

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

The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators^a *Durham, NC*

Background Atrial fibrillation (AF), the most common significant cardiac arrhythmia, increases the risk of stroke, particularly in the elderly. Warfarin is effective in reducing stroke risk but is burdensome to patients and is difficult to control. Rivaroxaban is an oral direct factor Xa inhibitor in advanced development as an alternative to warfarin for the prevention and treatment of thromboembolic disorders.

Methods ROCKET AF is a randomized, double-blind, double-dummy, event-driven trial, which aims to establish the noninferiority of rivaroxaban compared with warfarin in patients with nonvalvular AF who have a history of stroke or at least 2 additional independent risk factors for future stroke. Patients are randomly assigned to receive rivaroxaban, 20 mg once daily (od), or dose-adjusted warfarin titrated to a target international normalized ratio (INR) of 2.5 (range 2.0-3.0, inclusive) using point-of-care INR devices to receive true or sham INR values, depending on the study drug allocation. The primary efficacy end point is a composite of all-cause stroke and noncentral nervous system systemic embolism. The primary safety end point is the composite of major and clinically relevant nonmajor bleeding events. Over 14,000 patients have been randomized at 1,100 sites across 45 countries, and will be followed until 405 primary outcome events are observed.

Conclusion The ROCKET AF study will determine the efficacy and safety of rivaroxaban as an alternative to warfarin for the prevention of thromboembolism in patients with AF. (Am Heart J 2010;159:340-347.e1.)

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance.¹ It affects 1% of the general population and up to 10% of those older than 80 years—representing 2.5 million people in the United States—with age-adjusted prevalence higher in men than in women.²⁻⁵ AF predisposes patients to the development of atrial thrombi and is associated with a 4- to 5-fold increase in the risk of ischemic stroke.⁶ Up to 15% of all strokes and 36% of strokes in those older than 80 years are attributable to AF.⁷ Moreover, ischemic strokes caused by AF tend to be more disabling than other etiologic subtypes

of ischemic stroke.⁸ Therefore, the burden of stroke caused by AF is substantial and likely to increase as the population ages unless effective, safe, and widely available prophylaxis can be implemented.^{9,10}

A recent meta-analysis of 6 trials investigating dose-adjusted warfarin in 2,900 patients with AF demonstrated a highly significant reduction in the relative risk of all stroke (ischemic and hemorrhagic) with warfarin compared with placebo or untreated controls (relative risk reduction 64%, 95% CI 49%-74%).¹¹ The proportional benefit was similar for both primary and secondary prevention.¹¹ By contrast, antiplatelet therapy with aspirin was associated with a small reduction in the incidence of stroke, compared with placebo (relative risk reduction 22%, 95% CI 2%-39%), presumably due to a reduction in noncardioembolic strokes.¹¹ Direct comparisons of vitamin K antagonist (VKA) therapy and aspirin antiplatelet therapy have demonstrated that VKA therapy is far superior in preventing stroke and other thromboembolism in patients with AF.¹¹ Although more intense antiplatelet therapy with clopidogrel plus aspirin is more

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effective than aspirin alone,¹² the ACTIVE-W trial makes clear that VKA anticoagulation is far superior to even clopidogrel plus aspirin.¹³

Limitations of warfarin

Although the efficacy of VKAs, and particularly warfarin, is well established for the prevention of stroke, the risk of major hemorrhage and the difficulties in managing these drugs complicate their use. The international normalized ratio (INR) target of 2.0 to 3.0, inclusive, optimizes the efficacy and safety of VKA therapy but is difficult to achieve consistently because VKA effect is modified by multiple environmental and genetic factors.¹⁴ Because of this variable patient response, frequent monitoring is required to maintain the INR within the target therapeutic range. However, even within the framework of stringent clinical trial conditions, INR ratios fall outside the therapeutic range one third of the time,¹⁵ with poor INR control associated with increased rates of stroke, bleeding, and death.¹⁶ The percentage of INR values outside the therapeutic range is even higher in clinical practice,^{17,18} with patients naïve to warfarin potentially representing the patient group with the highest percentages out of range.¹³ These drawbacks limit the use and effectiveness of warfarin in patients with AF in usual clinical care. Multiple surveys indicate that roughly half of AF patients in the United States with indications for anticoagulation are actually taking the drug. Further control of anticoagulation intensity within the specified INR range of 2.0 to 3.0 is highly variable with reports of less than 50% time in therapeutic range in clinical practice.¹⁹ Rates of bleeding may be substantially higher in practice than the rates seen in randomized trials.^{20,21} In France for example, a survey by the Agence de Santé indicated that the rates of iatrogenic hospital admissions for major hemorrhage caused by the use of a VKA were as high as 13% of all admissions.

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor in advanced development for the prevention and treatment of thromboembolic disorders. Rivaroxaban exhibits predictable, dose-proportional pharmacokinetics (PK), with high oral bioavailability and a rapid onset of action (maximum plasma concentrations are reached after 3.0-4.0 hours).²² The pharmacodynamics (PD) of rivaroxaban correlate closely with its plasma concentrations, with little observed interindividual variability based on age, gender, or body weight.²²

Rivaroxaban has a dual mode of elimination. Approximately one third of rivaroxaban is eliminated unchanged by the kidneys. The remaining approximately two thirds of the drug is metabolized by the liver, after which half of the metabolized fraction is excreted in urine and the

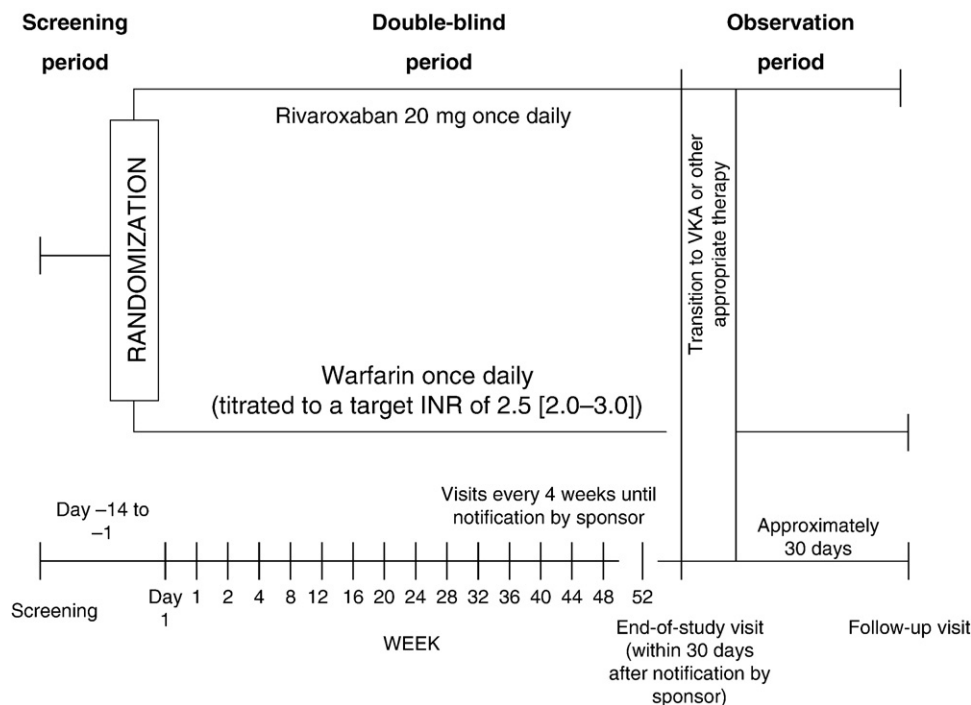
other half excreted in feces.²³ Rivaroxaban has a low propensity for drug-drug interactions, including medications such as digoxin, acetylsalicylic acid (ASA), or nonsteroidal antiinflammatory drugs that patients may be receiving for concomitant conditions.²⁴⁻²⁶ There are no reported food-drug interactions, and dietary restrictions are not necessary in patients receiving rivaroxaban.²⁷ The combination of these attributes means that monitoring of anticoagulation intensity should not be required with rivaroxaban.

Results from the phase III RECORD program, which investigated rivaroxaban for the prevention of venous thromboembolism (VTE) after total hip replacement (THR) and total knee replacement (TKR), demonstrated that rivaroxaban, 10 mg od, was significantly superior to enoxaparin, 40 mg od, in the prevention of VTE after THR (35 days of prophylaxis)^{28,29} and TKR (10-14 days of prophylaxis),³⁰ with rates of major bleeding that were not statistically significantly different in any study and with an otherwise similar safety profile.²⁸⁻³¹ In a second study after TKR, rivaroxaban, 10 mg od, was superior to enoxaparin, 30 mg bid, the prevention of VTE (10-14 days).³¹ In addition, the potential of rivaroxaban for the treatment of VTE has been demonstrated in 2 phase IIb studies: ODIXa-DVT³² and EINSTEIN DVT.³³ This extensive phase II dose-finding program investigated both od and bid doses of rivaroxaban (total daily doses between 20 and 60 mg) compared with standard regimens of low-molecular-weight heparin or unfractionated heparin, followed by dose-adjusted VKA for up to 12 weeks. These studies indicated that both od and bid rivaroxaban regimens had a similar efficacy and safety profile to the current standard of care.

This report describes the rationale and design for a large international phase III study evaluating rivaroxaban compared with dose-adjusted warfarin for the prevention of thromboembolic events in patients with nonvalvular AF. During the design of this study, the executive committee considered the following key design issues that will be highlighted: blinding versus open label, patient risk for thromboembolic events, dosing, non-inferiority design, and global trial conduct with varying practice patterns.

Objectives

The primary objective of the ROCKET AF trial is to compare the efficacy of rivaroxaban with dose-adjusted warfarin titrated to a target INR of 2.5 (range 2.0-3.0, inclusive) for the prevention of thromboembolic events in patients with nonvalvular AF. The primary efficacy end point is the composite of stroke (ischemic and hemorrhagic) and noncentral nervous system (CNS) systemic embolism. Secondary efficacy end points include all-cause death, vascular death, and myocardial infarction (MI).

Figure 1

ROCKET AF study flow diagram.

The principal safety objective is to compare the rate of major and clinically relevant, nonmajor bleeding events in patients assigned to rivaroxaban with those given dose-adjusted warfarin.

Additional exploratory analyses include the evaluation of the PK and PD of rivaroxaban and identification of genetic factors that may influence the PK/PD and safety/tolerability of rivaroxaban, the effect of rivaroxaban on health care resource use, and treatment satisfaction with anticoagulant therapy.

Study design

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) is a randomized, double-blind, double-dummy, multicenter, event-driven study (Figure 1). The study is divided into a screening period, a double-blind treatment period (closing with an end of double-blind treatment visit), and a posttreatment observation period (closing with a follow-up visit). At the end of double-blind treatment visit (or earlier if patients discontinue study drugs prematurely), patients are transitioned from study drug to an open-label VKA or other appropriate regimen. Patients may discontinue study drug for any of the following reasons: safety concerns, pregnancy,

stroke or systemic embolism, diagnosis of HIV, abnormal liver function, creatinine clearance <25 mL/min on 2 consecutive measurements, noncompliance, or the need for an excluded medication. The expected duration of the study is 40 months (minimum duration approximately 14 months); it may extend up to 4 years, depending upon the rate of patient recruitment and end point event rates.

A double-blind design was chosen to minimize bias in cointerventions and interpretation of clinical events. To maintain blinding in ROCKET AF, sham INR results are provided. A point-of-care coagulation testing device displays a code number that, when entered into the Interactive Voice Response System along with the subject's study identification number, is decoded and generates either the subject's real INR or a sham INR value, depending on the patient's blinded treatment. Warfarin and matching rivaroxaban placebo, or rivaroxaban and matching warfarin placebo, are dose adjusted based on either real or sham INR values, respectively. The sham INR results are based on actual patient data, taking study drug doses, age, and sex into account and generated according to a validated algorithm reflecting the distribution of INR values from a population of patients using warfarin with characteristics similar to the study population. The algorithm is periodically updated based on the distribution of INR values from study

patients assigned to warfarin. During the study, INR monitoring occurs as often as clinically indicated but no less frequently than every 4 weeks. An unblinded physician, not affiliated with the conduct of the study, will monitor the warfarin management to ensure clinical sites respond to values out of range. Finally, the time in therapeutic range for the patients treated with warfarin will be reported at the conclusion of the study.

Patient population

To ensure a study population at high enough risk to test the efficacy of rivaroxaban, the ROCKET AF trial will enroll adult patients with nonvalvular AF at moderate to high risk for future thromboembolic events and who therefore qualify for anticoagulant therapy.³⁴ We sought moderate- to high-risk patient population out of concern that decreasing stroke rates would blunt comparison between rivaroxaban and warfarin. A history of stroke, transient ischemic attack (TIA), or systemic embolism was determined by the executive steering committee to carry the highest risk, followed by VKA naïve status, and traditional risk factors for stroke. Therefore, qualifying criteria include prior stroke, TIA, or systemic embolism, or 2 or more of the following risk factors: clinical heart failure and/or left ventricular ejection fraction $\leq 35\%$, hypertension, age ≥ 75 years, or diabetes mellitus (CHADS₂). In addition, the patients with only 2 risk factors will be capped at 10% of the overall trial population, with the remaining patients requiring ≥ 3 risk factors (CHADS₂ ≥ 3) or a prior stroke, TIA, or systemic embolism. Patients with AF and hemodynamically significant mitral stenosis or any valve prostheses are excluded, despite their clear need for anticoagulant therapy because previous placebo-controlled studies of warfarin therapy did not include these patients. Additional exclusion criteria include transient AF caused by a reversible disorder, excessive hemorrhagic risk, and planned cardioversion (Table D).

The ROCKET AF study will also seek to preferentially enroll patients naïve to VKA because such patients may reflect a more realistic experience with anticoagulants than patients successfully taking oral anticoagulant therapy prior to enrollment. Signed informed consent is required from each patient in accordance with protocol regulations approved by local institutional review boards governing research involving human subjects, national regulatory agencies, and the Declaration of Helsinki.

Intervention

Over 14,000 patients have been randomized in the ROCKET AF trial at 1,100 sites across 45 countries. Patients are allocated to 1 of 2 study regimens: rivaroxaban or warfarin. Patients assigned to rivaroxaban receive oral rivaroxaban, 20 mg od, plus oral warfarin

placebo od titrated to a target sham INR of 2.5 (range 2.0-3.0, inclusive). Patients allocated to warfarin receive oral warfarin od, titrated to a target INR of 2.5 (range 2.0-3.0, inclusive), plus oral rivaroxaban placebo od.

The choice of the rivaroxaban, 20 mg od, dose is based on results of 2 phase II studies investigating the efficacy and safety of rivaroxaban for the treatment of VTE. All rivaroxaban doses tested (total daily doses of 20-60 mg) demonstrated efficacy.^{32,33} The lowest total daily dose (20 mg) had consistently lower bleeding rates than the other doses. Therefore, given the increasing age and comorbidity of patients with AF, this dose was felt to offer the best balance of efficacy and safety from phase II studies and was chosen as the principal dose for the ROCKET AF study. Patients with a calculated creatinine clearance of 30 to 49 mL/min per 1.73 m² received a reduced dose of rivaroxaban of 15 mg od. Regimen allocation is balanced according to country, prior use of VKA, and history of stroke, TIA, or non-CNS systemic embolism. To effect concealment of randomization, treatment allocation is randomized using a blinded, central telephonic Interactive Voice Response System. Investigators will manage anticoagulation with warfarin per routine clinical care.

Concurrent interventions

Medical

To ensure the evaluation of rivaroxaban in a setting reflective of current clinical practice around the world, investigators are encouraged to manage the patients according to the local standard of care, including the use of antiarrhythmic drugs and cardiovascular therapies. The use of concomitant ASA up to 100 mg/day is permitted in accordance with treatment guidelines for patients with AF and atherosclerotic disease.³⁴ Thienopyridines are not permitted for 5 days before randomization or during the study, and fibrinolytic therapy is not permitted for 10 days before randomization. However, during the study, patients who undergo appropriate vascular interventions can receive dual antiplatelet therapy with ASA and thienopyridine at the investigator's discretion. Chronic use of nonsteroidal antiinflammatory drugs, defined as daily use for >2 weeks, is prohibited. Specific strong cytochrome P450 3A4 inhibitors and inducers (Table D) are also prohibited.

Surgical

In an effort to maintain consistency of care in the trial, specific recommendations are provided to investigators for patients undergoing invasive procedures. During the conduct of the study, patients might undergo scheduled elective, semiurgent, and emergency procedures. For elective procedures, patients should stop the warfarin/warfarin-placebo therapy 4 days before the planned procedure and the rivaroxaban/rivaroxaban-placebo

Table I. Principal inclusion and exclusion criteria for the ROCKET AF study

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Age ≥ 18 years • Persistent or paroxysmal AF documented on ≥ 2 episodes (one of which is electrocardiographically documented within 30 days of enrollment) • Risk for future stroke, including the history of stroke/TIA or systemic embolism OR ≥ 2 of the following: <ul style="list-style-type: none"> –Congestive heart failure or left ventricular ejection fraction $\leq 35\%$ –Hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg) –Age ≥ 75 years –Diabetes mellitus 	<p>Cardiovascular-related conditions</p> <ul style="list-style-type: none"> • Prosthetic heart valve • Planned cardioversion • AF secondary to reversible disorders (ie, thyrotoxicosis) • Known presence of atrial myxoma or left ventricular thrombus • Active endocarditis • Hemodynamically significant mitral stenosis <p>Hemorrhage risk-related criteria</p> <ul style="list-style-type: none"> • Active internal bleeding • History of, or condition associated with, increased bleeding risk, including <ul style="list-style-type: none"> –Major surgical procedure or trauma within 30 days before randomization –Clinically significant gastrointestinal bleeding within 6 months before randomization –History of intracranial, intraocular, spinal, or atraumatic intraarticular bleeding –Chronic hemorrhagic disorder –Known intracranial neoplasm, arteriovenous malformation, or aneurysm –Planned invasive procedure with potential for uncontrolled bleeding, including major surgery <p>Concomitant conditions and therapies</p> <ul style="list-style-type: none"> • Any stroke within 14 days before randomization • TIA within 3 days before randomization • Indication for anticoagulant therapy for a condition other than AF (eg, VTE) • Treatment with <ul style="list-style-type: none"> –ASA >100 mg daily –ASA in combination with thienopyridines within 5 days before randomization –Intravenous antiplatelets within 5 days before randomization –Fibrinolytics within 10 days before randomization –Anticipated need for long-term treatment with a nonsteroidal antiinflammatory drug –Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the period of the study –Treatment with a strong inducer of cytochrome P450 3A4, such as rifampicin, phenytoin, phenobarbital, or carbamazepine, within 4 days before randomization, or planned treatment during the period of the study –Anemia (hemoglobin level <10 g/dL) at the screening visit –Pregnancy or breastfeeding –Known HIV infection at time of screening –Calculated creatinine clearance <30 mL/min at the screening visit –Known significant liver disease (eg, acute clinical hepatitis, chronic active hepatitis, cirrhosis) or alanine aminotransferase $>3\times$ the upper limit of normal

AF, Atrial fibrillation; TIA, transient ischemic attack; VTE, venous thromboembolism; ASA, acetylsalicylic acid.

therapy 2 days before the procedure. Point-of-care INR measurements should be performed daily, and patients may undergo procedures when the values are deemed appropriate by the treating physician. Bridging with parental or subcutaneous antithrombotic agents during this time is allowed. For semiurgent procedures, the study drug is stopped and blinded point-of-care INR testing using the point-of-care device is recommended. If possible, the procedure should be delayed for 24 hours. Sham INR values decrease appropriately as study drugs are stopped before procedures. For emergency procedures, blinding should be maintained, and the investigators should manage the subject in the same manner as if

warfarin therapy was administered. For some procedures (eg, urgent percutaneous coronary intervention [PCI]), use of study drug may continue without interruption. In the periprocedural period, INR tests should be performed as necessary using the point-of-care device. With all procedures, study drug should be resumed when hemostasis is achieved and the treating physician considers that oral anticoagulant therapy is appropriate.

Efficacy and safety evaluations

An independent academic clinical events committee (CEC) applies the protocol definitions and adjudicates

and classifies clinical events. The primary efficacy end point is the composite of stroke and non-CNS systemic embolism. Stroke is defined as a sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause, such as a tumor or seizure. An event matching this definition that lasts <24 hours is considered a TIA. Advanced brain imaging is sought in each case to help distinguish hemorrhagic from ischemic stroke. The outcome of all strokes is classified according to the modified Rankin scale at hospital discharge. Subjects dying from any cause within 30 days of the onset of stroke are regarded as having fatal stroke. Non-CNS systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (eg, trauma, atherosclerosis, or instrumentation). In the presence of atherosclerotic peripheral arterial disease, the diagnosis of embolism to the lower extremities requires angiographic demonstration of abrupt arterial occlusion.

Secondary end points include the composite of TIA, all-cause death, vascular death, and MI. The adjudication of MI as a clinical end point considers the occurrence relative to PCI or coronary artery bypass graft surgery. In the absence of PCI or coronary artery bypass graft, MI is defined by clinical symptoms consistent with MI and cardiac biomarker elevation (troponin I or T, creatine kinase-muscle and brain subunit) greater than the upper limit of normal, the development of new pathologic Q waves in ≥ 2 contiguous electrocardiographic leads, or confirmed by autopsy. Deaths are adjudicated as having been caused by vascular causes (eg, stroke, embolism, or acute MI) or nonvascular due to conditions such as malignancy or hemorrhage.

The primary safety end point is the composite of major and clinically relevant nonmajor bleeding events. Major bleeding is defined as clinically overt bleeding associated with any of the following: fatal outcome, involving a critical site (ie, intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or clinically overt bleeding associated with a fall in hemoglobin concentration of ≥ 2 g/dL, or leading to transfusion of ≥ 2 units of packed red blood cells or whole blood. All intracerebral (or intraparenchymal) bleeding is included in the primary end point analysis as hemorrhagic strokes. Clinically relevant, nonmajor bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician (visit or telephone call), temporary (ie, by delaying the next study drug administration) cessation of study drug, pain, or impairment of daily activities. All other overt bleeding episodes not meeting the criteria for major or clinically relevant nonmajor bleeding are classified as minor bleeding. Liver function tests will be

collected during screening visits and during regularly scheduled routine follow-up.

Follow-up

When randomized, all patients will be observed for the duration of the study to ascertain clinical events. Patients will be seen at 1, 2, and 4 weeks, and every month thereafter for detection of primary efficacy end point events, as well as TIA, MI, bleeding complications, procedures, and vital status evaluation. A standardized questionnaire and examination will be used to screen for stroke symptoms and clinical events that will prompt further evaluation.

Statistical analysis plan

The proven efficacy of VKAs for prevention of thromboembolism in patients with AF has made this type of anticoagulation the standard of care for patients with AF at risk of stroke. Hence, placebo-controlled trials are unethical in this patient population, and rivaroxaban is compared with warfarin, INR 2 to 3, in this study. The study is powered to determine noninferiority of rivaroxaban compared with warfarin for prevention of the primary efficacy end point. If the noninferiority hypothesis is satisfied, the possibility of superiority will then be assessed. The primary efficacy analysis (noninferiority) will be undertaken in the per-protocol population, which comprises all randomized patients who have received study drug, except those who have major protocol violations before a primary end point event. If the noninferiority criterion is satisfied, then superiority for the primary efficacy end point will be tested in the safety population. In addition, if noninferiority for the primary efficacy end point on the per-protocol population is satisfied, then a closed testing procedure will be conducted for other efficacy end points.³⁵

The analysis population consists of randomized subjects who have taken at least one dose of study drug. Finally, an independent statistician will perform all analyses.

Noninferiority design consideration

The executive steering committee favored a noninferiority design based on the proven efficacy of warfarin for the prevention of thromboembolism in patients with AF leading to its use as standard of care rendering future placebo-controlled trials unethical. As a conceptual method for comparing rivaroxaban with warfarin, a finding of statistical noninferiority implies that the efficacy of rivaroxaban is superior or similar to warfarin (ie, 1-sided instead of 2-sided test). The noninferiority boundary needs to be set to ensure that a conclusion of noninferiority implies rivaroxaban would preserve a prespecified portion of the benefit of warfarin over placebo. Once noninferiority is established, patients

and clinicians could then choose one therapy over another on the basis of other factors, such as ease of use, safety, or tolerability.^{36,37}

For the ROCKET AF trial, the first step in selecting the noninferiority margin was to estimate the minimum acceptable retention of warfarin efficacy over placebo. A meta-analysis of 6 warfarin trials was used to estimate the risk ratio during therapy with warfarin compared to placebo as 0.38 (95% CI 0.28-0.52).³⁸ The reciprocal estimate of the risk ratio of placebo to warfarin was 2.63 (1.92-3.57). Regulatory guidelines require that the noninferiority margin would, at the least, rule out the minimum warfarin effect versus placebo,³⁹ making the most liberal noninferiority margin 1.92. The margin corresponding to preservation of 50% of the warfarin effect is 1.82 (95% CI 1.46-2.29). The most conservative approach was chosen, selecting the lower limit, 1.46, of this confidence boundary. To obtain a 95% power with a 1-sided α equal to .025 in this event-driven trial with a noninferiority margin of 1.46 for the risk ratio (rivaroxaban/warfarin), 363 events are required from the per-protocol population. The number of events was increased to 405 to provide robust evaluation across all subgroups. The total number of randomized subjects required to observe 405 events with a 14% dropout rate was estimated to be 14,000. The expected study duration rate is approximately 40 months from first patient enrolled to the occurrence of the last event. However, the duration may be extended or the sample size increased to observe the prespecified needed number of outcome events. All determinations regarding study duration or sample size will be based upon review of blinded data.

Administrative organization

The ROCKET AF study is conducted under the supervision of an executive steering committee [Appendix A], which developed the protocol and provides oversight of trial execution, oversees the independent database, and is accountable for analysis of the results and publication. Patient safety is monitored by an independent data safety and monitoring board [DSMB—Appendix B]. The DSMB was constituted with a charter to perform interim analyses to ensure patient safety and detect adverse outcomes between study groups during the study. The DSMB will provide recommendations regarding terminating, continuing, or modifying the study protocol in the event of differential safety findings in the 2 treatment groups or differential efficacy favoring warfarin.

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support this work, and the authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the article and its final contents.

As ROCKET AF is a large international study, a steering committee of investigators and national coordinators was also formed to provide periodic feedback to the executive steering committee about study progress and the protocol. This steering committee also provided insight into regional patterns of care for patients with AF and feedback regarding study procedures. The independent, blinded CEC reviews reports of all suspected study events. The CEC adjudicates stroke, systemic embolism, MI, death, and major bleeding events based on event-specific forms and data collected from individual sites. The decisions of the CEC will be used to perform the final statistical analyses. Finally, operational oversight of the study will be performed through collaboration among an academic research organization, the Duke Clinical Research Institute, Parexel International, a clinical research organization, and the sponsors, Johnson & Johnson Pharmaceutical Research & Development and Bayer Schering Pharma.

Conclusions

Rivaroxaban is an oral, direct factor Xa inhibitor under investigation in an od regimen for prevention of stroke and systemic embolism in patients with AF. The ROCKET AF study is a randomized, blinded, noninferiority study comparing rivaroxaban, 20 mg od, with dose-adjusted warfarin targeted at INR 2 to 3. The first patient was enrolled in December 2006, and randomization was completed ($n = 14,269$) in June 2009. The median age of the enrolled population is 73 years, and 39% are female. An estimated 93% have hypertension, 40% have diabetes, 38% were on prior long-term ASA therapy, and 62% had prior VKA therapy. This event-driven trial is expected to last 42 months. At completion, ROCKET AF will determine the efficacy and safety of rivaroxaban compared with warfarin for the prevention of thromboembolism in a moderate to high-risk set of patients with AF.

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Appendix A.

Executive Steering Committee members

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Steering Committee (National Coordinators)

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Appendix B.

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