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Representativeness of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database

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Objective: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban, apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE, ROCKET-AF). This study aimed to assess the degree of generalisability of the results from RE-LY, ARISTOTLE, and ROCKET-AF to the real-world AF population, particularly the population eligible for anticoagulants, in the UK.

Design: A cross-sectional database analysis was conducted.

Setting: A dataset derived from the General Practice Research Database (GPRD).

Primary and secondary outcomes measure: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF were compared. The results were then stratified by risk of stroke using $CHADS_2$ and CHA_2DS_2-VASc.

Results: 83,898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc ≥1; n=78,783 [94%]), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI:67.7%-68.3%; n=53,640), compared with 65% (95% CI:64.7%-65.3%; n=51,163) eligible for ARISTOTLE (apixaban) and 51% (95% CI:50.7%-51.4%; n=39,892) eligible for ROCKET-AF (rivaroxaban). Using the $CHADS_2$ method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment ($CHADS_2$ ≥1; n=71,493 [85%]), the proportion eligible for inclusion into RE-LY was 74% (95% CI:73.7%-74.3%; n=52,783), compared with 72% (95% CI:71.7%-72.3%; n=51,415) for ARISTOTLE and 56% (95% CI:55.6%-56.4%; n=39,892) for ROCKET-AF.

Conclusions: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast to patients enrolled within ROCKET-AF who were a more narrowly-defined group of patients at higher risk of stroke. Differences between trials should be taken into account when considering the generalisability of clinical trial findings.

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Article summary

Article focus

- The focus of this study was to assess the generalisability of the findings of three randomised, controlled trials for stroke prevention in patients with atrial fibrillation (AF) to the real-world UK population of individuals with this condition, particularly to patients who would be eligible for anticoagulation under current guidelines.
- The three studies were RE-LY, ARISTOTLE and ROCKET-AF that investigated the efficacy and safety of dabigatran etexilate (dabigatran), apixaban and rivaroxaban compared to warfarin, respectively.

Key messages

- Patients enrolled in RE-LY and ARISTOTLE were more reflective than patients enrolled in ROCKET-AF with respect to the real-world AF population in the UK, including the population eligible for anticoagulation.
- About 2/3 of patients recommended for anticoagulation would have been eligible to enrol into the clinical study investigating dabigatran (68%) or apixaban (65%) , but only about half of the patients would have been eligible for the rivaroxaban study (51%).
- Differences in generalisibility should be taken into account when transferring study findings to patient populations in routine care.

Strengths and limitations of this study

- The source population for this research, i.e. 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.

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- 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 in some instances assumptions.

- 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.

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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 four- to five-fold 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 aging 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.[7-9]

In RE-LY (n=18,113; 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% Confidence Interval [CI]: 0.65, 0.52-0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI: 0.93, 0.81-1.07; 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, 0.74-1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI: 0.80, 0.70-0.93; 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, 0.66-0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI: 0.69, 0.60-0.80; 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%

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CI: 0.88, 0.75-1.03; 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, 0.90-1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban are currently approved in Europe for stroke prevention in patients with AF.[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. Therefore it is unknown 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: Representativeness and generalisability of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world AF patients in the United Kingdom) 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 United Kingdom (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.

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 generalisability to real-world AF populations, particularly for those eligible for anticoagulant treatment based on current guidelines.

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Design

Objectives

The objective of this study was to assess the generalisability 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 centralize 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% to 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 31st March 2008, and were aged ≥18 years of age. An artificial randomisation date was defined for 31st March 2008 to allow sufficient time for the application of prospective exclusion criteria.

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

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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 Supplementary Material. 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 mmHg or diastolic blood pressure ≥100 mmHg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mmHg or persistent diastolic blood pressure >90 mmHg)[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 (e.g. long term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (e.g. abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The $CHADS_2$ and CHA_2DS_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 transient ischemic attack (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_2DS_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_2DS_2-VASc indicates an intermediate risk of stroke, and a score of ≥2 indicates a high risk of stroke.[16]

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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_2DS_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 Chi-squared test at a significance level of 5%.

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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- 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 hypertension, where 81% of the GPRD AF population met this criterion in ROCKET-AF, compared to 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

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differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion 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).

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Discussion

The results of this analysis demonstrate that the pivotal trials for the novel oral anticoagulants dabigatran (RE-LY), apixaban (ARISTOTLE), and rivaroxaban (ROCKET-AF) vary in the generalisability 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 to the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate- 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, 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 generalizing 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 randomised controlled trials. The

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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 regards 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 or high risk population by CHA_2DS_2-VASc included 7,290 more patients than did the intermediate or high risk population by $CHADS_2$. These patients are at risk of stroke but may not

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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% per year to 3.2% per year when subdivided by CHA_2DS_2-VASc score.[28] The 2010 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_2DS_2-VASc.[1]

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.[29] 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.

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Conclusion

Trial generalisability is an important consideration for the National Institute of Health and Clinical Excellence (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.[30-32] 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 generalizable to the general anticoagulant eligible AF population.

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Author contributions

SL was responsible for study design, data extraction, and statistical analysis; BM, AC, MB, and GL contributed to study concept, design, and data interpretation. All authors reviewed and significantly contributed to the initial draft manuscript and approved the final submitted version.

Conflict of interest

SL, BM, AC, and MB are employees of Boehringer Ingelheim. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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Tables

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% [63.59-64.41])	51,415 (61% [60.58-61.42])	39,892 (48% [47.66-48.34])
Intermediate- or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71,493 (85%)	52,783 (74% [73.68-74.32])	51,415 (72% [71.67-72.33])	39,892 (56% [55.64-56.36])
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78,783 (94%)	53,640 (68% [67.67-68.33])	51,163 (65% [64.67-65.33])	39,892 (51% [50.65-51.35])
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49,099 (59%)	38,493 (78% [77.63-78.37])	35,712 (73% [72.61-73.39])	39,892 (81% [80.65-81.35])
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72,824 (87%)	53,059 (73% [72.68-73.32])	50,623 (70% [69.67-70.33])	39,835 (55% [54.64-55.36])

AF: Atrial Fibrillation; CI: Confidence Interval; GPRD: General Practice Research Database

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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)	83,898 (100)
Risk factors	Age ≥ 75 years	51,034 (61)	51,267 (61)	51,034 (61)
	Stroke, TIA, systemic embolism	11,632 (14)	10,577 (13)	11,632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16,184 (19)	16,009 (19)
	Age ≥ 65 years	70,047 (83)	-	-
	Diabetes mellitus	3945 (5)	14,940 (18)	14,850 (18)
	Hypertension	49,747 (59)	49,747 (59)	67,833 (81)
	Coronary artery disease	28,687 (34)	-	-
Overall inclusion criteria		64,710 (77)*	67,956 (81)†	52,540 (63)‡
Exclusion				
Reversible causes of AF		1,124 (1)	2,938 (4)	350 (<1)
Mitral valve stenosis		-	1,213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5,202 (6)	5,202 (6)	5,202 (6)
	Heart valve disorder	4,792 (6)		0 (0)
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	-	-	71 (<1)
Increased risk of bleeding		1,044 (1)	1,044 (1)	1,044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		-	-	2350 (3)
Uncontrolled hypertension		2,014 (2)	2,014 (2)	2,014 (2)
Planned cardioversion		-	-	843 (1)
Renal impairment		2,149 (3)	2,149 (3)	2,149 (3)
Other concomitant treatments	ASA at specified dose	-	1,629 (2)	1,767 (2)
	ASA + thienopyridine	-	203 (<1)	203 (<1)
	Intravenous antiplatelets	-	-	0 (0)
	Fibrinolytics	0 (0)	-	0 (0)
	NSAID	-	-	2,729 (3)
	P450 3A4 inhibitor	-	-	4 (<1)
	P450 3A4 inducer	-	-	1,125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other comcomitant conditions	Liver disease	1,547 (2)	-	1,547 (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		-	3,513 (4)	-
Overall inclusion and exclusion criteria		**53,640 (64%)**	**51,415 (61%)**	**39,892 (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

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AF: Atrial Fibrillation; ASA: acetylsalicylic acid; GPRD: General Practice Research Database; HIV: Human Immunodeficiency Virus; INR: International Normalised Ratio; NSAID: Non-Steroidal Anti-Inflammatory Drug; TIA: Transient Ischemic Attack

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Supplementary data

A description of the inclusion and exclusion criteria for each trial is provided in the table.

Table: Inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF

Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
Inclusion			
Age	≥18 years	≥18 years	≥18 years
AF	AF documented by ECG on enrolment; or symptomatic episode of paroxysmal or persistent AF documented by 12-lead ECG within 6 months before randomisation; or asymptomatic or symptomatic paroxysmal or persistent AF on 2 separate occasions, at least 1 day apart, one of which is within 6 months of randomisation, lasting ≥30 seconds and documented by 12-lead ECG, rhythm strip, pacemaker/ICD electrogram or Holter monitor	AF or atrial flutter documented by ECG on enrolment; or AF or atrial flutter documented by ECG or as an episode lasting ≥1 minute on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 weeks apart in 12 months before enrolment	AF documented by ECG evidence (e.g. 12-lead ECG, rhythm strip, Holter monitor, or pacemaker interrogation) within 30 days of randomisation plus medical evidence (e.g. from medical chart, hospital discharge summary) of atrial fibrillation within 1 year before and at least one day before the qualifying ECG evidence. Subjects with newly diagnosed AF are eligible permitting: there is evidence that the AF is non-valvular; cardioversion is not planned; and there is ECG evidence on 2 occasions 24 hours apart demonstrating AF
Risk factors	At least 1 of: history of stroke, transient ischemic attack, or systemic embolism; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram in the last 6 months; symptomatic heart failure, age ≥75 years; OR age at least 65 years with at least one of: diabetes mellitus on treatment; documented coronary artery disease (prior MI, positive stress test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing at least 75% stenosis in a major coronary artery); hypertension requiring medical treatment	At least one of: history of stroke, transient ischemic attack, or systemic embolus; symptomatic heart failure; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram; age ≥75 years; diabetes mellitus; hypertension requiring medical treatment	History of stroke, TIA, or non-CNS systemic embolism; OR at least 2 of: heart failure and/or left ventricular fraction ≤35%; hypertension defined by use of antihypertensive within 6 months of screening visit or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg*; age ≥75 years; diabetes mellitus defined as history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within 6 months of screening visit
Exclusion			
Reversible causes of AF	Reversible causes of AF (e.g. cardiac surgery, pulmonary embolism, or untreated hyperparathyroidism)	Reversible causes of AF (e.g. thyrotoxicosis or pericarditis)	Reversible causes of AF (i.e. thyrotoxicosis)
Mitral valve stenosis	-	Clinically significant moderate or severe mitral valve stenosis	Haemodynamically significant mitral valve stenosis
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	History of heart valve disorder (e.g. prosthetic valve or haemodynamically relevant valve disease); anticoagulant treatment for disorders other than AF	Prosthetic mechanical heart valve; anticoagulant treatment for disorders other than AF	Prosthetic heart valve; anticoagulant treatment for disorders other than AF
Recent stroke or TIA	Severe, disabling stroke within 6 months, or any stroke within 14 days	Stroke within 7 days	Severe, disabling stroke within 3 months or any stroke within 14 days; TIA within 3 days
Concomitant conditions associated with increased risk of bleeding	Major surgery within one month; planned surgery or intervention within next three months; history of intracranial, intraocular, spinal,	Planned major surgery; platelet count ≤100,000/mm^3; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood	Active internal bleeding; major surgical procedure or trauma within 30 days of randomisation; clinically significant GI bleeding within

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Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
	retroperitoneal or atraumatic intra-articular bleeding; GI haemorrhage within the past year; symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive 3 years	pressure ≥100 mmHg)	six months of randomisation; history of intracranial, intraocular, spinal, or intra-articular bleeding; chromic haemorrhagic disorder; known intracranial neoplasm, arteriovenous malformation or aneurysm; planned invasive procedure with potential for uncontrolled bleeding; platelet count <90,000/μL at screening; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive three years
Planned AF ablation procedure	Planned AF ablation procedure	Planned AF ablation procedure	-
Planned cardioversion	-	-	Planned cardioversion
Renal impairment	Creatine clearance ≤30 mL/minute	Creatine clearance <25 mL/minute or serum creatine <2.5 mg/dL	Creatine clearance <30 mL/minute
Contraindication to warfarin treatment	Contraindication to warfarin treatment	-	Contraindication to warfarin treatment
Concomitant treatments	Fibrinolytic agents within 48 hours of study entry; investigational drug within 30 days	Treatment with >165 mg ASA daily; ASA in combination with thienopyridines; investigational drug within 30 days	Treatment with >100 mg ASA daily; ASA in combination with thienopyridines within 5 days of randomisation; intravenous antiplatelets within 5 days of randomisation; fibrinolytic agents within 10 days of randomisation; anticipated need for chronic treatment with NSAID; systemic treatment with a strong inhibitor of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study; systemic treatment with strong inducer of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study
Other concomitant conditions	Active liver disease (e.g. persistent ALT, AST, or ALP >2 ULN; active hepatitis C; active hepatitis B; or active hepatitis A); anemia; pregnancy; active infection endocarditis; substance abuse disorder; life expectancy less than duration of trial; other conditions not allowing safe participation	ALT or AST >2 ULN; total bilirubin >1.5 ULN; haemoglobin level <9 g/dL; pregnancy; severe comorbid condition with life expectancy ≤1 year; substance abuse disorder	Left ventricular thrombus; HIV infection; anemia at screening visit; pregnancy or breastfeeding; TIA within 3 days of randomisation; active endocarditis; known liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 ULN; severe comorbid condition with life expectancy ≤2 years; substance abuse within 3 years of randomisation; psychosocial disorder
INR monitoring	-	Inability to comply with INR monitoring	-

Source: [1-3] with clarification from [4-6]

*There is a contradiction between the hypertension criterion defined in the supplementary appendix to the primary ROCKET-AF publication[4] and the ROCKET-AF rationale and design publication published by the ROCKET-AF trial investigators.[2] In this instance, the criterion from the supplementary appendix to the primary ROCKET-AF publication was used as it was deemed

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more inclusive than the ROCKET-AF rationale and design publication.

AF: Atrial Fibrillation; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; ASA: acetylsalicylic acid; AST: Aspartate Transaminase; CABG: Coronary Artery Bypass Graft; ECG: Echocardiogram; GI: Gastrointestinal; HIV: Human Immunodeficiency Virus; MI: Myocardial Infarction; NSAID: Non-Steroidal Anti-Inflammatory Drug; PCI: Percutaneous Coronary Intervention; Transient Ischemic Attack; ULN: Upper Limit of Normal

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Representativeness of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database

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Objective: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban, apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE, ROCKET-AF). This study aimed to assess the representativeness of the results from RE-LY, ARISTOTLE, and ROCKET-AF to the real-world AF population, particularly the population eligible for anticoagulants, in the UK.

Design: A cross-sectional database analysis was conducted.

Setting: A dataset derived from the General Practice Research Database (GPRD).

Primary and secondary outcomes measure: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF were compared. The results were then stratified by risk of stroke using $CHADS_2$ and CHA_2DS_2-VASc.

Results: 83,898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc ≥1; n=78,783 [94%]), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI:67.7%-68.3%; n=53,640), compared with 65% (95% CI:64.7%-65.3%; n=51,163) eligible for ARISTOTLE (apixaban) and 51% (95% CI:50.7%-51.4%; n=39,892) eligible for ROCKET-AF (rivaroxaban). Using the $CHADS_2$ method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment ($CHADS_2$ ≥1; n=71,493 [85%]), the proportion eligible for inclusion into RE-LY was 74% (95% CI:73.7%-74.3%; n=52,783), compared with 72% (95% CI:71.7%-72.3%; n=51,415) for ARISTOTLE and 56% (95% CI:55.6%-56.4%; n=39,892) for ROCKET-AF.

Conclusions: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast to patients enrolled within ROCKET-AF who were a more narrowly-defined group of patients at higher risk of stroke. Differences between trials should be taken into account when considering the applicability of clinical trial findings.

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Article summary

Article focus

- The focus of this study was to assess the applicability of the findings of three randomised, controlled trials for stroke prevention in patients with atrial fibrillation (AF) to the real-world UK population of individuals with this condition, particularly to patients who would be eligible for anticoagulation under current guidelines.
- The three studies were RE-LY, ARISTOTLE and ROCKET-AF that investigated the efficacy and safety of dabigatran etexilate (dabigatran), apixaban and rivaroxaban compared to warfarin, respectively.

Key messages

- Patients enrolled in RE-LY and ARISTOTLE were more reflective than patients enrolled in ROCKET-AF with respect to the real-world AF population in the UK, including the population eligible for anticoagulation.
- About 2/3 of patients recommended for anticoagulation would have been eligible to enrol into the clinical study investigating dabigatran (68%) or apixaban (65%) , but only about half of the patients would have been eligible for the rivaroxaban study (51%).
- Differences in representativeness should be taken into account when transferring study findings to patient populations in routine care.

Strengths and limitations of this study

- The source population for this research, i.e. 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.

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- 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 in some instances assumptions.

- 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.

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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 four- to five-fold 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 aging 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.[7-9]

In RE-LY (n=18,113; 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% Confidence Interval [CI]: 0.65, 0.52-0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI: 0.93, 0.81-1.07; 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, 0.74-1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI: 0.80, 0.70-0.93; 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, 0.66-0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI: 0.69, 0.60-0.80; 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%

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CI: 0.88, 0.75-1.03; 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, 0.90-1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban are currently approved in Europe for stroke prevention in patients with AF.[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 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: Representativeness and generalisability of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world AF patients in the United Kingdom) 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 United Kingdom (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

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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 centralize 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% to 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 31st March 2008, and were aged ≥18 years of age. An artificial start date was defined for 31st March 2008 to allow sufficient time for the application of prospective exclusion criteria, such as 'clinically significant GI bleeding within six months of randomisation'.

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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 Supplementary Material. Of note, the ROCKET-AF trial required patients to have a history of stroke, TIA, or systemic embolism (i.e. secondary prevention cohort) or had to have *two* of the following: age ≥75 years, congestive heart failure or ejection fraction ≤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 mmHg or diastolic blood pressure ≥100 mmHg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mmHg or persistent diastolic blood pressure >90 mmHg)[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 (e.g. long term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (e.g. abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The $CHADS_2$ and CHA_2DS_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 transient

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ischemic attack (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_2DS_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_2DS_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_2DS_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 Chi-squared test at a significance level of 5%. All analyses are descriptive and exploratory.

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Results

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

In total, 83,898 patients with AF were identified from the GPRD (Table 1~~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- 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~~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~~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 to 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

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major driver for differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion 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).

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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 to the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate- 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 generalizing the trial results from the high risk subpopulation seen in ROCKET-AF to the general AF population encountered in clinical practice.

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Trial generalisability (external validity) is a recognised problem in randomised controlled trials. 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 regards 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 or high risk population by CHA_2DS_2-VASc included 7,290 more patients than did the

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intermediate 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% per year to 3.2% per year when subdivided by CHA_2DS_2-VASc score.[28] The 2010 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_2DS_2-VASc.[1] In the 2012 focussed update of the ESC guidelines, the only recommended stroke risk score is CHA_2DS_2-VASc, with the initial focus on identification 'truly low risk' patients (that is, age <65 and lone AF, or CHA_2DS_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

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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, Health Technology Assessment (HTA) bodies (such as 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 National Institute of Health and Clinical Excellence (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 generalizable to the general anticoagulant eligible AF population.

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Author contributions

SL was responsible for study design, data extraction, and statistical analysis; BM, AC, MB, and GL contributed to study concept, design, and data interpretation. All authors reviewed and significantly contributed to the initial draft manuscript and approved the final submitted version.

Conflict of interest

SL, BM, AC, and MB are employees of Boehringer Ingelheim, the manufacturer of dabigatran. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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Tables

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% [63.59-64.41])	51,415 (61% [60.58-61.42])	39,892 (48% [47.66-48.34])
Intermediate- or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71,493 (85%)	52,783 (74% [73.68-74.32])	51,415 (72% [71.67-72.33])	39,892 (56% [55.64-56.36])
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78,783 (94%)	53,640 (68% [67.67-68.33])	51,163 (65% [64.67-65.33])	39,892 (51% [50.65-51.35])
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49,099 (59%)	38,493 (78% [77.63-78.37])	35,712 (73% [72.61-73.39])	39,892 (81% [80.65-81.35])
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72,824 (87%)	53,059 (73% [72.68-73.32])	50,623 (70% [69.67-70.33])	39,835 (55% [54.64-55.36])

AF: Atrial Fibrillation; CI: Confidence Interval; GPRD: General Practice Research Database

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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)	83,898 (100)
Risk factors	Age ≥ 75 years	51,034 (61)	51,267 (61)	51,034 (61)
	Stroke, TIA, systemic embolism	11,632 (14)	10,577 (13)	11,632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16,184 (19)	16,009 (19)
	Age ≥ 65 years	70,047 (83)	-	-
	Diabetes mellitus	3945 (5)	14,940 (18)	14,850 (18)
	Hypertension	49,747 (59)	49,747 (59)	67,833 (81)
	Coronary artery disease	28,687 (34)	-	-
Overall inclusion criteria		64,710 (77)*	67,956 (81)†	52,540 (63)‡
Exclusion				
Reversible causes of AF		1,124 (1)	2,938 (4)	350 (<1)
Mitral valve stenosis		-	1,213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5,202 (6)	5,202 (6)	5,202 (6)
	Heart valve disorder	4,792 (6)		0 (0)
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	-	-	71 (<1)
Increased risk of bleeding		1,044 (1)	1,044 (1)	1,044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		-	-	2350 (3)
Uncontrolled hypertension		2,014 (2)	2,014 (2)	2,014 (2)
Planned cardioversion		-	-	843 (1)
Renal impairment		2,149 (3)	2,149 (3)	2,149 (3)
Other concomitant treatments	ASA at specified dose	-	1,629 (2)	1,767 (2)
	ASA + thienopyridine	-	203 (<1)	203 (<1)
	Intravenous antiplatelets	-	-	0 (0)
	Fibrinolytics	0 (0)	-	0 (0)
	NSAID	-	-	2,729 (3)
	P450 3A4 inhibitor	-	-	4 (<1)
	P450 3A4 inducer	-	-	1,125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other comcomitant conditions	Liver disease	1,547 (2)	-	1,547 (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		-	3,513 (4)	-
Overall inclusion and exclusion criteria		**53,640 (64%)**	**51,415 (61%)**	**39,892 (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

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AF: Atrial Fibrillation; ASA: acetylsalicylic acid; GPRD: General Practice Research Database; HIV: Human Immunodeficiency Virus; INR: International Normalised Ratio; NSAID: Non-Steroidal Anti-Inflammatory Drug; TIA: Transient Ischemic Attack

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Representativeness of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database

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Abstract Word count: 287 words (maximum 300 words)

Objective: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban, apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE, ROCKET-AF). This study aimed to assess the ~~degree of generalisability~~representativeness of the results from RE-LY, ARISTOTLE, and ROCKET-AF to the real-world AF population, particularly the population eligible for anticoagulants, in the UK.

Design: A cross-sectional database analysis was conducted.

Setting: A dataset derived from the General Practice Research Database (GPRD).

Primary and secondary outcomes measure: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF were compared. The results were then stratified by risk of stroke using $CHADS_2$ and CHA_2DS_2-VASc.

Results: 83,898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc ≥1; n=78,783 [94%]), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI:67.7%-68.3%; n=53,640), compared with 65% (95% CI:64.7%-65.3%; n=51,163) eligible for ARISTOTLE (apixaban) and 51% (95% CI:50.7%-51.4%; n=39,892) eligible for ROCKET-AF (rivaroxaban). Using the $CHADS_2$ method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment ($CHADS_2$ ≥1; n=71,493 [85%]), the proportion eligible for inclusion into RE-LY was 74% (95% CI:73.7%-74.3%; n=52,783), compared with 72% (95% CI:71.7%-72.3%; n=51,415) for ARISTOTLE and 56% (95% CI:55.6%-56.4%; n=39,892) for ROCKET-AF.

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Conclusions: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast to patients enrolled within ROCKET-AF who were a more narrowly-defined group of patients at higher risk of stroke. Differences between trials should be taken into account when considering the ~~generalisability~~ applicability of clinical trial findings.

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Article summary

Article focus

- The focus of this study was to assess the ~~generalisability~~ applicability of the findings of three randomised, controlled trials for stroke prevention in patients with atrial fibrillation (AF) to the real-world UK population of individuals with this condition, particularly to patients who would be eligible for anticoagulation under current guidelines.
- The three studies were RE-LY, ARISTOTLE and ROCKET-AF that investigated the efficacy and safety of dabigatran etexilate (dabigatran), apixaban and rivaroxaban compared to warfarin, respectively.

Key messages

- Patients enrolled in RE-LY and ARISTOTLE were more reflective than patients enrolled in ROCKET-AF with respect to the real-world AF population in the UK, including the population eligible for anticoagulation.
- About 2/3 of patients recommended for anticoagulation would have been eligible to enrol into the clinical study investigating dabigatran (68%) or apixaban (65%) , but only about half of the patients would have been eligible for the rivaroxaban study (51%).
- Differences in ~~generalisibility~~ representativeness should be taken into account when transferring study findings to patient populations in routine care.

Strengths and limitations of this study

- The source population for this research, i.e. 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.

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- 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 in some instances assumptions.

- 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.

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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 four- to five-fold 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 aging 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.[7-9]

In RE-LY (n=18,113; 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% Confidence Interval [CI]: 0.65, 0.52-0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI: 0.93, 0.81-1.07; 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, 0.74-1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI: 0.80, 0.70-0.93; 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, 0.66-0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI: 0.69, 0.60-0.80; 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%

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CI: 0.88, 0.75-1.03; 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, 0.90-1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban are currently approved in Europe for stroke prevention in patients with AF.[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 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: Representativeness and generalisability of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world AF patients in the United Kingdom) 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 United Kingdom (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 ~~generalisability~~ representativeness to real-world AF populations, particularly for those eligible for anticoagulant

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treatment based on current guidelines.

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Design

Objectives

The objective of this study was to assess the ~~generalisability~~ 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 centralize 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% to 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 31st March 2008, and were aged ≥18 years of age. An artificial ~~randomisation~~ start date was defined for 31st March 2008 to allow sufficient time for the application of prospective exclusion criteria, such as 'clinically significant GI bleeding within six months of randomisation'.

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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 Supplementary Material. Of note, the ROCKET-AF trial required patients to have a history of stroke, TIA, or systemic embolism (i.e. secondary prevention cohort) or had to have *two* of the following: age ≥75 years, congestive heart failure or ejection fraction ≤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 mmHg or diastolic blood pressure ≥100 mmHg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mmHg or persistent diastolic blood pressure >90 mmHg)[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 (e.g. long term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (e.g. abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The $CHADS_2$ and CHA_2DS_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 transient

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ischemic attack (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_2DS_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_2DS_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_2DS_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 Chi-squared test at a significance level of 5%. All analyses are descriptive and exploratory.

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Results

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

In total, 83,898 patients with AF were identified from the GPRD (Table 1~~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- 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~~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~~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 to 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

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major driver for differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion 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).

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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 ~~generalisability~~ 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 to the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate- 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] ~~Indeed, a~~ 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 generalizing the trial results from the high risk subpopulation seen in ROCKET-AF to the general AF population encountered in clinical practice.

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Trial generalisability (external validity) is a recognised problem in randomised controlled trials. 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 regards 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 or high risk population by CHA_2DS_2-VASc included 7,290 more patients than did the

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intermediate 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% per year to 3.2% per year when subdivided by CHA_2DS_2-VASc score.[28] The 2010 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_2DS_2-VASc.[1] In the 2012 focussed update of the ESC guidelines, the only recommended stroke risk score is CHA_2DS_2-VASc, with the initial focus on identification 'truly low risk' patients (that is, age <65 and lone AF, or CHA_2DS_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.[3029] 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

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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, Health Technology Assessment (HTA) bodies (such as 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 National Institute of Health and Clinical Excellence (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 generalizable to the general anticoagulant eligible AF population.

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Author contributions

SL was responsible for study design, data extraction, and statistical analysis; BM, AC, MB, and GL contributed to study concept, design, and data interpretation. All authors reviewed and significantly contributed to the initial draft manuscript and approved the final submitted version.

Conflict of interest

SL, BM, AC, and MB are employees of Boehringer Ingelheim, the manufacturer of dabigatran. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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Tables

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% [63.59-64.41])	51,415 (61% [60.58-61.42])	39,892 (48% [47.66-48.34])
Intermediate- or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71,493 (85%)	52,783 (74% [73.68-74.32])	51,415 (72% [71.67-72.33])	39,892 (56% [55.64-56.36])
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78,783 (94%)	53,640 (68% [67.67-68.33])	51,163 (65% [64.67-65.33])	39,892 (51% [50.65-51.35])
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49,099 (59%)	38,493 (78% [77.63-78.37])	35,712 (73% [72.61-73.39])	39,892 (81% [80.65-81.35])
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72,824 (87%)	53,059 (73% [72.68-73.32])	50,623 (70% [69.67-70.33])	39,835 (55% [54.64-55.36])

AF: Atrial Fibrillation; CI: Confidence Interval; GPRD: General Practice Research Database

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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)	83,898 (100)
Risk factors	Age ≥ 75 years	51,034 (61)	51,267 (61)	51,034 (61)
	Stroke, TIA, systemic embolism	11,632 (14)	10,577 (13)	11,632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16,184 (19)	16,009 (19)
	Age ≥ 65 years	70,047 (83)	-	-
	Diabetes mellitus	3945 (5)	14,940 (18)	14,850 (18)
	Hypertension	49,747 (59)	49,747 (59)	67,833 (81)
	Coronary artery disease	28,687 (34)	-	-
Overall inclusion criteria		64,710 (77)*	67,956 (81)†	52,540 (63)‡
Exclusion				
Reversible causes of AF		1,124 (1)	2,938 (4)	350 (<1)
Mitral valve stenosis		-	1,213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5,202 (6)	5,202 (6)	5,202 (6)
	Heart valve disorder	4,792 (6)		0 (0)
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	-	-	71 (<1)
Increased risk of bleeding		1,044 (1)	1,044 (1)	1,044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		-	-	2350 (3)
Uncontrolled hypertension		2,014 (2)	2,014 (2)	2,014 (2)
Planned cardioversion		-	-	843 (1)
Renal impairment		2,149 (3)	2,149 (3)	2,149 (3)
Other concomitant treatments	ASA at specified dose	-	1,629 (2)	1,767 (2)
	ASA + thienopyridine	-	203 (<1)	203 (<1)
	Intravenous antiplatelets	-	-	0 (0)
	Fibrinolytics	0 (0)	-	0 (0)
	NSAID	-	-	2,729 (3)
	P450 3A4 inhibitor	-	-	4 (<1)
	P450 3A4 inducer	-	-	1,125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other comcomitant conditions	Liver disease	1,547 (2)	-	1,547 (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		-	3,513 (4)	-
Overall inclusion and exclusion criteria		**53,640 (64%)**	**51,415 (61%)**	**39,892 (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

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AF: Atrial Fibrillation; ASA: acetylsalicylic acid; GPRD: General Practice Research Database; HIV: Human Immunodeficiency Virus; INR: International Normalised Ratio; NSAID: Non-Steroidal Anti-Inflammatory Drug; TIA: Transient Ischemic Attack

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Supplementary data

A description of the inclusion and exclusion criteria for each trial is provided in the table.

Table: Inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF

Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
Inclusion			
Age	≥18 years	≥18 years	≥18 years
AF	AF documented by ECG on enrolment; or symptomatic episode of paroxysmal or persistent AF documented by 12-lead ECG within 6 months before randomisation; or asymptomatic or symptomatic paroxysmal or persistent AF on 2 separate occasions, at least 1 day apart, one of which is within 6 months of randomisation, lasting ≥30 seconds and documented by 12-lead ECG, rhythm strip, pacemaker/ICD electrogram or Holter monitor	AF or atrial flutter documented by ECG on enrolment; or AF or atrial flutter documented by ECG or as an episode lasting ≥1 minute on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 weeks apart in 12 months before enrolment	AF documented by ECG evidence (e.g. 12-lead ECG, rhythm strip, Holter monitor, or pacemaker interrogation) within 30 days of randomisation plus medical evidence (e.g. from medical chart, hospital discharge summary) of atrial fibrillation within 1 year before and at least one day before the qualifying ECG evidence. Subjects with newly diagnosed AF are eligible permitting: there is evidence that the AF is non-valvular; cardioversion is not planned; and there is ECG evidence on 2 occasions 24 hours apart demonstrating AF
Risk factors	At least 1 of: history of stroke, transient ischemic attack, or systemic embolism; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram in the last 6 months; symptomatic heart failure, age ≥75 years; OR age at least 65 years with at least one of: diabetes mellitus on treatment; documented coronary artery disease (prior MI, positive stress test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing at least 75% stenosis in a major coronary artery); hypertension requiring medical treatment	At least one of: history of stroke, transient ischemic attack, or systemic embolus; symptomatic heart failure; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram; age ≥75 years; diabetes mellitus; hypertension requiring medical treatment	History of stroke, TIA, or non-CNS systemic embolism; OR at least 2 of: heart failure and/or left ventricular fraction ≤35%; hypertension defined by use of antihypertensive within 6 months of screening visit or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg*; age ≥75 years; diabetes mellitus defined as history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within 6 months of screening visit
Exclusion			
Reversible causes of AF	Reversible causes of AF (e.g. cardiac surgery, pulmonary embolism, or untreated hyperparathyroidism)	Reversible causes of AF (e.g. thyrotoxicosis or pericarditis)	Reversible causes of AF (i.e. thyrotoxicosis)
Mitral valve stenosis	-	Clinically significant moderate or severe mitral valve stenosis	Haemodynamically significant mitral valve stenosis
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	History of heart valve disorder (e.g. prosthetic valve or haemodynamically relevant valve disease); anticoagulant treatment for disorders other than AF	Prosthetic mechanical heart valve; anticoagulant treatment for disorders other than AF	Prosthetic heart valve; anticoagulant treatment for disorders other than AF
Recent stroke or TIA	Severe, disabling stroke within 6 months, or any stroke within 14 days	Stroke within 7 days	Severe, disabling stroke within 3 months or any stroke within 14 days; TIA within 3 days
Concomitant conditions associated with increased risk of bleeding	Major surgery within one month; planned surgery or intervention within next three months; history of intracranial, intraocular, spinal,	Planned major surgery; platelet count ≤100,000/mm^3; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood	Active internal bleeding; major surgical procedure or trauma within 30 days of randomisation; clinically significant GI bleeding within

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Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
	retroperitoneal or atraumatic intra-articular bleeding; GI haemorrhage within the past year; symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive 3 years	pressure ≥100 mmHg)	six months of randomisation; history of intracranial, intraocular, spinal, or intra-articular bleeding; chromic haemorrhagic disorder; known intracranial neoplasm, arteriovenous malformation or aneurysm; planned invasive procedure with potential for uncontrolled bleeding; platelet count <90,000/μL at screening; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive three years
Planned AF ablation procedure	Planned AF ablation procedure	Planned AF ablation procedure	-
Planned cardioversion	-	-	Planned cardioversion
Renal impairment	Creatine clearance ≤30 mL/minute	Creatine clearance <25 mL/minute or serum creatine <2.5 mg/dL	Creatine clearance <30 mL/minute
Contraindication to warfarin treatment	Contraindication to warfarin treatment	-	Contraindication to warfarin treatment
Concomitant treatments	Fibrinolytic agents within 48 hours of study entry; investigational drug within 30 days	Treatment with >165 mg ASA daily; ASA in combination with thienopyridines; investigational drug within 30 days	Treatment with >100 mg ASA daily; ASA in combination with thienopyridines within 5 days of randomisation; intravenous antiplatelets within 5 days of randomisation; fibrinolytic agents within 10 days of randomisation; anticipated need for chronic treatment with NSAID; systemic treatment with a strong inhibitor of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study; systemic treatment with strong inducer of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study
Other concomitant conditions	Active liver disease (e.g. persistent ALT, AST, or ALP >2 ULN; active hepatitis C; active hepatitis B; or active hepatitis A); anemia; pregnancy; active infection endocarditis; substance abuse disorder; life expectancy less than duration of trial; other conditions not allowing safe participation	ALT or AST >2 ULN; total bilirubin >1.5 ULN; haemoglobin level <9 g/dL; pregnancy; severe comorbid condition with life expectancy ≤1 year; substance abuse disorder	Left ventricular thrombus; HIV infection; anemia at screening visit; pregnancy or breastfeeding; TIA within 3 days of randomisation; active endocarditis; known liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 ULN; severe comorbid condition with life expectancy ≤2 years; substance abuse within 3 years of randomisation; psychosocial disorder
INR monitoring	-	Inability to comply with INR monitoring	-

Source: [1-3] with clarification from [4-6]

*There is a contradiction between the hypertension criterion defined in the supplementary appendix to the primary ROCKET-AF publication[4] and the ROCKET-AF rationale and design publication published by the ROCKET-AF trial investigators.[2] In this instance, the criterion from the supplementary appendix to the primary ROCKET-AF publication was used as it was deemed

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more inclusive than the ROCKET-AF rationale and design publication.

AF: Atrial Fibrillation; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; ASA: acetylsalicylic acid; AST: Aspartate Transaminase; CABG: Coronary Artery Bypass Graft; ECG: Echocardiogram; GI: Gastrointestinal; HIV: Human Immunodeficiency Virus; MI: Myocardial Infarction; NSAID: Non-Steroidal Anti-Inflammatory Drug; PCI: Percutaneous Coronary Intervention; Transient Ischemic Attack; ULN: Upper Limit of Normal

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Representativeness of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database

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Objective: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban, apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE, ROCKET-AF). This study aimed to assess the representativeness for the real-world AF population, particularly the population eligible for anticoagulants.

Design: A cross-sectional database analysis.

Setting: Dataset derived from the General Practice Research Database (GPRD).

Primary and secondary outcomes measure: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF were compared. The results were then stratified by risk of stroke using $CHADS_2$ and CHA_2DS_2-VASc.

Results: 83,898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc ≥1; n=78,783 [94%]), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI:67.7%-68.3%; n=53,640), compared with 65% (95% CI:64.7%-65.3%; n=51,163) eligible for ARISTOTLE (apixaban) and 51% (95% CI:50.7%-51.4%; n=39,892) eligible for ROCKET-AF (rivaroxaban). Using the $CHADS_2$ method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment ($CHADS_2$ ≥1; n=71,493 [85%]), the proportion eligible for inclusion into RE-LY was 74% (95% CI:73.7%-74.3%; n=52,783), compared with 72% (95% CI:71.7%-72.3%; n=51,415) for ARISTOTLE and 56% (95% CI:55.6%-56.4%; n=39,892) for ROCKET-AF.

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Conclusions: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast to patients enrolled within ROCKET-AF who were a more narrowly-defined group of patients at higher risk of stroke. Differences between trials should be taken into account when considering the applicability of findings from randomised clinical trials. However, assessing representativeness is not a substitute for assessing generalisibility, that is, how well clinical trial results would translate into effectiveness and safety in everyday routine care.

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Article summary

Article focus

- The focus of this study was to assess the applicability of the findings of three randomised, controlled trials for stroke prevention in patients with atrial fibrillation (AF) to the real-world UK population of individuals with this condition, particularly to patients who would be eligible for anticoagulation under current guidelines.
- The three studies were RE-LY, ARISTOTLE and ROCKET-AF that investigated the efficacy and safety of dabigatran etexilate (dabigatran), apixaban and rivaroxaban compared to warfarin, respectively.

Key messages

- Patients enrolled in RE-LY and ARISTOTLE were more reflective than patients enrolled in ROCKET-AF with respect to the real-world AF population in the UK, including the population eligible for anticoagulation.
- About 2/3 of patients recommended for anticoagulation would have been eligible to enrol into the clinical study investigating dabigatran (68%) or apixaban (65%) , but only about half of the patients would have been eligible for the rivaroxaban study (51%).
- Differences in representativeness should be taken into account when transferring study findings to patient populations in routine care.

Strengths and limitations of this study

- The source population for this research, i.e. 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.

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- 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 in some instances assumptions.

- 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, i.e. 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.

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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 four- to five-fold 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 aging 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.[7-9]

In RE-LY (n=18,113; 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% Confidence Interval [CI]: 0.65, 0.52-0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI: 0.93, 0.81-1.07; 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, 0.74-1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI: 0.80, 0.70-0.93; 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, 0.66-0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI: 0.69, 0.60-0.80; 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%

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CI: 0.88, 0.75-1.03; 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, 0.90-1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban are currently approved in Europe for stroke prevention in patients with AF.[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 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: Representativeness and generalisability of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world AF patients in the United Kingdom) 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 United Kingdom (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

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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 centralize 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% to 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 31st March 2008, and were aged ≥18 years of age. An artificial start date was defined for 31st March 2008 to allow sufficient time for the application of prospective exclusion criteria, such as 'clinically significant GI bleeding within six months of randomisation'.

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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 Supplementary Material. Of note, the ROCKET-AF trial required patients to have a history of stroke, TIA, or systemic embolism (i.e. secondary prevention cohort) or had to have *two* of the following: age ≥75 years, congestive heart failure or ejection fraction ≤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 mmHg or diastolic blood pressure ≥100 mmHg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mmHg or persistent diastolic blood pressure >90 mmHg)[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 (e.g. long term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (e.g. abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The $CHADS_2$ and CHA_2DS_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 transient

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ischemic attack (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_2DS_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_2DS_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_2DS_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 Chi-squared test at a significance level of 5%. All analyses are descriptive and exploratory.

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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- 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 to 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

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major driver for differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion 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).

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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 to the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate- 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 generalizing the trial results from the high risk subpopulation seen in ROCKET-AF to the general AF population encountered in clinical practice.

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Trial generalisability (external validity) is a recognised problem in randomised controlled trials. 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 regards 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 or high risk population by CHA_2DS_2-VASc included 7,290 more patients than did the

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intermediate 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% per year to 3.2% per year when subdivided by CHA_2DS_2-VASc score.[28] The 2010 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_2DS_2-VASc.[1] In the 2012 focussed update of the ESC guidelines, the only recommended stroke risk score is CHA_2DS_2-VASc, with the initial focus on identification 'truly low risk' patients (that is, age <65 and lone AF, or CHA_2DS_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

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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, Health Technology Assessment (HTA) bodies (such as 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 National Institute of Health and Clinical Excellence (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 generalizable to the general anticoagulant eligible AF population.

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Author contributions

SL was responsible for study design, data extraction, and statistical analysis; BM, AC, MB, and GL contributed to study concept, design, and data interpretation. All authors reviewed and significantly contributed to the initial draft manuscript and approved the final submitted version.

Conflict of interest

SL, BM, AC, and MB are employees of Boehringer Ingelheim, the manufacturer of dabigatran. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

Data Sharing Statement

There is no additional data available

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Tables

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% [63.59-64.41])	51,415 (61% [60.58-61.42])	39,892 (48% [47.66-48.34])
Intermediate- or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71,493 (85%)	52,783 (74% [73.68-74.32])	51,415 (72% [71.67-72.33])	39,892 (56% [55.64-56.36])
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78,783 (94%)	53,640 (68% [67.67-68.33])	51,163 (65% [64.67-65.33])	39,892 (51% [50.65-51.35])
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49,099 (59%)	38,493 (78% [77.63-78.37])	35,712 (73% [72.61-73.39])	39,892 (81% [80.65-81.35])
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72,824 (87%)	53,059 (73% [72.68-73.32])	50,623 (70% [69.67-70.33])	39,835 (55% [54.64-55.36])

AF: Atrial Fibrillation; CI: Confidence Interval; GPRD: General Practice Research Database

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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)	83,898 (100)
Risk factors	Age ≥ 75 years	51,034 (61)	51,267 (61)	51,034 (61)
	Stroke, TIA, systemic embolism	11,632 (14)	10,577 (13)	11,632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16,184 (19)	16,009 (19)
	Age ≥ 65 years	70,047 (83)	-	-
	Diabetes mellitus	3945 (5)	14,940 (18)	14,850 (18)
	Hypertension	49,747 (59)	49,747 (59)	67,833 (81)
	Coronary artery disease	28,687 (34)	-	-
Overall inclusion criteria		64,710 (77)*	67,956 (81)†	52,540 (63)‡
Exclusion				
Reversible causes of AF		1,124 (1)	2,938 (4)	350 (<1)
Mitral valve stenosis		-	1,213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5,202 (6)	5,202 (6)	5,202 (6)
	Heart valve disorder	4,792 (6)		0 (0)
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	-	-	71 (<1)
Increased risk of bleeding		1,044 (1)	1,044 (1)	1,044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		-	-	2350 (3)
Uncontrolled hypertension		2,014 (2)	2,014 (2)	2,014 (2)
Planned cardioversion		-	-	843 (1)
Renal impairment		2,149 (3)	2,149 (3)	2,149 (3)
Other concomitant treatments	ASA at specified dose	-	1,629 (2)	1,767 (2)
	ASA + thienopyridine	-	203 (<1)	203 (<1)
	Intravenous antiplatelets	-	-	0 (0)
	Fibrinolytics	0 (0)	-	0 (0)
	NSAID	-	-	2,729 (3)
	P450 3A4 inhibitor	-	-	4 (<1)
	P450 3A4 inducer	-	-	1,125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other comcomitant conditions	Liver disease	1,547 (2)	-	1,547 (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		-	3,513 (4)	-
Overall inclusion and exclusion criteria		**53,640 (64%)**	**51,415 (61%)**	**39,892 (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

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AF: Atrial Fibrillation; ASA: acetylsalicylic acid; GPRD: General Practice Research Database; HIV: Human Immunodeficiency Virus; INR: International Normalised Ratio; NSAID: Non-Steroidal Anti-Inflammatory Drug; TIA: Transient Ischemic Attack

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Representativeness of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database

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Abstract Word count: 300

Objective: Three oral anticoagulants have reported study results for stroke prevention in patients with atrial fibrillation (AF) (dabigatran etexilate, rivaroxaban, apixaban); all demonstrated superiority or non-inferiority compared with warfarin (RE-LY, ARISTOTLE, ROCKET-AF). This study aimed to assess the representativeness ~~of the results from RE-LY, ARISTOTLE, and ROCKET-AF to~~for the real-world AF population, particularly the population eligible for anticoagulants~~, in the UK~~.

Design: A cross-sectional database analysis~~ was conducted~~.

Setting: D~~A d~~ataset derived from the General Practice Research Database (GPRD).

Primary and secondary outcomes measure: The proportion of real-world patients with AF who met the inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF were compared. The results were then stratified by risk of stroke using $CHADS_2$ and CHA_2DS_2-VASc.

Results: 83,898 patients with AF were identified in the GPRD. For the population at intermediate or high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc ≥1; n=78,783 [94%]), the proportion eligible for inclusion into RE-LY (dabigatran etexilate) was 68% (95% CI:67.7%-68.3%; n=53,640), compared with 65% (95% CI:64.7%-65.3%; n=51,163) eligible for ARISTOTLE (apixaban) and 51% (95% CI:50.7%-51.4%; n=39,892) eligible for ROCKET-AF (rivaroxaban). Using the $CHADS_2$ method of risk stratification, for the population at intermediate or high risk of stroke and eligible for anticoagulation treatment ($CHADS_2$ ≥1; n=71,493 [85%]), the proportion eligible for inclusion into RE-LY was 74% (95% CI:73.7%-74.3%; n=52,783), compared with 72% (95% CI:71.7%-72.3%; n=51,415) for ARISTOTLE and 56% (95% CI:55.6%-56.4%; n=39,892) for ROCKET-AF.

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Conclusions: Patients enrolled within RE-LY and ARISTOTLE were more reflective of the 'real-world' AF population in the UK, in contrast to patients enrolled within ROCKET-AF who were a more narrowly-defined group of patients at higher risk of stroke. Differences between trials should be taken into account when considering the applicability of findings from randomised clinical trials. However, assessing representativeness is not a substitute for assessing generalisibility, that is, how well clinical trial results would translate into effectiveness and safety in everyday routine care.

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Article summary

Article focus

- The focus of this study was to assess the applicability of the findings of three randomised, controlled trials for stroke prevention in patients with atrial fibrillation (AF) to the real-world UK population of individuals with this condition, particularly to patients who would be eligible for anticoagulation under current guidelines.
- The three studies were RE-LY, ARISTOTLE and ROCKET-AF that investigated the efficacy and safety of dabigatran etexilate (dabigatran), apixaban and rivaroxaban compared to warfarin, respectively.

Key messages

- Patients enrolled in RE-LY and ARISTOTLE were more reflective than patients enrolled in ROCKET-AF with respect to the real-world AF population in the UK, including the population eligible for anticoagulation.
- About 2/3 of patients recommended for anticoagulation would have been eligible to enrol into the clinical study investigating dabigatran (68%) or apixaban (65%) , but only about half of the patients would have been eligible for the rivaroxaban study (51%).
- Differences in representativeness should be taken into account when transferring study findings to patient populations in routine care.

Strengths and limitations of this study

- The source population for this research, i.e. 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.

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- 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 in some instances assumptions.

- 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, i.e. 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.

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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 four- to five-fold 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 aging 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.[7-9]

In RE-LY (n=18,113; 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% Confidence Interval [CI]: 0.65, 0.52-0.81; p<0.001 for superiority) and did not significantly increase major bleeding (RR, 95% CI: 0.93, 0.81-1.07; 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, 0.74-1.10; p<0.001 for non-inferiority) but significantly reduced major bleeding compared with warfarin (RR, 95% CI: 0.80, 0.70-0.93; 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, 0.66-0.95; p<0.001 for non-inferiority; p=0.01 for superiority) and reduced rates of major bleeding (HR, 95% CI: 0.69, 0.60-0.80; 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%

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CI: 0.88, 0.75-1.03; 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, 0.90-1.20; p=0.58, safety on treatment population).[8] Of these three anticoagulants, only dabigatran and rivaroxaban are currently approved in Europe for stroke prevention in patients with AF.[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 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: Representativeness and generalisability of the dabigatran, apixaban, and rivaroxaban clinical trial populations to real-world AF patients in the United Kingdom) 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 United Kingdom (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

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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 centralize 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% to 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 31st March 2008, and were aged ≥18 years of age. An artificial start date was defined for 31st March 2008 to allow sufficient time for the application of prospective exclusion criteria, such as 'clinically significant GI bleeding within six months of randomisation'.

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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 Supplementary Material. Of note, the ROCKET-AF trial required patients to have a history of stroke, TIA, or systemic embolism (i.e. secondary prevention cohort) or had to have *two* of the following: age ≥75 years, congestive heart failure or ejection fraction ≤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 mmHg or diastolic blood pressure ≥100 mmHg)[22] and in the supplementary appendix of the results publication (use of antihypertensives within 6 months before screening or persistent systolic blood pressure >140 mmHg or persistent diastolic blood pressure >90 mmHg)[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 (e.g. long term non-steroidal anti-inflammatory drug usage), and test results were used to identify patients meeting criterion (e.g. abnormal platelet and haemoglobin levels) forming part of the exclusion criteria for the trials.

The $CHADS_2$ and CHA_2DS_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 transient

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ischemic attack (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_2DS_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_2DS_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_2DS_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 Chi-squared test at a significance level of 5%. All analyses are descriptive and exploratory.

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Results

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

In total, 83,898 patients with AF were identified from the GPRD (Table 1~~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- 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~~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~~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 to 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

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major driver for differences in overall inclusion eligibility for the trials. Instead, the differences in inclusion eligibility were not driven by an individual inclusion 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).

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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 to the populations enrolled according to the exclusion/inclusion criteria for the other trials. Overall, 68% of intermediate- 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 generalizing the trial results from the high risk subpopulation seen in ROCKET-AF to the general AF population encountered in clinical practice.

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Trial generalisability (external validity) is a recognised problem in randomised controlled trials. 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 regards 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 or high risk population by CHA_2DS_2-VASc included 7,290 more patients than did the

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intermediate 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% per year to 3.2% per year when subdivided by CHA_2DS_2-VASc score.[28] The 2010 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_2DS_2-VASc.[1] In the 2012 focussed update of the ESC guidelines, the only recommended stroke risk score is CHA_2DS_2-VASc, with the initial focus on identification 'truly low risk' patients (that is, age <65 and lone AF, or CHA_2DS_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

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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, Health Technology Assessment (HTA) bodies (such as 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 National Institute of Health and Clinical Excellence (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 generalizable to the general anticoagulant eligible AF population.

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Author contributions

SL was responsible for study design, data extraction, and statistical analysis; BM, AC, MB, and GL contributed to study concept, design, and data interpretation. All authors reviewed and significantly contributed to the initial draft manuscript and approved the final submitted version.

Conflict of interest

SL, BM, AC, and MB are employees of Boehringer Ingelheim, the manufacturer of dabigatran. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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Tables

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% [63.59-64.41])	51,415 (61% [60.58-61.42])	39,892 (48% [47.66-48.34])
Intermediate- or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71,493 (85%)	52,783 (74% [73.68-74.32])	51,415 (72% [71.67-72.33])	39,892 (56% [55.64-56.36])
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78,783 (94%)	53,640 (68% [67.67-68.33])	51,163 (65% [64.67-65.33])	39,892 (51% [50.65-51.35])
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49,099 (59%)	38,493 (78% [77.63-78.37])	35,712 (73% [72.61-73.39])	39,892 (81% [80.65-81.35])
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72,824 (87%)	53,059 (73% [72.68-73.32])	50,623 (70% [69.67-70.33])	39,835 (55% [54.64-55.36])

AF: Atrial Fibrillation; CI: Confidence Interval; GPRD: General Practice Research Database

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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)	83,898 (100)
Risk factors	Age ≥ 75 years	51,034 (61)	51,267 (61)	51,034 (61)
	Stroke, TIA, systemic embolism	11,632 (14)	10,577 (13)	11,632 (14)
	Congestive heart failure Ejection fraction	1737 (2)	16,184 (19)	16,009 (19)
	Age ≥ 65 years	70,047 (83)	-	-
	Diabetes mellitus	3945 (5)	14,940 (18)	14,850 (18)
	Hypertension	49,747 (59)	49,747 (59)	67,833 (81)
	Coronary artery disease	28,687 (34)	-	-
Overall inclusion criteria		64,710 (77)*	67,956 (81)†	52,540 (63)‡
Exclusion				
Reversible causes of AF		1,124 (1)	2,938 (4)	350 (<1)
Mitral valve stenosis		-	1,213 (1)	1213 (1)
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	Conditions other than AF requiring chronic anticoagulant treatment	5,202 (6)	5,202 (6)	5,202 (6)
	Heart valve disorder	4,792 (6)		0 (0)
Stroke or TIA	Recent stroke	429 (1)	62 (<1)	429 (1)
	Recent TIA	-	-	71 (<1)
Increased risk of bleeding		1,044 (1)	1,044 (1)	1,044 (1)
Intracranial neoplasm, arteriovenous malformation, or aneurysm		-	-	2350 (3)
Uncontrolled hypertension		2,014 (2)	2,014 (2)	2,014 (2)
Planned cardioversion		-	-	843 (1)
Renal impairment		2,149 (3)	2,149 (3)	2,149 (3)
Other concomitant treatments	ASA at specified dose	-	1,629 (2)	1,767 (2)
	ASA + thienopyridine	-	203 (<1)	203 (<1)
	Intravenous antiplatelets	-	-	0 (0)
	Fibrinolytics	0 (0)	-	0 (0)
	NSAID	-	-	2,729 (3)
	P450 3A4 inhibitor	-	-	4 (<1)
	P450 3A4 inducer	-	-	1,125 (1)
	Investigational drug	0 (0)	0 (0)	0 (0)
Other comcomitant conditions	Liver disease	1,547 (2)	-	1,547 (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		-	3,513 (4)	-
Overall inclusion and exclusion criteria		**53,640 (64%)**	**51,415 (61%)**	**39,892 (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

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AF: Atrial Fibrillation; ASA: acetylsalicylic acid; GPRD: General Practice Research Database; HIV: Human Immunodeficiency Virus; INR: International Normalised Ratio; NSAID: Non-Steroidal Anti-Inflammatory Drug; TIA: Transient Ischemic Attack

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Supplementary data

A description of the inclusion and exclusion criteria for each trial is provided in the table.

Table: Inclusion/exclusion criteria for RE-LY, ARISTOTLE, and ROCKET-AF

Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
Inclusion			
Age	≥18 years	≥18 years	≥18 years
AF	AF documented by ECG on enrolment; or symptomatic episode of paroxysmal or persistent AF documented by 12-lead ECG within 6 months before randomisation; or asymptomatic or symptomatic paroxysmal or persistent AF on 2 separate occasions, at least 1 day apart, one of which is within 6 months of randomisation, lasting ≥30 seconds and documented by 12-lead ECG, rhythm strip, pacemaker/ICD electrogram or Holter monitor	AF or atrial flutter documented by ECG on enrolment; or AF or atrial flutter documented by ECG or as an episode lasting ≥1 minute on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 weeks apart in 12 months before enrolment	AF documented by ECG evidence (e.g. 12-lead ECG, rhythm strip, Holter monitor, or pacemaker interrogation) within 30 days of randomisation plus medical evidence (e.g. from medical chart, hospital discharge summary) of atrial fibrillation within 1 year before and at least one day before the qualifying ECG evidence. Subjects with newly diagnosed AF are eligible permitting: there is evidence that the AF is non-valvular; cardioversion is not planned; and there is ECG evidence on 2 occasions 24 hours apart demonstrating AF
Risk factors	At least 1 of: history of stroke, transient ischemic attack, or systemic embolism; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram in the last 6 months; symptomatic heart failure, age ≥75 years; OR age at least 65 years with at least one of: diabetes mellitus on treatment; documented coronary artery disease (prior MI, positive stress test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing at least 75% stenosis in a major coronary artery); hypertension requiring medical treatment	At least one of: history of stroke, transient ischemic attack, or systemic embolus; symptomatic heart failure; ejection fraction ≤40% documented by ECG, radionuclide, or contrast angiogram; age ≥75 years; diabetes mellitus; hypertension requiring medical treatment	History of stroke, TIA, or non-CNS systemic embolism; OR at least 2 of: heart failure and/or left ventricular fraction ≤35%; hypertension defined by use of antihypertensive within 6 months of screening visit or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg*; age ≥75 years; diabetes mellitus defined as history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within 6 months of screening visit
Exclusion			
Reversible causes of AF	Reversible causes of AF (e.g. cardiac surgery, pulmonary embolism, or untreated hyperparathyroidism)	Reversible causes of AF (e.g. thyrotoxicosis or pericarditis)	Reversible causes of AF (i.e. thyrotoxicosis)
Mitral valve stenosis	-	Clinically significant moderate or severe mitral valve stenosis	Haemodynamically significant mitral valve stenosis
Heart valve disorders and conditions other than AF that require chronic anticoagulant treatment	History of heart valve disorder (e.g. prosthetic valve or haemodynamically relevant valve disease); anticoagulant treatment for disorders other than AF	Prosthetic mechanical heart valve; anticoagulant treatment for disorders other than AF	Prosthetic heart valve; anticoagulant treatment for disorders other than AF
Recent stroke or TIA	Severe, disabling stroke within 6 months, or any stroke within 14 days	Stroke within 7 days	Severe, disabling stroke within 3 months or any stroke within 14 days; TIA within 3 days
Concomitant conditions associated with increased risk of bleeding	Major surgery within one month; planned surgery or intervention within next three months; history of intracranial, intraocular, spinal,	Planned major surgery; platelet count ≤100,000/mm^3; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood	Active internal bleeding; major surgical procedure or trauma within 30 days of randomisation; clinically significant GI bleeding within

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Criterion type	RE-LY	ARISTOTLE	ROCKET-AF
	retroperitoneal or atraumatic intra-articular bleeding; GI haemorrhage within the past year; symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive 3 years	pressure ≥100 mmHg)	six months of randomisation; history of intracranial, intraocular, spinal, or intra-articular bleeding; chromic haemorrhagic disorder; known intracranial neoplasm, arteriovenous malformation or aneurysm; planned invasive procedure with potential for uncontrolled bleeding; platelet count <90,000/μL at screening; uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg); malignancy or radiation therapy within 6 months and not expected to survive three years
Planned AF ablation procedure	Planned AF ablation procedure	Planned AF ablation procedure	-
Planned cardioversion	-	-	Planned cardioversion
Renal impairment	Creatine clearance ≤30 mL/minute	Creatine clearance <25 mL/minute or serum creatine <2.5 mg/dL	Creatine clearance <30 mL/minute
Contraindication to warfarin treatment	Contraindication to warfarin treatment	-	Contraindication to warfarin treatment
Concomitant treatments	Fibrinolytic agents within 48 hours of study entry; investigational drug within 30 days	Treatment with >165 mg ASA daily; ASA in combination with thienopyridines; investigational drug within 30 days	Treatment with >100 mg ASA daily; ASA in combination with thienopyridines within 5 days of randomisation; intravenous antiplatelets within 5 days of randomisation; fibrinolytic agents within 10 days of randomisation; anticipated need for chronic treatment with NSAID; systemic treatment with a strong inhibitor of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study; systemic treatment with strong inducer of cytochrome P450 3A4 within 4 days of randomisation or anticipated treatment during study
Other concomitant conditions	Active liver disease (e.g. persistent ALT, AST, or ALP >2 ULN; active hepatitis C; active hepatitis B; or active hepatitis A); anemia; pregnancy; active infection endocarditis; substance abuse disorder; life expectancy less than duration of trial; other conditions not allowing safe participation	ALT or AST >2 ULN; total bilirubin >1.5 ULN; haemoglobin level <9 g/dL; pregnancy; severe comorbid condition with life expectancy ≤1 year; substance abuse disorder	Left ventricular thrombus; HIV infection; anemia at screening visit; pregnancy or breastfeeding; TIA within 3 days of randomisation; active endocarditis; known liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 ULN; severe comorbid condition with life expectancy ≤2 years; substance abuse within 3 years of randomisation; psychosocial disorder
INR monitoring	-	Inability to comply with INR monitoring	-

Source: [1-3] with clarification from [4-6]

*There is a contradiction between the hypertension criterion defined in the supplementary appendix to the primary ROCKET-AF publication[4] and the ROCKET-AF rationale and design publication published by the ROCKET-AF trial investigators.[2] In this instance, the criterion from the supplementary appendix to the primary ROCKET-AF publication was used as it was deemed

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more inclusive than the ROCKET-AF rationale and design publication.

AF: Atrial Fibrillation; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; ASA: acetylsalicylic acid; AST: Aspartate Transaminase; CABG: Coronary Artery Bypass Graft; ECG: Echocardiogram; GI: Gastrointestinal; HIV: Human Immunodeficiency Virus; MI: Myocardial Infarction; NSAID: Non-Steroidal Anti-Inflammatory Drug; PCI: Percutaneous Coronary Intervention; Transient Ischemic Attack; ULN: Upper Limit of Normal

References

1 Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009;**157**:805-10, 810.

2 Patel M. Rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010;**159**:340-7.

3 Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010;**159**:331-9.

4 Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (with supplementary appendix). *New Engl J Med* 2011;**365**:883-91.

5 Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation (with supplementary appendix and study protocol). *New Engl J Med* 2011;**365**:981-92.

6 Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (with supplementary appendix). *N Engl J Med* 2009;**361**:1139-51.

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