ARTICLE SUMMARY

Strengths and limitations of this study

- The source population for this research, that is, the General Practice Research Database (GPRD) is the largest primary care database in the world, containing the records of a representative sample of the British population.
- Operationalisation of the inclusion and exclusion criteria of the clinical studies in order to assess the eligibility for study enrolment of patients seen in routine care required assumptions in some instances.
- AF diagnosis in the GPRD may not always be accurate. However, the majority of AF cases were correctly coded according to a recent systematic review, and any errors would not be expected to systematically bias the findings of this research in favour of one study.
- Assessing representativeness cannot substitute for the assessment of generalisibility, that is, how well the clinical trial results translate into effectiveness and safety in routine care. This will need to be assessed once the drugs under study have been used for several years in daily practice.

BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with an increased risk of stroke and other thromboembolic events. Approximately one in five of all strokes are caused by AF,[1] with the risk of stroke increased by fourfold to fivefold in patients with AF compared with the general population.[2] The condition is often asymptomatic,[3] but mortality in patients with chronic AF has been reported to be up to 2.5 times higher than in the general population, with the relative risk of death higher in women than in men.[4] The economic burden of AF is also high, with a key cost-driver being hospitalisation. This economic burden of AF has increased significantly over the last few decades, and is expected to increase even more in future due to ageing populations.[5]

Oral anticoagulants form the current standard of care for patients with AF considered at intermediate to high risk of stroke, and are effective therapies for stroke prevention.[1 3 6] For many decades, warfarin was the only anticoagulant available; for now, three novel oral anticoagulant agents (dabigatran etexilate (later referred to as dabigatran), apixaban and rivaroxaban) have demonstrated superiority or non-inferiority to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism in phase III randomised controlled trials (RCT).[7–9]

In RE-LY (n=18 113; intention-to-treat (ITT) population), dabigatran at a dose of 150 mg twice daily was associated with a lower rate of stroke or systemic embolism (relative risk (RR), 95% CI 0.65, 0.52 to 0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI 0.93, 0.81 to 1.07; p=0.32) when compared with warfarin. At a lower dose (110 mg, twice daily), dabigatran was associated with rates of stroke or systemic embolism that were similar to warfarin (RR, 95% CI 0.90, 0.74 to 1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI 0.80, 0.70 to 0.93; p=0.003).[7 10] In ARISTOTLE (n=18 201; ITT population), apixaban (5 mg, twice daily) was associated with a lower rate of stroke or systemic embolism (hazard ratio (HR), 95% CI 0.79, 0.66 to 0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI 0.69, 0.60 to 0.80; p<0.001) when compared with warfarin.[9] In ROCKET-AF (n=14 171; ITT population), rivaroxaban (20 mg, once daily) was associated with a similar rate of stroke or systemic embolism compared with warfarin (HR, 95% CI 0.88, 0.75 to 1.03; p<0.001 for non-inferiority, p=0.12 for superiority; ITT population) with no significant improvement in the rate of major bleeding (HR, 95% CI 1.04, 0.90 to 1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban were approved in Europe for stroke prevention in patients with AF at the time of study conduct and peer-review[11 12]

Although these three RCTs have demonstrated that the three new anticoagulants are superior or non-inferior to warfarin in terms of stroke prevention, these studies applied specific inclusion and exclusion criteria that may have excluded patients who would otherwise be treated in real-life clinical practice, currently with warfarin. Therefore, it is unknown as to whether the patient populations included in RE-LY, ARISTOTLE and ROCKET-AF reflect 'real-world' patients with AF, and therefore whether the study results can be generalised to the wider patient population.

To date there have been no studies comparing the eligibility criteria of these three trials. This study (RADAR: *R*epresentativeness *a*nd generalisability of the *d*abigatran, *a*pixaban and *r*ivaroxaban clinical trial populations to real-world AF patients in the UK) aimed to assess the differences between the three trial populations of RE-LY, ARISTOTLE and ROCKET-AF and the real-world patients with AF recorded within the General Practice Research Database (GPRD) in the UK. An analysis on patients at intermediate or high risk of stroke allowed a focus on patients for whom, according to current clinical guidelines,[1 3 6 13–15] an anticoagulant could be prescribed. Risk of stroke is commonly assessed using stroke risk scores, such as the $CHADS_2$ score.[16] The CHA_2DS_2-VASc score has also been introduced and, based on multiple validation studies, is more accurate in identifying truly low-risk patients who do not require anticoagulation therapy and is at least as good as (possibly superior to) $CHADS_2$ in identifying high-risk patients who develop thrombembolism.[16] Both $CHADS_2$ and CHA_2DS_2-VASc scores were used to stratify patients in the current study. The CHA_2DS_2-VASc scoring became available after the three clinical studies had been initiated.

It was hypothesised that the trial populations within RE-LY, ROCKET-AF and ARISTOTLE, as selected by the

trial protocol inclusion and exclusion criteria, would vary in their representativeness to real-world AF populations, particularly for those eligible for anticoagulant treatment based on current guidelines.

DESIGN
Objectives
The objective of this study was to assess the representativeness of RE-LY, ARISTOTLE and ROCKET-AF to the real-world AF population in the UK. The study design was a cross-sectional database analysis.

Data source
The GPRD was used as a source of information on the general AF population. In the UK, patients are semi-permanently registered at a specific practice where general practitioners (GPs) provide primary care and make specialist referrals. These practices centralise the medical information from the GPs themselves, and also information from the specialist referrals and hospitalisations.[17] The GPRD is a computerised database comprising anonymous medical records from over 630 practices in the UK, covering approximately 8% of the UK population.[18] The database contains longitudinal data on patient demographics, diagnoses, referrals, prescribing and health outcomes and has a geographical distribution that is representative of the UK population.[19] The median proportion of diagnoses correctly coded by the GPRD was recently demonstrated to be 89% (range 24–100%) in a systematic literature review of GPRD studies.[20] The GPRD has obtained ethical approval from a Multicentre Research Ethics Committee for all purely observational research using GPRD data; specifically, studies which do not include patient involvement.[21]

Population
Patients from the GPRD were included if they had a diagnosis of non-valvular AF, were still alive and registered with a GP practice on the 31 March 2008, and were aged ≥ 18 years of age. An artificial start date was defined for 31 March 2008 to allow sufficient time for the application of prospective exclusion criteria, such as 'clinically significant gastrointestinal bleeding within 6 months of randomisation'.

Inclusion/exclusion criteria
The inclusion/exclusion criteria from RE-LY, ROCKET-AF and ARISTOTLE were derived primarily from the trial design and rationale publications,[22–24] with clarification sought from supplementary appendices and primary clinical trial result publications[7–9] where required. A full description of the inclusion and exclusion criteria applied is provided in the online supplementary data. Of note, the ROCKET-AF trial required patients to have a history of stroke, transient ischaemic attack (TIA) or systemic embolism (ie, secondary prevention cohort) or had to have *two* of the following: age

≥ 75 years, congestive heart failure or ejection fraction $\leq 35\%$, diabetes or hypertension.

With respect to the ROCKET-AF trial, there was a contradiction between the hypertension risk factor inclusion criterion described in the ROCKET-AF rationale and design publication (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mm Hg or persistent diastolic blood pressure >90 mm Hg).[8] In the current analysis the more inclusive criterion from the supplementary appendix has been used in place of the trial design publication.

The inclusion/exclusion criteria were then used to identify the total number of patients with AF in the GPRD who would meet the trial eligibility criteria. READ codes were used as the principal method of identifying patients from the GPRD who would meet the trial inclusion/exclusion criteria. READ codes are a coded thesaurus of clinical terms and form the basic means through which physicians record patient findings and interventions in health and social care IT systems within the UK.[25] Prescription data were also used to identify patients prescribed medications that may have affected their eligibility for one or more of the trials (eg, long-term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (eg, abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were then used to stratify patients from the GPRD by risk of stroke (low, medium and high). CHADS$_2$ assigns one point to patients for chronic heart failure, hypertension, age ≥ 75 years, and/or diabetes and two points for history of stroke or TIA. A score of 1 indicates an intermediate risk of stroke, a score of ≥ 2 indicates a high risk of stroke.[3] In contrast, CHA$_2$DS$_2$-VASc assigns one point for congestive heart failure, hypertension, diabetes, vascular disease, female gender and/or age 65–74 years and two points for history of stroke or TIA and/or age ≥ 75 years.[16] As with CHADS$_2$, a score of 1 on the CHA$_2$DS$_2$-VASc indicates an intermediate risk of stroke, and a score of ≥ 2 indicates a high risk of stroke.[16]

Outcomes
The outcomes of interest were the proportion of real-world patients with AF in the GPRD who would meet the inclusion/exclusion criteria for each of the three trials (RE-LY, ARISTOTLE and ROCKET-AF), as well as the proportion of real-world patients with AF classified at intermediate or high risk of stroke who would meet the respective inclusion/exclusion criteria, stratified by the risk of stroke according to both the CHADS$_2$ and the CHA$_2$DS$_2$-VASc. The specific inclusion and exclusion criteria for each of the three trials were also examined to determine if there were key criteria causing differences between trials.

Statistical analysis

The proportion of patients from the GPRD who would be eligible for RE-LY was compared with the proportion that would be eligible for ARISTOTLE and ROCKET-AF using the χ^2 test at a significance level of 5%. All analyses are descriptive and exploratory.

RESULTS

Patients eligible for RE-LY, ARISTOTLE and ROCKET-AF

In total, 83 898 patients with AF were identified from the GPRD (table 1). Of these patients, 64% met the inclusion/exclusion criteria for enrolment into RE-LY. This compares with 61% of patients who were eligible for inclusion into ARISTOTLE and 48% of patients who were eligible for inclusion into ROCKET-AF. The proportion of real-world patients who would be eligible for inclusion within the RE-LY trial was statistically significantly higher than the proportion of real-world patients who would be eligible for ARISTOTLE or ROCKET-AF (p<0.001 for both comparisons), though the small difference against ARISTOTLE is probably not clinically meaningful.

Intermediate-risk and high-risk patients eligible for RE-LY, ARISTOTLE and ROCKET-AF

In clinical practice, only patients considered at intermediate or high risk of stroke would receive anticoagulation therapy. Using the $CHADS_2$ score, 71 493 (85%) patients from the total GPRD AF population would be eligible for anticoagulant therapy, of which 74% would meet the RE-LY inclusion/exclusion criteria, 72% would meet the ARISTOTLE criteria and 56% would meet the ROCKET-AF criteria (table 1). Using the CHA_2DS_2-VASc score, 78 783 (94%) patients from the total GPRD population would be eligible for anticoagulant therapy, of which 68% would meet the RE-LY inclusion/exclusion criteria, 65% would meet the ARISTOTLE criteria and 51% would meet the ROCKET-AF criteria (table 1).

Eligibility by individual inclusion and exclusion criterion

The inclusion rather than exclusion criteria were the primary determinants for the trial population in RE-LY (77% of GPRD AF population eligible), ARISTOTLE (81% of GPRD AF population eligible) and ROCKET-AF (63% of GPRD AF population eligible), as would be expected (table 2). Within the inclusion criteria, the greatest difference between trials was seen with the hypertension definition, where 81% of the GPRD AF population met this criterion in ROCKET-AF, compared with 59% of real-world patients for the RE-LY and ARISTOTLE hypertension criteria (table 2). This difference, which favours ROCKET-AF over RE-LY and ARISTOTLE with respect to inclusivity, did not appear to be a major driver for differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion

Table 1 Proportion of GPRD AF patients who met inclusion/exclusion criteria for RE-LY, ARISTOTLE and ROCKET-AF, stratified by risk of stroke and assessment method

Patient population	Anticoagulant eligibility	GPRD AF patient population, N (%)	RE-LY GPRD AF patients meeting trial criteria, n (% (95% CI))	ARISTOTLE GPRD AF patients meeting trial criteria n (% (95% CI))	ROCKET-AF GPRD AF patients meeting trial criteria, n (% (95% CI))
Total GPRD AF population	Not anticoagulant-eligible/potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	83 898 (100)	53 640 (64 (63.59 to 64.41))	51 415 (61 (60.58 to 61.42))	39 892 (48 (47.66 to 48.34))
Intermediate-risk or high-risk patients					
$CHADS_2$ ≥1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71 493 (85)	52 783 (74 (73.68 to 74.32))	51 415 (72 (71.67 to 72.33))	39 892 (56 (55.64 to 56.36))
CHA_2DS_2-VASc ≥1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78 783 (94)	53 640 (68 (67.67 to 68.33))	51 163 (65 (64.67 to 65.33))	39 892 (51 (50.65 to 51.35))
High-risk patients					
$CHADS_2$ ≥2	Should receive anticoagulant according to guidelines	49 099 (59)	38 493 (78 (77.63 to 78.37))	35 712 (73 (72.61 to 73.39))	39 892 (81 (80.65 to 81.35))
CHA_2DS_2-VASc ≥2	Should receive anticoagulant according to guidelines	72 824 (87)	53 059 (73 (72.68 to 73.32))	50 623 (70 (69.67 to 70.33))	39 835 (55 (54.64 to 55.36))

AF, atrial fibrillation; GPRD, General Practice Research Database.

Table 2 Proportion of GPRD AF patients eligible for trial participation according to each inclusion/exclusion criteria identified for RE-LY, ARISTOTLE and ROCKET-AF

Criterion		RE-LY N (%) real-world AF patients meeting criterion	ARISTOTLE N (%) real-world patients meeting criterion	ROCKET-AF N (%) real-world patients meeting criterion
Inclusion				
AF		83 898 (100)	83 898 (100)	83898 (100)
Risk factors	Age ≥75 years	51 034 (61)	51 267 (61)	51034 (61)
	Stroke, TIA, systemic embolism	11 632 (14)	10 577 (13)	11632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16 184 (19)	16009 (19)
	Age ≥65 years	70 047 (83)	–	–
	Diabetes mellitus	3945 (5)	14 940 (18)	14850 (18)
	Hypertension	49 747 (59)	49 747 (59)	67833 (81)
	Coronary artery disease	28 687 (34)	–	–
Overall inclusion criteria		64 710 (77)*	67956 (81)†	52540 (63)‡
Exclusion				
Reversible causes of AF		1124 (1)	2938 (4)	350 (<1)
Mitral valve stenosis		–	1213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5202 (6)	5202 (6)	5202 (6)
	Heart valve disorder	4792 (6)	–	–
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	–	–	71 (<1)
Increased risk of bleeding		1044 (1)	1044 (1)	1044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		–	–	2350 (3)
Uncontrolled hypertension		2014 (2)	2014 (2)	2014 (2)
Planned cardioversion		–	–	843 (1)
Renal impairment		2149 (3)	2149 (3)	2149 (3)
Other concomitant treatments	ASA at specified dose	–	1629 (2)	1767 (2)
	ASA + thienopyridine	–	203 (<1)	203 (<1)
	Intravenous antiplatelets	–	–	0 (0)
	Fibrinolytics	0 (0)	–	0 (0)
	NSAID	–	–	2729 (3)
	P450 3A4 inhibitor	–	–	4 (<1)
	P450 3A4 inducer	–	–	1125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other concomitant conditions	Liver disease	1547 (2)	–	1547 (2)
	Hepatitis A, B or C	698 (<1)	–	
	HIV	–	–	14 (<1)
	Active infective endocarditis	8 (<1)	8 (<1)	8 (<1)
	Anemia	794 (1)	794 (1)	794 (1)
	Substance abuse and psychosocial	28 (<1)	28 (<1)	–
INR monitoring		–	3513 (4)	–
Overall inclusion and exclusion criteria		53 640 (64%)	51 415 (61%)	39892 (48%)

*Inclusion criteria for RE-LY specify AF plus at least one of age ≥75 years; history of previous stroke, TIA or systemic embolism; ejection fraction <40%; or symptomatic heart failure OR AF plus age ≥65 years plus one of diabetes mellitus; documented coronary artery disease or hypertension requiring medical treatment.[7]
†Inclusion criteria for ARISTOTLE specify AF plus at least one of age ≥75 years; prior stroke; symptomatic congestive heart failure or ejection fraction ≤40%; diabetes; or hypertension requiring pharmacological treatment.[23]
‡Inclusion criteria for ROCKET-AF specify AF plus history of stroke, TIA, or systemic embolism OR AF plus at least two of age ≥75 years; congestive heart failure or ejection fraction ≤35%; or diabetes or hypertension.[22]
Note that the planned cardioversion exclusion criterion within the ROCKET-AF trial was conceptualised within the study by excluding patients having cardioversion within 12 months of the index date.
AF, Atrial Fibrillation; ASA, acetylsalicylic acid; GPRD, General Practice Research Database; INR, International Normalised Ratio; NSAID, Non-steroidal anti-inflammatory drug; TIA, transient ischaemic attack.

criterion, but by the different combinations of individual inclusion criteria within the trials.

For the exclusion criteria specifically, the requirement for anticoagulant treatment for conditions other than AF excluded 6% of GPRD patients with AF from all trials, with renal impairment excluding a further 3% of the GPRD AF population. Although the exclusion criteria differed between trials, none of the individual criteria appear to be a key driver of the different proportions of real-world patients eligible for the trials (table 2).

DISCUSSION

The results of this analysis demonstrate that the warfarin-controlled pivotal trials for the novel oral anticoagulants dabigatran (RE-LY), apixaban (ARISTOTLE) and rivaroxaban (ROCKET-AF) vary in their representativeness of the AF population enrolled. Based on GPRD, the RE-LY trial enrolled a patient population that is most closely matched to patients with AF seen in general practice within the UK compared with the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate-risk or high-risk patients with AF captured within the GPRD would be eligible for inclusion into RE-LY, as compared with 65% and 51% for ARISTOTLE and ROCKET-AF, respectively (as categorised by CHA_2DS_2-VASc ≥ 1). Being more inclusive and representative of the general AF population allows trial findings to be more readily generalised to patients seen in everyday clinical practice (and eligible for anticoagulant therapy). The RE-LY patient population is also slightly more inclusive of AF patients eligible for anticoagulant treatment, than the population in the ARISTOTLE trial (difference of 3%; p<0.001) but this statistically significant difference between the RE-LY and ARISTOTLE populations would not necessarily translate into clinically meaningful differences for the real-world population.

It is important to note that a higher-risk patient population was intentionally enrolled in ROCKET-AF (mean $CHADS_2$ risk score of 3.48) compared with both the RE-LY (mean $CHADS_2$ risk score of 2.1) and ARISTOTLE (mean $CHADS_2$ risk score of 2.2) trials, and thus, a large number of patients who would be eligible for anticoagulant treatment under current guidelines would not have been entered into ROCKET-AF. Indeed, there are no data for patients with a $CHADS_2$ score 0–1 in ROCKET-AF, and only 13% of this trial population had a $CHADS_2$ score of 2.[8] A significant number of patients who could be eligible for anticoagulation in general practice (intermediate or high risk of stroke according to the $CHADS_2$ risk score) and who would be included within RE-LY are excluded from ROCKET-AF (18%). In total, 13 748 patients with AF eligible for the RE-LY study would have been excluded from the ROCKET-AF trial within the total GPRD AF population (low, intermediate or high risk of stroke).

Thus, some care should be taken when generalising the trial results from the high-risk subpopulation seen in ROCKET-AF to the general AF population encountered in clinical practice.

Trial generalisability (external validity) is a recognised problem in RCTs. The trial participants enrolled in a trial may differ considerably from the target population/clinical practice in which the trial's findings are later used, and trial eligibility criteria can contribute to this lack of generalisability.[26] The current analysis indicates that the rate of inclusion observed within the RE-LY trial (and probably, ARISTOTLE) is at least as representative of the general population as other pivotal trials have been found to be. For example, a recent analysis of patients enrolled in eight placebo-controlled clinical trials for amyotrophic lateral sclerosis (ALS) found that 66% of patients diagnosed with ALS in Italy between 2003 and 2008 met the eligibility criteria for the trials.[27] However, this analysis reported that the ALS patients enrolled within the clinical trials were demographically and clinically different from the patients within the national ALS population, with the differences between the trial cohorts and patient population resulting in part from the different eligibility criteria used and in part from factors unrelated to enrolment criteria. With respect to risk of stroke as determined by $CHADS_2$ score, 26% of individuals in a study of the incidence and prevalence of chronic AF in the UK (using also the GPRD as a data source), had a CHADS2 score of ≥ 3,[17] compared with 33% in RE-LY,[7] 32% in ARISTOTLE[9] and 87% in ROCKET-AF.[8] This demonstrates that both RE-LY and ARISTOTLE were substantially more reflective of the real-world AF population (based on the GPRD) than ROCKET-AF when considering the proportion of the population at differing risk of stroke. It is interesting to note that little research has actually been conducted to quantify the representativeness of trial populations with regard to real-life populations. This is surprising given that the external validity of trials is always questioned, especially in the context of reimbursement decisions and Health Technology Assessments (HTA). More systematic research in this area appears to be warranted, particularly with respect to how the external validity of a trial then affects the 'translation' of efficacy to effectiveness.

When classifying patient risk, risk groups stratified by the CHA_2DS_2-VASc score may be considered to be more accurate than those stratified by $CHADS_2$, particularly to identify 'truly low risk' patients who do not need any antithrombotic therapy, due to the more inclusive nature of common stroke risk factors in CHA_2DS_2-VASc.[16] This is important when considering the results of the current study, since the intermediate-risk or high-risk population by CHA_2DS_2-VASc included 7290 more patients than did the intermediate-risk or high-risk population by $CHADS_2$. These patients are at risk of stroke but may not receive treatment if miscategorised as low risk by the $CHADS_2$ score; indeed, one recent analysis suggests that a $CHADS_2$ score=0 is not low risk with stroke rates that can range

between 0.8% and 3.2% per year when subdivided by CHA$_2$DS$_2$-VASc score.[28] The 2010 European Society of Cardiology (ESC) guidelines suggest that although CHADS$_2$ is useful as a simple initial means of assessing risk, patients scoring 0 or 1 should undergo more comprehensive assessment, for example with CHA$_2$DS$_2$-VASc.[1] In the 2012 focused update of the ESC guidelines, the only recommended stroke risk score is CHA$_2$DS$_2$-VASc, with the initial focus on identification 'truly low risk' patients (ie, age <65 and lone AF, or CHA$_2$DS$_2$-VASc=0) who do not need any antithrombotic therapy. Those with ≥1 stroke risk factors can be offered effective stroke prevention, which is oral anticoagulation.[29]

LIMITATIONS

It should be noted that a number of the criteria included in the trial design for RE-LY, ARISTOTLE and ROCKET-AF were not recorded in the GPRD or were difficult to extract. For example, planned major surgery would not be captured within the database, nor would a life expectancy of less than 1 year, both of which are exclusion criteria in one or more of the trials. However, these criteria were likely to have had minimal impact on the final populations included within the RCTs, since many of the criteria that could not be applied to the GPRD population were consistent across all three trials. This means that the impact of applying the individual criterion would be the same across RE-LY, ARISTOTLE and ROCKET-AF, with only the order of magnitude affected. A potential limitation of the current study is that the analyses were reliant on the quality of GP coding in the GPRD dataset. A recent systematic review of the validity of diagnostic coding in the GPRD reported that >80% of events such as myocardial infarction and stroke were correctly coded, but a lower proportion (64.4%) of AF cases were correctly coded.[30] This means that there may be some error in the characteristics of the GPRD population taken to be a reflection of the general AF population in the UK. However, this is unlikely to affect the conclusion drawn from the current study, since the errors in coding are unlikely to be focused on a specific subgroup of patients and instead would be expected to be distributed across the whole AF population in the UK. Although the total number of patients classified as having AF in the GPRD may be lower than the total number of patients with AF in the UK, there is no reason to suspect that the patients miscoded would have systematically differed in characteristics to those correctly coded within the database.

In order to answer the question of generalisibility, it would be necessary to compare clinical trial results with effectiveness and safety findings observed in routine care. However, to undertake such real-life assessments typically takes several years as the drugs in question need to become used widely. Therefore, HTA bodies (such as National Institute of Health and Clinical Excellence (NICE) in the UK) often request that evidence is presented to what extent a trial population is reflective of the population for which the coverage decision has to be taken and for which the drug is likely to be used in routine practice. If a study population is very different from the one for which the drug will be used in routine care, this will increase the uncertainty in such HTA decisions. Such assessment as ours therefore can serve as a first indication of generalisability. A further limitation is that other study factors that can influence generalisability have not been investigated in this research, such as the countries participating in the studies or the quality of the warfarin arm as an indicator for the quality of patient care.[31]

CONCLUSION

Trial generalisability is an important consideration for the NICE in the UK and other such HTA bodies, with past criticisms focusing on the lack of generalisability of trials as a result of the eligibility criteria applied.[32–34] The current analysis demonstrates that the data from RE-LY and ARISTOTLE are applicable to a larger proportion of real-world AF patients than data from ROCKET-AF, meaning that the results from the study supporting the use of dabigatran and apixaban are more generalisable to the general anticoagulant eligible AF population.

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