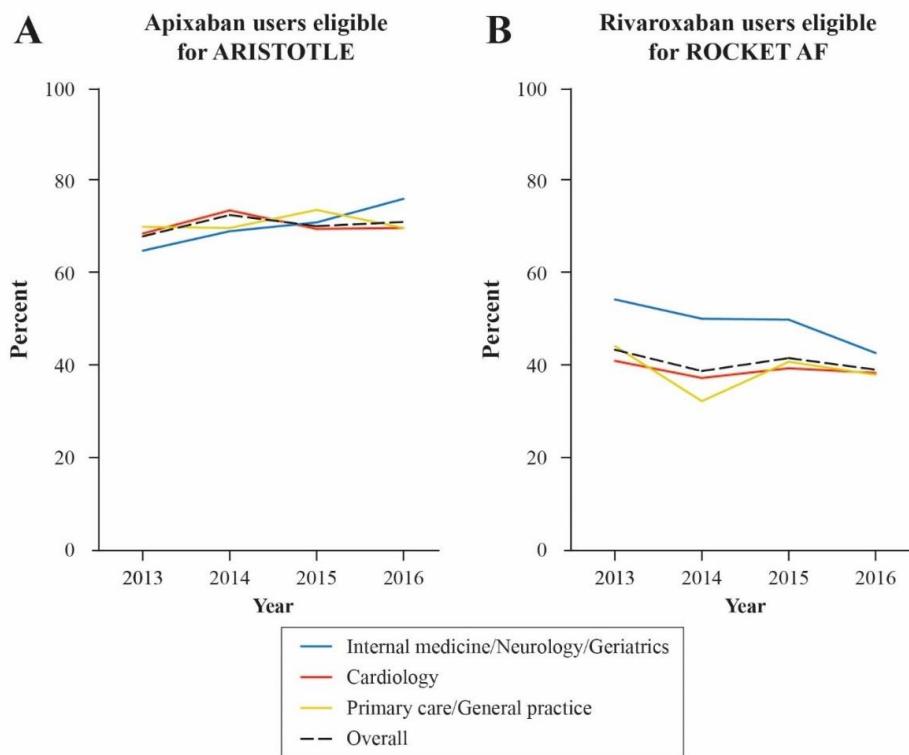
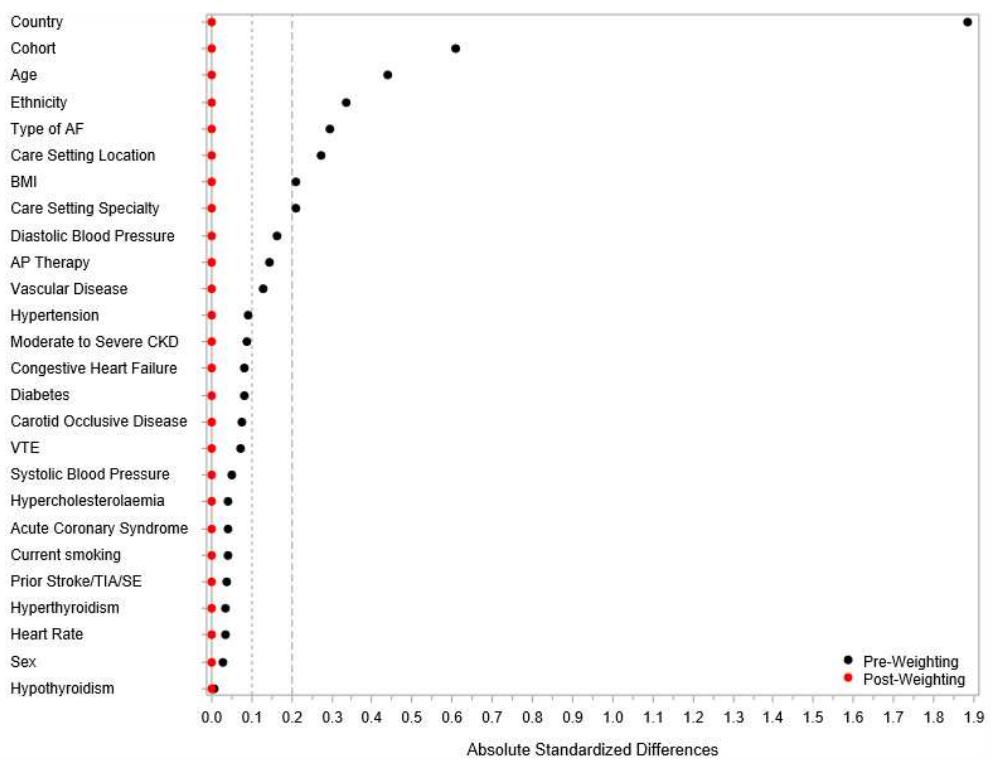


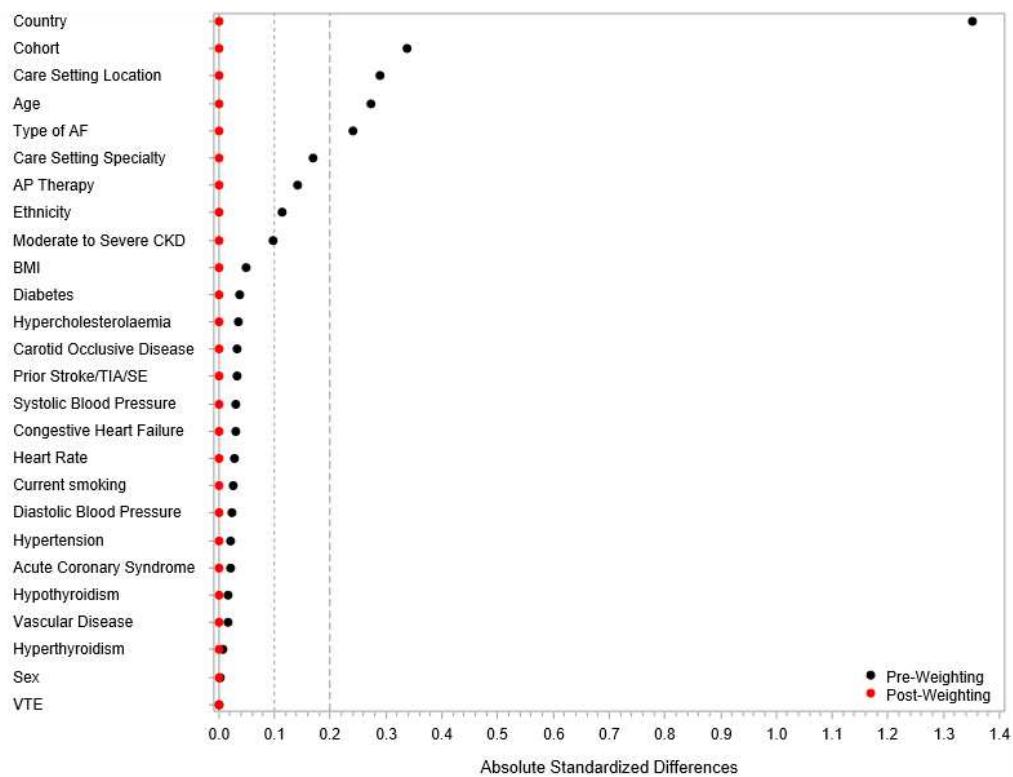
Supplementary Information



Supplementary Figure S1. Annual eligibility of patients in GARFIELD-AF for inclusion in the emulated trials. A) Proportion of apixaban patients in GARFIELD-AF eligible for ARISTOTLE over time by care setting specialty of diagnosis. Year: 2013, N = 135; Year: 2014, N = 929; Year: 2015, N = 1558; Year: 2016, N = 993. B) Proportion of rivaroxaban patients in GARFIELD-AF eligible for ROCKET AF over time by care setting specialty of diagnosis. Year: 2013, N = 645; Year: 2014, N = 1114; Year: 2015, N = 1945; Year: 2016, N = 1210.



Supplementary Figure S2. Balance of variables associated with apixaban treatment in reference to VKA treatment at baseline, before and after propensity score weighting.
AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.



Supplementary Figure S3. Balance of variables associated with rivaroxaban treatment in reference to VKA treatment at baseline, before and after propensity score weighting. AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

Supplementary Table S1. Inclusion and exclusion criteria in ARISTOTLE and ROCKET AF, and their presence or operationalisation in GARFIELD-AF.

	Trial criteria	ARISTOTLE	ROCKET AF
Inclusion criteria	Age	IC	IC
	Stroke, TIA or systemic embolism history	IC	IC
	Heart failure history	IC ¹	IC
	Hypertension history	IC	IC ²
	Hypertension treatment	IC ³	IC ⁴
	Diabetes mellitus history	IC	IC
	Diabetes mellitus treatment		IC ⁵
	LVEF	IC	IC
	Reversible cause for AF	EC ⁶	EC ⁶
	Pregnancy or breastfeeding	EC	EC
Exclusion criteria	Uncontrolled hypertension	EC ⁷	EC ⁸
	Severe renal insufficiency history	EC ⁹	EC ¹⁰
	High bleeding risk	EC ¹¹	EC ¹¹
	Recent ischemic stroke	EC ¹²	EC ¹²
	Recent TIA		EC ¹²
	Severe prior stroke		EC ¹³
	Bleeding history	EC ¹⁴	EC
	Recent gastrointestinal bleeding		EC
	Active internal bleeding		EC
	Planned major surgery	EC	EC
	Recent major surgery	EC	EC
	Alcohol abuse	EC	EC
	Drug abuse	EC	EC
	Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)	EC	EC ¹⁵
	High-dose aspirin treatment	EC ¹⁶	EC ¹⁶
	Recent intravenous antiplatelet use		EC
	Chronic NSAID use		EC ¹⁷
	Use of cytochrome P450 3A4 inhibitor		EC
	Use of cytochrome P450 3A4 inducer		EC
	Anaemia	EC ¹⁸	EC ¹⁹
	Thrombocytopenia	EC ²⁰	EC ²¹
	Inability to comply with INR monitoring	EC ²²	EC
	Heart valve disease history	EC ²³	EC ²⁴
	Atrial myxoma or left ventricular thrombus		EC ²⁵
	Contraindication to VKA		EC ²⁶
	Planned cardioversion therapy		EC ²⁷
	Active liver disease		EC ²⁸
	Liver function tests	EC	EC
	Active hepatitis A, B or C		EC
	Adequate contraceptive use	EC	EC
	Anticoagulation use for chronic condition	EC	
	Prior indication for anticoagulation, other than AF		EC ²⁹
	Active infective endocarditis	EC	EC

Planned AF ablation procedure	EC	
Recent use of investigational drug or device	EC	EC
Prior randomization into NOAC trial	EC	EC
Short life expectancy	EC	EC
Psychosocial reasons that make study participation impractical	EC	EC
Prisoner	EC	
Compulsorily detained for treatment of illness	EC	
Haemorrhagic disorder or bleeding diathesis		EC
Recent fibrinolytic agents use		EC ¹⁷
Patients considered unreliable		EC
Known intracranial neoplasm, arteriovenous malformation, or aneurysm		EC
Known HIV history at baseline		EC
Known allergy to VKA or investigational drug		EC
Employees of the investigator or study centre		EC

Colours: green, in trial protocol and present in the registry as defined by the trial protocol; yellow, in trial protocol and can be operationalised with sufficient validity from the registry although not recorded in the registry precisely as defined by the trial protocol (see comments below for operational definition applied in the registry); red, in trial protocol however not present or cannot be operationalised with sufficient validity in the registry; grey, not part of a trial's inclusion and exclusion criteria.

Abbreviations: AF, atrial fibrillation; ALT, alanine transaminase; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AST, aspartate transaminase; EC, in the study as exclusion criterion; GARFIELD-AF, Global Anticoagulant Registry in the FIELD; IC, in the study as inclusion criterion; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K oral anticoagulant; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Criteria:

¹ Defined in ARISTOTLE as symptomatic congestive heart failure within three months, operationalised in GARFIELD-AF as history of congestive heart failure;

² Defined in ROCKET AF as use of antihypertensive medications within six months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg, operationalised in GARFIELD-AF as hypertension history or use of ≥ 2 antihypertensive drugs at baseline;

³ Defined in GARFIELD-AF as use of ≥ 2 antihypertensive drugs at baseline;

⁴ Defined in ROCKET AF as use of antihypertensive medications within six months before the screening visit, operationalised in GARFIELD-AF as use of ≥ 2 antihypertensive drugs at baseline;

⁵ Defined in ROCKET AF as use of antidiabetic medications within six months before screening visit, operationalised in GARFIELD-AF as use of antidiabetic drugs at baseline;

⁶ Patients with reversible cause for AF were excluded from GARFIELD-AF;

⁷ Defined in ARISTOTLE as persistent, uncontrolled hypertension (systolic blood pressure (SBP) >180 mm Hg, or diastolic blood pressure (DBP) >100 mmHg), operationalised in GARFIELD-AF as baseline SBP >180 or DBP >100 mmHg;

- ⁸ Defined in ROCKET AF as SBP ≥ 180 mmHg or DBP ≥ 100 mmHg;
- ⁹ Defined in ARISTOTLE as serum creatinine > 2.5 mg/dL or calculated creatinine clearance < 25 mL/min, operationalised in GARFIELD-AF as chronic kidney disease (CKD) class IV or V;
- ¹⁰ Defined in ROCKET AF as calculated creatinine clearance < 30 mL/min as per Cockcroft and Gault formulas at the screening visit, operationalised in GARFIELD-AF as chronic kidney disease (CKD) class IV or V;
- ¹¹ Operationalised in GARFIELD-AF as history of bleeding, dementia, compliance concern of dementia or baseline GARFIELD-AF bleeding score $> 4\%$ at two years;
- ¹² Medical history element recorded in GARFIELD-AF, without date of diagnosis;
- ¹³ Defined in ROCKET AF as modified Rankin score of 4 to 5;
- ¹⁴ In ARISTOTLE as part of the high bleeding risk criterion, defined as increased bleeding risk that is believed to be a contraindication to oral anticoagulation (e.g. previous intracranial haemorrhage);
- ¹⁵ Defined in ROCKET AF as aspirin in combination with thienopyridines within five days before randomization, operationalised in GARFIELD-AF as concomitant aspirin and thienopyridine use at baseline;
- ¹⁶ Use of this medication was scored in GARFIELD-AF without dosage information
- ¹⁷ Medication use recorded in the registry, without date of (last) usage;
- ¹⁸ Defined in ARISTOTLE as haemoglobin < 10 g/dL, baseline laboratory test results or anaemia history were not included in the GARFIELD-AF CRF;
- ¹⁹ Defined in ROCKET AF as haemoglobin < 10 g/dL, baseline laboratory test results or anaemia history were not included in the GARFIELD-AF CRF;
- ²⁰ Defined in ARISTOTLE as platelet count $\leq 100,000/\text{mm}^3$, baseline laboratory test results or thrombocytopenia history were not included in the GARFIELD-AF CRF;
- ²¹ Defined in ROCKET AF as platelet count $< 90,000/\mu\text{L}$, baseline laboratory test results or thrombocytopenia history were not included in the GARFIELD-AF CRF;
- ²² Operationalised in GARFIELD-AF as compliance concern of limited access to INR monitoring;
- ²³ Defined in ARISTOTLE as mitral valve stenosis, which is not specifically recorded in GARFIELD-AF;
- ²⁴ Defined in ROCKET AF as hemodynamically significant mitral valve stenosis or prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted), neither of which were specifically recorded in GARFIELD-AF;
- ²⁵ Operationalised in GARFIELD-AF as presence of intracardiac thrombus;
- ²⁶ Defined in GARFIELD-AF as dementia history, dementia as compliance concern, or bleeding risk, fall risk or previous bleeding event as reason not to start oral anticoagulation;
- ²⁷ Operationalised in GARFIELD-AF as cardioversion at baseline or ≤ 48 days of registry enrolment;
- ²⁸ Operationalised in GARFIELD-AF as cirrhosis history;
- ²⁹ Defined in GARFIELD-AF as any prior use of vitamin K anticoagulants

Supplementary Table S2. Missingness proportion (%) for selected variables by study population and baseline treatment.

Variable	ROCKET AF trial eligible patients		ARISTOTLE trial eligible patients	
	Rivaroxaban (N = 2005)	VKA (N = 4368)	Apixaban (N = 2570)	VKA (N = 8005)
Country	0.0	0.0	0.0	0.0
Cohort	0.0	0.0	0.0	0.0
Sex	0.0	0.0	0.0	0.0
Race/ethnicity	1.7	1.8	3.2	1.7
Type of AF	0.0	0.0	0.0	0.0
Care setting location	0.0	0.0	0.0	0.0
Care setting specialty	0.0	0.0	0.0	0.0
Heart failure	0.0	0.0	0.0	0.0
Vascular disease	1.1	1.0	1.1	1.0
ACS	0.6	0.7	0.7	0.6
Carotid occlusive disease	2.2	2.4	1.6	2.1
Prior stroke/TIA/SE	0.7	1.0	1.1	0.9
Prior bleeding	0.3	0.5	0.5	0.4
VTE	0.7	0.8	0.7	0.7
Hypertension	0.1	0.3	0.2	0.2
Hypercholesterolaemia	3.6	4.5	2.1	4.9
Diabetes	0.0	0.0	0.0	0.0
Cirrhosis	2.0	2.2	1.6	2.2
CKD	3.9	6.7	3.3	6.9
Dementia	0.8	0.5	0.8	0.6
Hyperthyroidism	2.7	3.0	2.3	3.1
Hypothyroidism	2.7	3.1	2.1	3.2
Alcohol consumption	16.1	15.1	18.9	15.0
Smoking status	9.6	8.2	11.0	7.9
Antiplatelet therapy	1.9	0.0	1.7	0.0
Age	0.0	0.0	0.0	0.0
SBP	5.1	7.3	5.5	6.4
DBP	5.1	7.3	5.5	6.4
Pulse	7.3	8.4	6.0	7.3
BMI	19.7	24.0	20.6	23.0

ACS, acute coronary syndromes; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SBP, systolic blood pressure; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

**Supplementary Table S3. Variables included in the propensity score weighting scheme.
All variables were assessed at baseline.**

General	Demographics	Vital signs	Medical history	Medication
Country of enrolment	Sex	BMI	Congestive heart failure	Antiplatelet use
Cohort of enrolment	Age	Heart rate	Acute coronary syndromes	
Care setting speciality	Ethnicity	Systolic blood pressure	Vascular disease	
Care setting location		Diastolic blood pressure	Carotid occlusive disease	
Current smoking			Prior stroke/TIA/SE	
Heavy alcohol consumption			Prior bleeding	
Type of AF			VTE	
			Hypertension	
			Hypercholesterolemia	
			Diabetes	
			Moderate to severe CKD	
			Hyperthyroidism	
			Hypothyroidism	

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

Supplementary Table S4. Frequency of reasons for exclusion of GARFIELD-AF patients in the ROCKET AF and ARISTOTLE trial emulation analyses.

Exclusion criterion	ROCKET AF	ARISTOTLE
Less than 2 risk factors for stroke (Age \geq 75 years, treated hypertension, low LVEF or current heart failure, diabetes)	60.9%	
No risk factors for stroke (Age \geq 75 years, prior TIA or stroke, treated hypertension, low LVEF or current heart failure, diabetes)		44.3%
<i>Age <75 years</i>	71.7%	66.5%
<i>No heart failure or low LVEF</i>	83.8%	82.9%
<i>Non-diabetic</i>	83.5%	82.3%
<i>No Treated Hypertension</i>	40.6%	59.4%
No prior stroke or TIA	92.4%	90.6%
Atrial myxoma or left ventricular thrombus	0.7%	
Planned cardioversion therapy	22.4%	
High bleeding risk	17.9%	35.0%
Uncontrolled hypertension	15.5%	17.9%
Prior indication for anticoagulation, other than AF	12.5%	
Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)	2.6%	5.3%
Contraindication to VKA	0.1%	
Inability to comply with INR monitoring		0.05%
Severe renal insufficiency history	2.6%	5.2%
Acute liver disease	0.9%	1.8%

Data are from GARFIELD-AF patients excluded from trial emulation analyses, presented with the percentage of ineligible patients per exclusion criterion. Exclusion criteria are not mutually exclusive; a GARFIELD-AF patient could be excluded for more than one reason. Operationalisation of exclusion factors in GARFIELD-AF is provided in the footnotes under Supplementary Table S1.

AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CKD, chronic kidney disease; INR, international normalized ratio; LVEF, left ventricular ejection fraction; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Supplementary Table S5. Crude event rates, unadjusted and adjusted hazard ratios in VKA and NOAC patients eligible for ARISTOTLE and ROCKET AF.

TRIAL Outcome <i>Treatment</i>	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
ARISTOTLE (n=10575)				
Stroke/SE				
VKA	152	1.02 (0.87-1.19)	1 (ref.)	1 (ref.)
<i>Apixaban</i>	32	0.65 (0.46-0.92)	0.64 (0.44-0.94)	0.57 (0.34-0.94)
Major bleeding				
VKA	165	1.11 (0.95-1.29)	1 (ref.)	1 (ref.)
<i>Apixaban</i>	40	0.81 (0.60-1.11)	0.74 (0.52-1.05)	0.76 (0.48-1.20)
All-cause mortality				
VKA	566	3.75 (3.46-4.08)	1 (ref.)	1 (ref.)
<i>Apixaban</i>	151	3.04 (2.60-3.57)	0.81 (0.68-0.97)	0.89 (0.70-1.12)
ROCKET AF (n=6373)				
Stroke/SE				
VKA	90	1.11 (0.90-1.37)	1 (ref.)	1 (ref.)
<i>Rivaroxaban</i>	39	1.03 (0.76-1.42)	0.93 (0.65-1.36)	0.90 (0.57-1.43)
Major bleeding				
VKA	98	1.21 (1.00-1.48)	1 (ref.)	1 (ref.)
<i>Rivaroxaban</i>	44	1.17 (0.87-1.57)	0.97 (0.68-1.38)	0.92 (0.59-1.43)
All-cause mortality				
VKA	371	4.54 (4.10-5.03)	1 (ref.)	1 (ref.)
<i>Rivaroxaban</i>	158	4.15 (3.55-4.85)	0.91 (0.76-1.10)	0.86 (0.69-1.08)

Event rates (per 100 person-years), unadjusted and adjusted¹ hazard ratios for selected outcomes at 2 years of follow-up by trial study population and treatment at baseline, in VKA and NOAC patients eligible for ARISTOTLE and ROCKET AF. ¹Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort of 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, VTE, hypertension, hypercholesterolemia, diabetes, 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.

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; HR, hazard ratio; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE, systemic embolism; VKA, vitamin K antagonist.

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