases were exposed to warfarin in the previous year, while only 2% of warfarin users were exposed to a DOAC in the previous year). And, as OAC switching is commonly associated with worse health outcomes, this scenario would bias the results—potentially overestimating risks associated with DOACs and underestimating risks associated with warfarin.

As the IMRD-UK is representative of the UK as a whole, our findings have good generalisability. A key strength of our study was the availability of data on age, bodyweight and renal function, which enabled more accurate categorisation of inappropriate/appropriate DOAC dosing. We assessed DOAC dosing appropriateness at the time of the event date in the nested case–control analyses to minimise exposure misclassification that can occur over lengthy follow-up durations, and we manually reviewed patient profiles to determine the study outcomes. Our study also has limitations. First, the classification of dosing appropriateness could not incorporate the individual clinical judgements made in the decision to prescribe standard/reduced DOAC doses. Second, dosing appropriateness was based on eGFR estimates obtained using the CKD-Epidemiology equation instead of the CG equation, which was used in the original clinical trials. However, this should have had only minimal impact because concordance between these two equations for dose reduction criteria has been shown to be quite high.[26] Third, residual confounding, bias (favouring warfarin) from preferential prescribing of DOACs to higher risk patients and differential exposure misclassification cannot be excluded, as previously discussed. Fourth, we were also unable to identify the time in therapeutic range for warfarin users or appropriate/inappropriate dosed warfarin users as comparison groups in the analyses of DOAC dosing appropriateness, meaning that all warfarin users were used as the comparator. Finally, the low numbers of exposed cases and controls in some strata—the inappropriate prescribing of standard DOAC dose (ie, overdosing) and the subgroup analyses—limited the meaningfulness of those results.

In conclusion, dosing appropriateness in NVAF was not associated with a significant difference in IS/SE risk or an increase in ICB risk when compared with warfarin. Considering the results of clinical trials, these findings may reflect clinical circumstances that could not be readily accounted for in our analyses, including residual confounding, biases, and differential exposure misclassification. They should, therefore, be interpreted with caution, and it is important that prescribers adhere to the dosing instructions in the respective Summary of Product Characteristics. More studies on this topic from real-world populations are needed to explore this further.

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Contributors AG-P contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. LR contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. PV contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. MES contributed to the study design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. GB contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. SF contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. LAGR contributed to the study concept and design, the analysis and interpretation of data, revising the intellectual content of the manuscript drafts, and final approval of the version to be published. LAGR is the guarantor.

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