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Comparative effectiveness of oral anticoagulants in everyday practice

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2020-318420).

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Received 8 October 2020
Revised 15 January 2021
Accepted 19 January 2021

To cite: Camm AJ, Fox KAA, Virdone S, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2020-318420

ABSTRACT

Objectives This study evaluated the comparative effectiveness of vitamin K antagonists (VKAs), direct thrombin inhibitors (DTIs) and factor Xa inhibitors (FXaI) in patients with atrial fibrillation (AF) at risk of stroke in everyday practice.

Methods Data from patients with AF and Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, prior Stroke, TIA, or thromboembolism, Vascular disease, Age 65-74 years, Sex category (CHA_2DS_2-VASc) score ≥2 (excluding gender) in the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation registry were analysed using an improved method of propensity weighting, overlap weights and Cox proportional hazards models.

Results All-cause mortality, non-haemorrhagic stroke/systemic embolism (SE) and major bleeding over 2 years were compared in 25 551 patients, 7162 (28.0%) not treated with oral anticoagulant (OAC) and 18 389 (72.0%) treated with OAC (FXaI (41.8%), DTI (11.4%) and VKA (46.8%)). OAC treatment compared with no OAC treatment was associated with decreased risk of all-cause mortality (HR 0.82 (95% CI 0.74 to 0.91)) and non-haemorrhagic stroke/SE (HR 0.71 (95% CI 0.57 to 0.88)) but increased risk of major bleeding (HR 1.46 (95% CI 1.15 to 1.86)). Non-vitamin K antagonist oral anticoagulant (NOAC) use compared with no OAC treatment was associated with lower risks of all-cause mortality and non-haemorrhagic stroke/SE (HR 0.67 (95% CI 0.59 to 0.77)) and 0.65 (95% CI 0.50 to 0.86)) respectively, with no increase in major bleeding (HR 1.10 (95% CI 0.82 to 1.47)). NOAC use compared with VKA use was associated with lower risk of all-cause mortality and major bleeding (rates/100 patient-years 3.6 (95% CI 3.3 to 3.9) vs 4.8 (95% CI 4.5 to 5.2) and 1.0 (95% CI 0.9 to 1.1) vs 1.4 (95% CI 1.2 to 1.6); HR 0.79 (95% CI 0.70 to 0.89) and 0.77 (95% CI 0.61 to 0.98) respectively), with similar risk of non-haemorrhagic stroke/SE (rates/100 patient-years 0.8 (95% CI 0.7 to 0.9) versus 1.0 (95% CI 0.8 to 1.1); HR 0.96 (95% CI 0.73 to 1.25).

Conclusion Important benefits in terms of mortality and major bleeding were observed with NOAC versus VKA with no difference among NOAC subtypes.

Trial registration number NCT01090362.

INTRODUCTION

Oral anticoagulation is recommended in patients with atrial fibrillation (AF) at moderate to high risk of stroke.[1 2] Oral anticoagulants (OACs) comprise vitamin K antagonists (VKAs, eg, warfarin) and the newer non-vitamin K antagonist oral anticoagulants (NOACs), direct thrombin inhibitors (DTIs) and factor Xa inhibitors (FXaI).[1 2] Anticoagulants reduced ischaemic stroke risk in randomised controlled trials (RCTs), but their use is associated with increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial haemorrhage.[1–3] In RCTs comparing NOACs and VKAs, NOACs have shown superiority or non-inferiority with regard to the reduction of stroke or systemic embolus and better safety, with less intracranial haemorrhage.[4–8] Although such trials are the gold standard for demonstrating the efficacy of a particular therapy, they are limited to patients who meet restrictive inclusion and exclusion criteria and in particular the exclusion of individuals with multiple comorbidities or perceived bleeding risks. Such trial patients inevitably do not reflect the full spectrum of patients managed in clinical practice. Evidence from suitably designed observational studies can complement findings from RCTs and provide information about outcomes in everyday practice.[9]

We aimed to examine the comparative effectiveness of VKAs, DTI and FXaI initiating treatment on 2-year outcomes in terms of mortality, stroke/systemic embolism (SE) and major bleeding in patients with newly diagnosed AF with an indication for oral anticoagulation included in The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF).[10] For this purpose, we used a newly developed method, overlap propensity weighting, which avoids excluding patients (as with matching improved) and gives the most weight to propensities where there is equipoise (see further).[11]

METHODS

Study design and participants

The GARFIELD-AF is a prospective, multinational, observational study of adults with recently diagnosed non-valvular AF and at least one risk factor for stroke.[10] GARFIELD-AF registry recruited patients from a range of representative care settings in each participating country.[10 12] Investigator sites were selected randomly (apart from 18 sites, out of >1000), in order to be representative of the different care settings in each participating country (office-based practice; hospital departments

including neurology, cardiology, geriatrics, internal medicine and emergency; anticoagulation clinics; and general or family practice). No specific treatments, tests or procedures were mandated by the study protocol. Treatment decisions (including no anticoagulation and no antithrombotic therapy) were solely at the discretion of treating physicians. Recruitment took place in five independent sequential cohorts from 35 countries (online supplemental table S1).[10] Cohorts 3–5, prospectively recruited

Table 1 Baseline characteristics by treatment at baseline

Baseline characteristics	Patients treated with OAC			Patients not treated with OAC (N=7162)
	FXaI (N=7694)	DTI (N=2090)	VKA (N=8605)	
Sex, n (%)				
Male	4084 (53.1)	1151 (55.1)	4501 (52.3)	3846 (53.7)
Female	3610 (46.9)	939 (44.9)	4104 (47.7)	3316 (46.3)
Age, median (Q1; Q3), years	75.0 (69.0; 81.0)	72.0 (66.0; 78.0)	73.0 (67.0; 79.0)	73.0 (66.0; 80.0)
Age, n (%), years				
<65	894 (11.6)	375 (17.9)	1468 (17.1)	1423 (19.9)
65–69	1322 (17.2)	454 (21.7)	1578 (18.3)	1223 (17.1)
70–74	1557 (20.2)	414 (19.8)	1708 (19.8)	1276 (17.8)
≥75	3921 (51.0)	847 (40.5)	3851 (44.8)	3240 (45.2)
Ethnicity, n (%)				
Caucasian	4876 (65.2)	1411 (68.7)	5954 (70.5)	3829 (54.5)
Hispanic/Latino	351 (4.7)	91 (4.4)	733 (8.7)	473 (6.7)
Asian	2089 (27.9)	510 (24.8)	1590 (18.8)	2602 (37.1)
Afro-Caribbean/mixed/other	164 (2.2)	42 (2.0)	166 (2.0)	118 (1.7)
Type of atrial fibrillation, n (%)				
Permanent	1026 (13.3)	184 (8.8)	1540 (17.9)	791 (11.0)
Persistent	1222 (15.9)	383 (18.3)	1325 (15.4)	698 (9.7)
Paroxysmal	2530 (32.9)	612 (29.3)	1784 (20.7)	2074 (29.0)
New onset (unclassified)	2916 (37.9)	911 (43.6)	3956 (46.0)	3599 (50.3)
Medical history, n (%)				
Heart failure	1840 (23.9)	566 (27.1)	2220 (25.8)	2110 (29.5)
Acute coronary syndromes	890 (11.6)	227 (10.9)	1171 (13.7)	1282 (18.1)
Vascular disease*	1933 (25.1)	590 (28.2)	2562 (29.8)	2818 (39.3)
Carotid occlusive disease	281 (3.7)	81 (3.9)	297 (3.5)	231 (3.3)
Venous thromboembolism	194 (2.5)	33 (1.6)	235 (2.7)	123 (1.7)
Prior stroke/TIA/SE	1030 (13.4)	266 (12.7)	1170 (13.6)	819 (11.4)
Prior bleeding	168 (2.2)	34 (1.6)	146 (1.7)	343 (4.8)
Hypertension	6291 (81.8)	1763 (84.4)	7299 (84.9)	5774 (80.7)
Hypercholesterolaemia	3449 (46.2)	1023 (50.3)	3927 (47.8)	2841 (42.0)
Diabetes	1969 (25.6)	569 (27.2)	2563 (29.8)	1882 (26.3)
Cirrhosis	26 (0.3)	6 (0.3)	49 (0.6)	55 (0.8)
Moderate to severe CKD	904 (12.2)	205 (10.1)	1202 (14.7)	849 (12.7)
Dementia	166 (2.2)	32 (1.5)	93 (1.1)	156 (2.2)
FXaI inhibitors medication, n (%)				
Rivaroxaban	3845 (50.0)	–	–	–
Apixaban	2945 (38.3)	–	–	–
Edoxaban	270 (3.5)	–	–	–
Other/unknown	634 (8.2)	–	–	–
AP treatment, n (%)	1416 (18.4)	369 (17.7)	2176 (25.3)	4626 (64.6)
CHA_2DS_2-VASc score, median (Q1; Q3)	4.0 (3.0; 4.0)	4.0 (3.0; 4.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)
HAS-BLED score,† median (Q1; Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)
GARFIELD-AF death score,‡ median (Q1; Q3)	4.8 (3.0; 8.2)	4.4 (2.6; 7.1)	5.9 (3.7; 9.8)	6.9 (4.0; 12.1)
GARFIELD-AF stroke score,§ median (Q1; Q3)	1.4 (1.1; 2.0)	1.3 (1.0; 1.8)	1.7 (1.3; 2.4)	2.4 (1.8; 3.5)
GARFIELD-AF bleeding score,¶ median (Q1; Q3)	1.7 (1.2; 2.3)	1.5 (1.1; 2.1)	2.3 (1.7; 3.2)	1.4 (1.0; 2.1)

*Defined as peripheral artery disease and/or coronary artery disease.
†The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).
‡Estimated probability of dying within two years of follow-up.
§Estimated probability of developing a non-haemorrhagic stroke/SE within two years of follow-up.
¶Estimated probability of developing a major bleeding within two years of follow-up.
AP, antiplatelet; CKD, chronic kidney disease; FXaI, factor Xa inhibitors; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischaemic attack.

Table 2 Event rates (per 100 person-years) within 2-year follow-up by treatment at baseline

	Outcome					
	All-cause mortality		Non-haemorrhagic stroke/SE		Major bleeding	
Treatment at baseline	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
FXaI	536	3.7 (3.4 to 4.0)	112	0.8 (0.6 to 0.9)	152	1.0 (0.9 to 1.2)
DTI	130	3.3 (2.8 to 3.9)	34	0.9 (0.6 to 1.2)	29	0.7 (0.5 to 1.1)
Any NOAC	666	3.6 (3.3 to 3.9)	146	0.8 (0.7 to 0.9)	181	1.0 (0.9 to 1.1)
VKA	773	4.8 (4.5 to 5.2)	153	1.0 (0.8 to 1.1)	223	1.4 (1.2 to 1.6)
Any OAC	1439	4.1 (3.9 to 4.4)	299	0.9 (0.8 to 1.0)	404	1.2 (1.1 to 1.3)
No OAC	737	5.6 (5.2 to 6.0)	168	1.3 (1.1 to 1.5)	102	0.8 (0.6 to 1.0)

DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SE, systemic embolism; VKA, vitamin K antagonist.

during April 2013–August 2016, were included in this analysis (NOACs had not yet been introduced into many countries during the recruitment period for cohorts 1 (2010–2011) and 2 (2011–2013)).

Men and women aged ≥18 years with non-valvular AF diagnosed according to standard local procedures within the previous 6 weeks, and with at least one additional risk factor for stroke as judged by the investigator, were eligible for inclusion in GARFIELD-AF; patients with a transient reversible cause of AF and those for whom follow-up was not envisaged or possible were excluded.[10] Only patients with a clear indication for anticoagulation (CHA_2DS_2-VASc score ≥2 for males and CHA_2DS_2-VASc score ≥3 for females) were included in this analysis.

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. Additional approvals were obtained from individual study sites. GARFIELD-AF is conducted in accordance with the principles of the Declaration of Helsinki, local

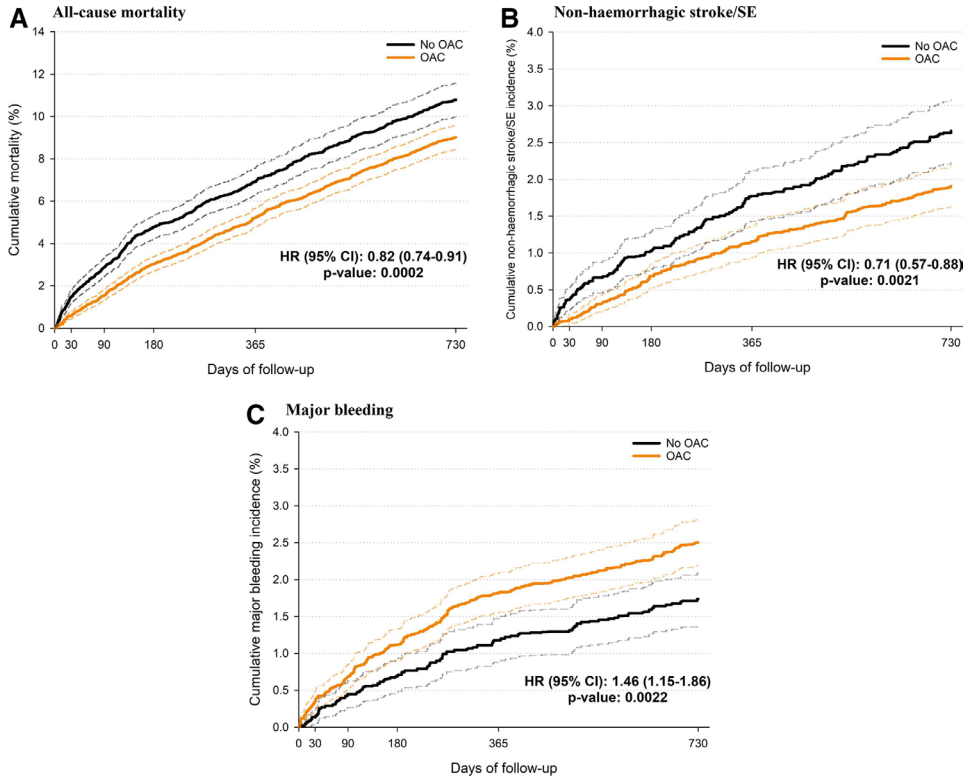

Figure 1 Adjusted* cumulative (A) mortality (B) non-haemorrhagic stroke/SE and (C) major bleeding incidence curves and HR of OAC treatment (ref.: no OAC treatment) at baseline. Solid lines represent the point estimate, and dashed lines represent the 95% CIs. *Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis and baseline antiplatelet use. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; OAC, oral anticoagulants; SE: Systemic embolism; TIA, transient ischaemic attack.

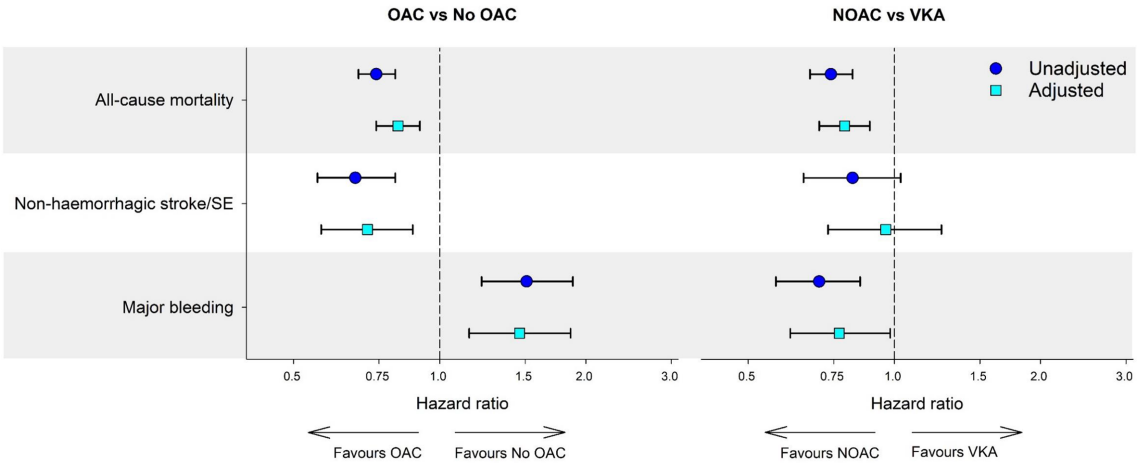

Figure 2 Unadjusted and adjusted* HRs and corresponding 95% CIs for selected outcomes at 2 years of follow-up by treatment at baseline. *Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis and baseline antiplatelet use. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; NOAC, non-vitamin K oral antagonist; OAC, oral anticoagulants; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonists.

regulatory requirements and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants.

Data collection and quality control

GARFIELD-AF data were captured using an electronic case report form (eCRF).[10] Oversight of operations and data management were performed by the coordinating centre, the Thrombosis Research Institute (TRI; London, UK), with support from Quintiles (Durham, North Carolina, USA), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group–Brigham and Women's Hospital (Boston, Massachusetts, USA) and AIXIAL (Paris, France). Submitted data were examined for completeness and accuracy by the coordinating centre, the TRI, and data queries were sent to study sites. The GARFIELD-AF protocol requires that 20% of all eCRFs are monitored against source documentation, that there is an electronic audit trail for all data modifications and that critical variables are subjected to additional audit.[10 13]

Baseline characteristics collected at study entry included: medical history, care setting, type of AF, date and method of diagnosis of AF, symptoms, antithrombotic treatment (VKAs, NOACs and antiplatelet (AP)), as well as all cardiovascular drugs. Race was classified by the investigator in agreement with the patient. Vascular disease included coronary artery disease and/or peripheral artery disease. Chronic kidney disease was

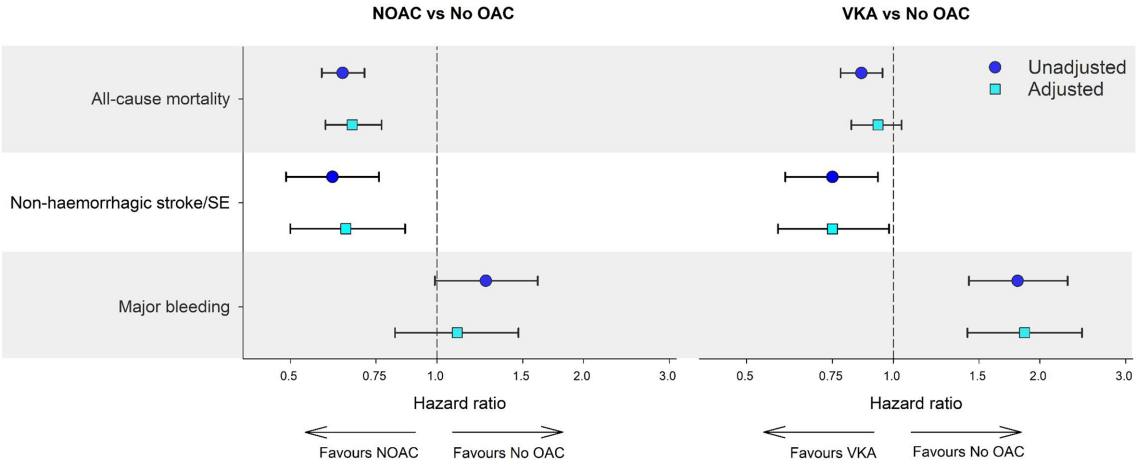

Figure 3 Unadjusted and adjusted* HRs and corresponding 95% CIs for selected outcomes at 2 years of follow-up by treatment at baseline. *Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis and baseline antiplatelet use. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; NOAC, non-vitamin K oral antagonist; OAC, oral anticoagulants; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonists.

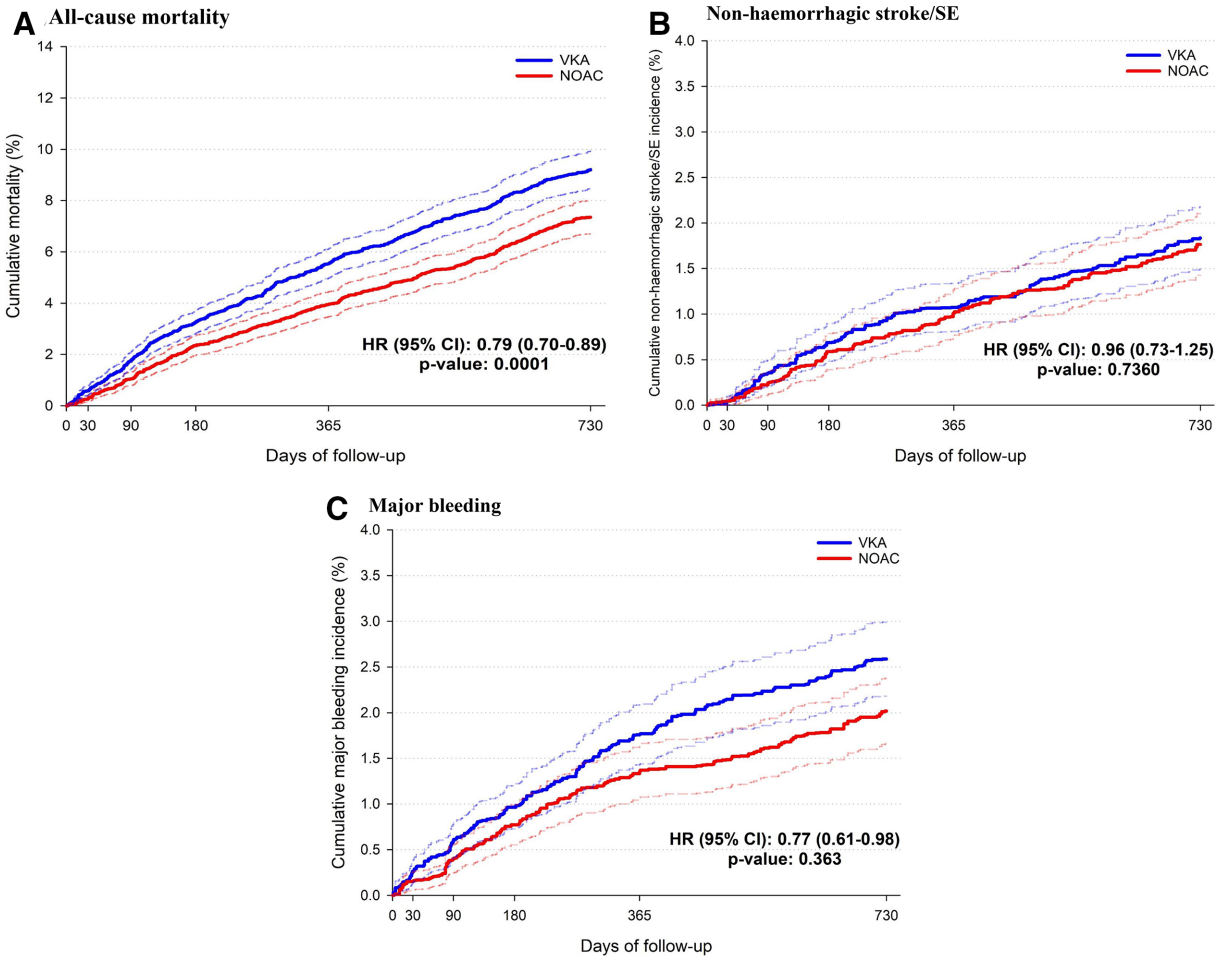

Figure 4 Adjusted* cumulative (A) mortality, (B) non-haemorrhagic stroke/SE and (C) major bleeding incidence curves and HR of NOAC treatment (ref.: VKA treatment) among OAC-treated patients at baseline. Solid lines represent the point estimate, and dashed lines represent the 95% CIs. *Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis and baseline antiplatelet use. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; NOAC, non-vitamin K oral antagonist; SE: systemic embolism; TIA, transient ischaemic attack. VKA, vitamin K antagonists.

classified according to National Kidney Foundation guidelines into moderate to severe (stages 3–5), mild (stages 1 and 2) or none. Cerebrovascular events defined as stroke included primary ischaemic stroke, primary intracerebral haemorrhage and secondary haemorrhagic ischaemic stroke. Acute coronary syndrome (ACS) included unstable angina, ST-elevation myocardial infarction (STEMI) and non-STEMI. Non-haemorrhagic stroke/SE includes either ischaemic stroke or unknown type of stroke. Major bleeding was defined as clinically overt bleeding associated with fall in haemoglobin of ≥2 g/dL, or associated with transfusion of packed red blood cells or whole blood, or bleeding in a critical site, namely intracranial (spontaneous intracerebral, intraventricular, subarachnoidal, subdural and epidural), intraspinal, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal, or leading to a fatal outcome.[10]

Data on components of the CHA_2DS_2-VASc, Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal renal or liver function, previous Stroke, Bleeding history or predisposition, Labile international normalized ratios, Elderly, and concomitant Drugs or alcohol excess (HAS-BLED) and GARFIELD-AF risk stratification schemes were collected and calculated retrospectively.[14–16] HAS-BLED scores were calculated excluding fluctuations in international normalised ratio. Collection of follow-up data occurred at 4-month intervals up to 24 months. Data for this report were extracted from the study database on 19 November 2018.

Statistical analysis

Clinical endpoints of the study were all-cause mortality, stroke/SE and major bleeding manifest over 2-year follow-up. Continuous baseline variables are expressed as median (IQR) and categorical variables as frequency and percentage. Occurrence of clinical outcomes is described using the number of events, event rate per 100 person-years and 95% CI. Person-year rates were estimated using a Poisson model, with the number of events as the dependent variable and the log of time as an offset (ie, a covariate with a known coefficient of 1). Only the first occurrence of each event was considered.

The Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool was used to ensure causal statements are

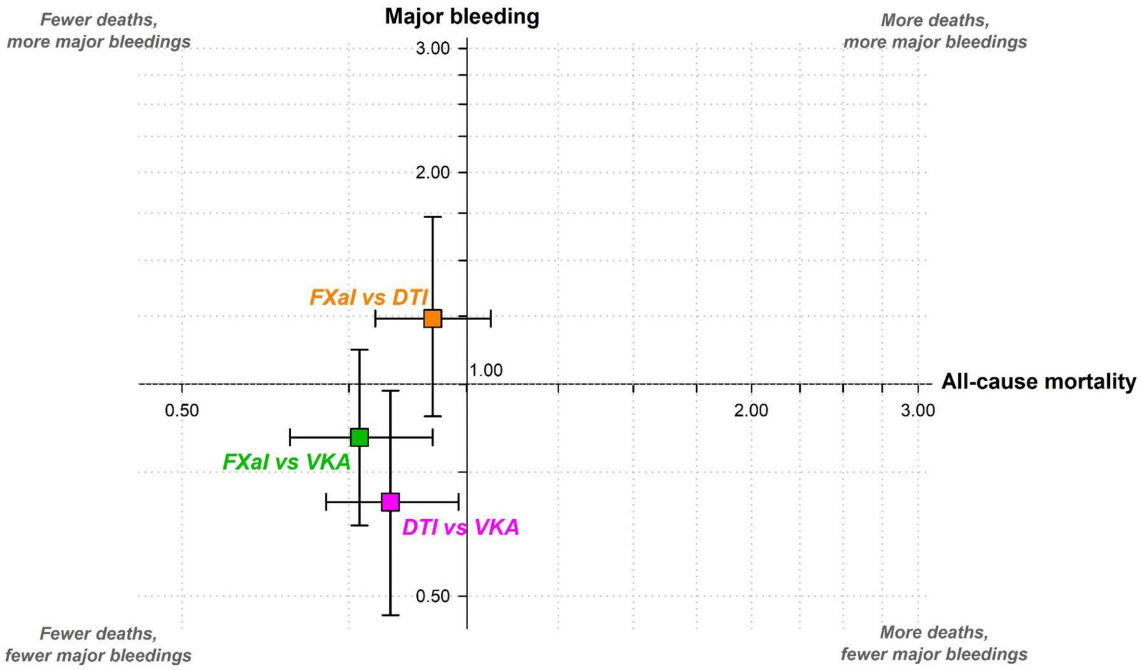

Figure 5 Adjusted* HRs and corresponding 95% CIs for selected outcomes at 2 years of follow-up by OAC treatment at baseline. The reference considered is the treatment reported as second. *Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrolment, sex, age, ethnicity, type of AF, care setting speciality and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolaemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis and baseline antiplatelet use. OAC, oral anticoagulants; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitors; VKA, vitamin K antagonists; NOAC, non-vitamin K oral antagonist; SE, systemic embolism; TIA, transient ischaemic attack.

valid.[17 18] Cumulative mortality, stroke/SE and major bleeding incidence and HRs for OAC versus no OAC, NOAC versus VKA, NOAC versus no OAC and VKA versus no OAC were obtained using a Cox proportional hazards model using a propensity method of overlap weighting to balance covariates in the population.[11] This applied method overlaps weights and optimises the efficiency of comparisons by defining the population with the most overlap in the covariates between treatment groups. This scheme eliminates the potential for outlier weights by avoiding a weight based on a ratio calculation using values bounded by 0 and 1. Thus, when using overlap weights, many of the concerns regarding the assessment and the trimming of the weights are eliminated (online supplemental figure S1 and S2). The comparison of DTI versus FXaI versus VKA is performed using a new method of generalised overlap weights for multiple treatments.[19] Covariates evaluated in the weighting scheme included demographic characteristics, medical history and other characteristics (online supplemental figure S3 and S4). Treatment was defined as the first treatment received at the time of enrolment, approximating 'intention-to-treat'. Patients with missing values were not removed from the study; single imputation was applied for the comparative effectiveness analysis. As a sensitivity analysis, all models were run on the five imputed datasets. The differences in model results were negligible so single imputation was retained. Data analysis was carried out at the TRI using SAS V.9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Study population

A total of 34 926 patients were enrolled in GARFIELD-AF cohorts 3, 4 and 5. After exclusion of patients with CHA_2DS_2-VASc score <2 (excluding gender), patients treated with VKAs before enrolment, and patients with missing treatment or follow-up information, the remaining study population comprised 25 551 patients, 7162 (28.0%) not treated with OACs and 18 389 (72.0%) patients treated with OACs (FXaI 7694 (41.8%), DTI 2090 (11.4%) and VKA 8605 (46.8%) (online supplemental figure S5). Baseline characteristics by treatment at baseline are shown in table 1 and online supplemental table S2 . Although most baseline characteristics were similar across groups, some features differed between OAC groups and the no OAC group. In the OAC groups, patients were more likely to be Caucasian and less likely to be Asian than in the no OAC group. The prevalence of paroxysmal AF was lower in the VKA subgroup, and the prevalence of unclassified (at baseline) AF was lower in the FXaI subgroup. The no OAC group had a higher proportion of patients with congestive heart failure, coronary artery disease, acute coronary syndrome, vascular disease and prior bleeding history than the OAC groups; they were also at higher risk of death and stroke/SE according to GARFIELD-AF risk score. Median HAS-BLED score was higher in the no OAC group compared with other groups (2.0 vs 1.0, respectively). The median (Q1; Q3) time in therapeutic range (TTR) among VKA-treated patients was 62% (41%; 77%).

Clinical outcomes

The rates per hundred patient-years of all cause death and of non-haemorrhagic stroke/SE were substantially lower and the risk of major bleeding substantially higher with OAC versus no OAC, 4.1 (95% CI 3.9 to 4.4) versus 5.6 (95% CI 5.2 to 6.0), 0.9 (95% CI 0.8 to 1.0) versus 1.3 (95% CI 1.1 to 1.5) and 1.2 (95% CI 1.1 to 1.3) versus 0.8 (95% CI 0.6 to 1.0) respectively. The rates per 100 patient-years of all cause death and of major bleeding were significantly lower with NOAC than with VKA,

3.6 (95% CI 3.3 to 3.9) versus 4.8 (95% CI 4.5 to 5.2) and 1.0 (95% CI 0.9 to 1.1) versus 1.4 (95% CI 1.2 to 1.6) respectively, whereas the rate of non-haemorrhagic stroke/SE was similar and 0.8 (95% CI 0.7 to 0.9) versus 1.0 (95% CI 0.8 to 1.1) (table 2).

OACs use compared with no OAC treatment was associated with a significant reduction in all-cause mortality and non-haemorrhagic stroke/SE risk (HR 0.82 (95% CI 0.74 to 0.91) and 0.71 (95% CI 0.57 to 0.88)), respectively, and with a significant increase in the risk of major bleeding (HR 1.46 (95% CI 1.15 to 1.86)) (figures 1 and 2, (online supplemental table S3) in adjusted analyses. NOACs use compared with no OAC treatment was associated with a significant reduction in all-cause mortality and non-haemorrhagic stroke/SE risk (HR 0.67 (95% CI 0.59 to 0.77)) and 0.65 (95% CI 0.50 to 0.86)), respectively, with no significant increase in the risk of major bleeding 1.10 (95% CI 0.82 to 1.47) (figure 3, online supplemental table S4). VKA use compared with no OAC treatment was associated with a significant reduction in non-haemorrhagic stroke/SE risk (HR 0.75 (95% CI 0.58 to 0.98)), a significant increase in major bleeding risk (HR 1.86 (95% CI 1.42 to 2.44)), and no significant difference in all-cause mortality and 0.93 (95% CI 0.82 to 1.04) (figure 3, online supplemental table S4). NOAC use compared with VKA use was associated with a significantly lower risk of all-cause mortality and of major bleeding (HR 0.79 (95% CI 0.70 to 0.89) and 0.77 (95% CI 0.61 to 0.98), respectively), but with similar risk of non-haemorrhagic stroke/SE (HR 0.96 (95% CI 0.73 to 1.25)) (figures 2 and 4, (online supplemental table S3).

The individual comparisons of DTI, FXaI and VKA are presented in online supplemental table S5, figure 5 and online supplemental figure S6. Use of both DTI and FXaI compared with VKA use is associated with a lower risk of all-cause mortality (HR 0.83 (95% CI 0.71 to 0.98) and 0.77 (95% CI 0.65 to 0.92)), respectively, with no difference between DTI and FXaI. There is no difference in the risk of stroke/SE between DTI, FXaI and VKA. Use of DTI compared with use of VKA is associated with a significantly lower risk of major bleeding (HR 0.68 (95% CI 0.47 to 0.98)), whereas the decrease in bleeding risk is non-significant with of FXaI (HR 0.84 (95% CI 0.63 to 1.12)). FXaI is associated with a non-significant higher risk of major bleeding compared with DTI (HR 1.24 (95% CI 0.90 to 1.73)).

DISCUSSION

In a broad clinical population of patients with new-onset AF, our study confirms that in patients with AF, OAC treatment is associated with a significantly lower risk of death and non-haemorrhagic stroke/SE compared with no OAC treatment at the cost of a significant increase in the risk of bleeding.[3] The most frequent reasons of no OAC in patients with a high risk of stroke was high bleeding risk/previous bleeding events followed by physician choice and patient refusal to take OAC. The risk reduction for death in our study is of lesser magnitude than that reported in previous meta-analysis.[3] This difference probably reflects differences between observational versus randomised trials; unidentified or unavailable factors for adjustment may have influenced treatment decisions and outcomes. Poor international normalised ratio (INR) control under VKA treatment may also be involved; in an analysis of GARFIELD-AF data, a large proportion of patients with AF treated with VKAs had poor control (TTR <65%), which was associated with 2.4-fold higher risk of death.[20]

However, NOAC use compared with no treatment brings important information as it is associated with a significant risk reduction for both death and non-haemorrhagic stroke/SE, without significant increase in the risk of bleeding, contrary to VKA use where a significant risk reduction for non-haemorrhagic stroke/SE was observed with no reduction in the risk of death and with a significant increase in bleeding. In Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, patients thought to be non-amenable to VKA were randomised to aspirin or apixaban. A significant risk reduction for stroke/SE without increase in the risk of major bleeding and intracranial haemorrhage was observed in patients who received apixaban versus aspirin.[21] Our observations carry an important message as they derive from an unselected real-world registry population followed up for 2 years with robust methods and quality control.[13] These results should encourage the prescription of NOAC in patients where perceived moderate bleeding risks inhibit the use of anticoagulation despite elevated stroke risks.

The individual comparisons of DTI, FXaI and VKA are consistent, in this non-trial population, with the advantages of NOACs over VKAs in terms of clinical outcomes in patients with AF, as demonstrated in pivotal trials, systematic reviews and meta-analyses. In our study, the results achieved with DTI and FXaI in comparison with VKAs are consistent across NOAC subtypes. Both classes are associated with a significant reduction in the risk of all-cause mortality. However, compared with VKA, the risk of stroke/SE is not significantly different. There is no difference in bleeding risk between DTI and FXaI, but compared with VKA, the DTI is associated with a significant reduction in major bleeding, while the risk reduction achieved with the FXaIs was not significant.

Our results are consistent with findings from another AF registry, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II registry, in which rates of major bleeding over 1-year follow-up in patients with newly diagnosed AF or recent initiation of a NOAC were similar among NOAC-treated and VKA-treated patients. However, that analysis did not involve multivariate adjustment, such that baseline differences in bleeding risk between patients on NOACs and VKAs were not taken into account.[22] Our results are also broadly consistent with a Swedish population-based study of 22 198 OAC-naive patients with AF initiated on anticoagulant therapy, which showed no significant difference in risk of transient ischaemic attack/ischaemic stroke/unspecified stroke/death (HR 0.97 (95% CI 0.87 to 1.08)) or severe bleed (HR 1.02 95% CI 0.88 to 1.20)) between NOACs and VKA in patients with CHA_2DS_2-VASc score ≥2. This study also showed lower rates of overall mortality with NOAC than VKA, but this analysis was for the overall population (ie, not restricted to patients with CHA_2DS_2-VASc score ≥2).[23]

Previous reports on the respective efficacy of NOAC versus VKA did not yield similar conclusions about risk of death, stroke/SE or bleeding. A significant reduction in all-cause mortality with NOAC verus VKAs was observed in trials of apixaban and edoxaban,[5 6] but not with dabigatran or rivaroxaban, although the point estimates in all four trials were similar.[4 7] In a meta-analysis of data from 71 638 participants in these pivotal phase III trials, RE-LY (dabigatran),[4] ROCKET AF (rivaroxaban),[7] ARISTOTLE (apixaban)[6] and ENGAGE AF-TIMI 48 (edoxaban),[5] NOACs reduced all-cause mortality (relative risk 0.90, 95% CI 0.85 to 0.95) and stroke/SE events (relative risk 0.81, 95% CI 0.73 to 0.91) in comparison with warfarin with a borderline difference in risk of major bleeding (relative risk vs warfarin 0.86, 95% CI 0.73 to 1.00).[8] In a systematic review and meta-analysis including phase II and phase III RCTs comparing NOACs with warfarin in a total of 77 011 patients with AF, NOACs reduced

the risk of stroke/SE (OR 0.85, 95% CI 0.75 to 0.98), intracranial haemorrhage (OR 0.48, 95% CI 0.40 to 0.57) and mortality (OR 0.86, 95% CI 0.82 to 0.91).[24] Benefits over VKAs have also been demonstrated for the two NOAC subtypes, FXaIs and DTIs, in systematic reviews of RCTs.[25 26] In a network meta-analysis of more than 90 000 patients, NOAC use compared with VKA was associated with reduced risks of both all-cause mortality and stroke/SE, with a similar risk of major bleeding.[27]

Strengths and limitations

As the largest multinational prospective registry in patients with AF, GARFIELD-AF captures the diversity of treatment and outcomes in populations beyond the constraints of RCTs, making it representative of the real-life management of AF worldwide. The registry uses regular audits, including a combination of remote and onsite monitoring to ascertain completeness and accuracy of all records. In addition, the country from which data were derived has a strong impact on the choice of therapy, particularly respective use OAC and of AP treatments that can influence the outcomes. The impact of these confounders on the observed differences in outcomes across the different treatments is difficult to assess. Applying appropriate statistical methods to balance these factors, such as used in this study, is of paramount importance. Dosing is not taken into account for this analyses, which may impact outcomes. Lastly, our analysis reflects the intention to treat over the duration of follow-up; treatments may have changed over time, and these changes would not be reflected in these analyses.

CONCLUSION

NOACs are recommended in international guidelines as broadly preferable to VKAs in the vast majority of patients with AF since the clinical trials have consistently shown non-inferiority in efficacy and better safety, with reduced risk of intracranial haemorrhage with NOACs.[1 2] Our results, from the real world, strengthen this recommendation and demonstrate the benefits of NOACs in everyday clinical practice in patients with AF with CHA_2DS_2-VASc score ≥2 (excluding gender).

Key messages

What is already known on this subject?

- Oral anticoagulation is recommended in patients with atrial fibrillation at moderate to high risk of stroke. Anticoagulants reduced ischaemic stroke risk in randomised controlled trials, but their use is associated with increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial haemorrhage.

What might this study add?

- In The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation registry, among patients newly diagnosed with atrial fibrillation and a CHA_2DS_2-VASc score ≥2 (excluding gender) anticoagulated in everyday clinical practice, direct thrombin inhibitors and factor Xa inhibitors showed clear advantages in term of mortality reduction compared with vitamin K antagonists, with similar efficacy on stroke/systemic embolism, and reduced risk of major bleeding.

How might this impact on clinical practice?

- Our results, from the real world, strengthen the international guidelines recommendation and demonstrate the benefits of non-vitamin K antagonist oral anticoagulants in everyday clinical practice in patients with atrial fibrillation with CHA_2DS_2-VASc score ≥2 (excluding gender).

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Acknowledgements We would like to thank the physicians, nurses and patients involved in the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) registry. Programming support was provided by Madhusudana Rao (Thrombosis Research Institute (TRI), London, UK). Editorial support was provided by Kate Ackrill and Dr Surekha Damineni (TRI).

Contributors AJC, KAAF, J-PB, DF, BJG, SG, ShG, SH, FM, AGGT, FWAV and AKK contributed to the study design. SV, SIB and KP analysed the data. All authors supervised the data analysis, provided the interpretation of results and contributed to the drafting and critical review of the manuscript. All authors approved the final draft.

Funding This work was supported by an unrestricted research grant from Bayer AG, Berlin, Germany, to the TRI, London, UK, which sponsors the GARFIELD-AF registry. The work is supported by KANTOR CHARITABLE FOUNDATION for the Kantor-Kakkar Global Centre for Thrombosis Science.

Disclaimer The sponsor had no involvement in the collection, analysis or interpretation of the data.

Competing interests AJC has received institutional grants and personal fees from Bayer, Boehringer Ingelheim, Pfizer/BMS and Daiichi Sankyo. KAAF has received grants and personal fees from Bayer/Janssen and AstraZeneca and personal fees from Sanofi/Regeneron and Verseon outside the submitted work. DF reports personal fees from Bayer outside the submitted work. BJG reports Data Safety Monitoring Board–Mount Sinai St Luke's, Boston Scientific Corporation, St Jude Medical Inc, Janssen Research & Development LLC, Thrombosis Research Institute, Duke Clinical Research Institute, Duke University, Kowa Research Institute Inc, Cardiovascular Research Foundation, and Medtronic and general consulting for Janssen Scientific Affairs, Xenon Pharmaceuticals and Sirtex Medical Limited. SG has received research support from BiO2 Medical, Boehringer-Ingelheim, BMS, Boston Scientific, Daiichi, Janssen, NHLBI and the Thrombosis Research Institute; has served as a consultant for, Bayer, Boehringer-Ingelheim, BMS, Daiichi and Janssen. ShG has received personal fees from the Thrombosis Research Institute, Harvard University, the American Heart Association, and grants from the Vehicle Racing Commemorative Foundation, Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering, Bristol-Myers Squibb, Sanofi, Ono and Pfizer. SH has received personal fees from Aspen, Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, Portola and Sanofi. FM is an employee of Bayer AG. AGGT has received personal fees from Bayer Healthcare, Janssen Pharmaceutical Research & Development LLC, Portola. FWAV has received grants from Bayer Healthcare; personal fees from Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, and Boehringer-Ingelheim. RC reports reports a research grants from Boston Scientific, Medtronic, Abbott, Pfizer, Daiichi Sankyo, Biosense Webster, Boehringer Ingelheim, Jhonson and Jhonson and personale fee from Boston Scientific, Medtronic, Biosense Webster, Abbott. AKK has received grants from Bayer AG and Sanofi; personal fees from Bayer AG, Janssen, Pfizer, Sanofi, Verseon and Anthos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Patient and public involvement statement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data underlying this article will be shared on reasonable request from KP (KPieper@tri-london.ac.uk).

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