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

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

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.