Baseline characteristics of the ROCKET AF study: comparison with recent atrial fibrillation studies

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Abstract

Background: Atrial fibrillation (AF), the most common cardiac arrhythmia, increases the risk of stroke. Warfarin is effective in reducing stroke risk but is burdensome and difficult to control. Rivaroxaban is an oral, once-daily (od), direct Factor Xa inhibitor.

Methods: ROCKET AF is a randomized, double-blind, double-dummy, event-driven trial, comparing rivaroxaban with warfarin in patients with AF who have a history of stroke or at least two risk factors for future stroke. Patients are randomly assigned to receive rivaroxaban (20 mg od, or 15 mg od for patients with moderate renal impairment) 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 sham or true INR values, depending on study drug allocation. The study is powered to show non-inferiority of rivaroxaban to warfarin for the composite of stroke and non-central nervous system (CNS) systemic embolism (primary efficacy endpoint); and if demonstrated, superiority will be tested. The primary safety endpoint is the composite of major and clinically relevant non-major bleeding events. 14,269 patients were randomized from December 2006 until June 2009, and the expected duration of this event-driven trial is about 40 months.

Results: Baseline patient data from ROCKET AF and a comparison of ROCKET AF demographics with those from other stroke prevention in AF trials are shown in Table 1.

Conclusion: ROCKET AF will determine the efficacy and safety of rivaroxaban compared with warfarin for the prevention of thromboembolism in patients with AF who are at risk of stroke. Compared with previous trials of novel agents, this trial includes a greater proportion of patients who are at higher risk of stroke who would be likely to receive an anticoagulant in real-world practice.

Introduction and purpose

- AF is the most prevalent cardiac arrhythmia of clinical significance[1]
  - It predisposes patients to the development of atrial thrombi, which may subsequently travel to the brain, resulting in ischaemic stroke
  - Patients with AF have an approximately fivefold increased risk of stroke compared with those in normal sinus rhythm[2]
  - Up to 15% of all strokes, and 36% of strokes in individuals aged >80 years, are attributable to AF[3]
  - AF-related stroke and its disabling consequences impose a considerable economic burden on healthcare systems, of which the main cost driver is inpatient care
  - Patients who have had prior stroke are at increased risk of a subsequent stroke
- Warfarin is the most effective therapy currently available for stroke prevention in patients with AF but its use is associated with an increased risk of adverse bleeding events,[4] particularly intracranial haemorrhage
- The use of warfarin is also associated with various practical challenges that limit its successful implementation in practice, including:
  - A high degree of inter- and intra-patient variability in dose response
  - The need for frequent coagulation monitoring and dose adjustments to maintain the INR within the target range (2.0–3.0)
  - The need for dietary restrictions, particularly regarding vitamin K content
  - These issues have led to the underuse of warfarin in routine practice, as demonstrated by the EuroHeart survey[5]
- The new oral anticoagulants in development may avoid many of the drawbacks associated with warfarin
  - There are two main classes: direct Factor Xa inhibitors and direct thrombin inhibitors
- Rivaroxaban is an oral, direct Factor Xa inhibitor approved in the EU for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery, based on the results of the phase III RECORD programme[6–8]
  - Across RECORD1, 2, 3 and 4, rivaroxaban consistently provided a significant relative risk reduction in the incidence of total VTE compared with enoxaparin, with similar rates of major bleeding[6-9]
- Rivaroxaban is also in advanced clinical development for the prevention or treatment of several thromboembolic disorders, including stroke prevention in AF
- The objectives of this poster are to:
  - Present the design and baseline patient characteristics of a large international phase III study comparing fixed-dose rivaroxaban administered orally od with dose-adjusted warfarin (INR 2.0–3.0) for the prevention of thromboembolism in patients with non-valvular AF
  - Compare the baseline patient characteristics of this trial with those of other vitamin K antagonist (VKA)-controlled trials for stroke prevention in AF
  - Discuss how differences between studies in baseline patient characteristics might influence the outcomes of ongoing studies of new oral anticoagulants

Methods

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 phase III, prospective, randomized, double-blind, double-dummy, active-controlled, multicentre, event-driven study[10] (Figure 1)
- A double-dummy approach was used to maintain blinding: patients were randomized to receive either warfarin plus rivaroxaban-placebo or rivaroxaban plus warfarin-placebo. Warfarin and warfarin-placebo were dose adjusted based on true or sham INR values, respectively, obtained from point-of-care INR devices
- The rivaroxaban dose was 20 mg od, except for patients with moderate renal impairment at baseline (creatinine clearance 30–49 ml/min) who received a reduced dose (15 mg od)
- Investigators were encouraged to manage patients with concurrent interventions in a manner consistent with local standards of care

Patient population

- The eligibility criteria were designed to include a higher-risk patient population than those studied in previous trials of stroke prevention in AF

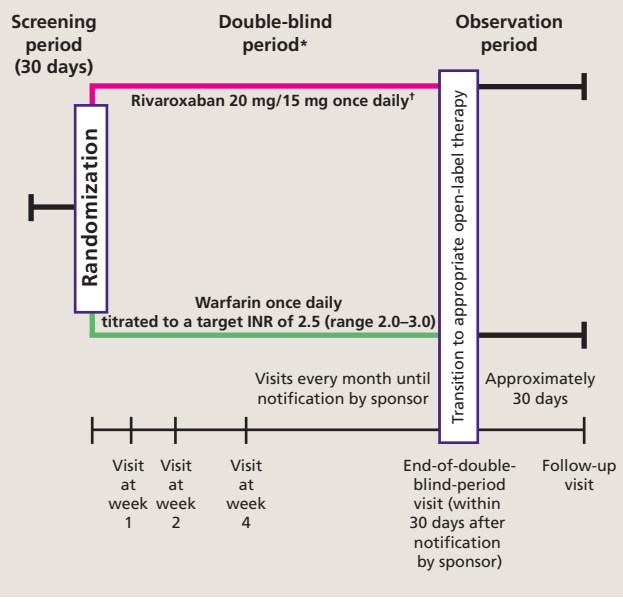

Figure 1. ROCKET AF study design. *During the double-blind period, patients receive either rivaroxaban plus warfarin-placebo or warfarin plus rivaroxaban-placebo. Duration of therapy varies patient to patient because this is an event-driven trial. †Rivaroxaban 20 mg once daily, or 15 mg once daily in patients with moderate renal impairment (creatinine clearance 30–49 ml/min). INR, international normalized ratio.

- Inclusion criteria: age ≥18 years with persistent or paroxysmal AF (≥2 episodes documented) and
  - **Either** a history of stroke, transient ischaemic attack (TIA) or non-CNS systemic embolism
  - **Or** ≥2 of the following risk factors: age ≥75 years; hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg); a clinical diagnosis of heart failure and/or left ventricular ejection fraction ≤35%; or diabetes mellitus (i.e. $CHADS_2$ score ≥2)
- To further enrich the risk profile of the total patient population, the proportion of patients enrolled with only two stroke risk factors was capped at approximately 10% of the overall study population; all subsequently enrolled patients were required to have ≥3 stroke risk factors or a history of stroke, TIA or systemic embolism
- Exclusion criteria included: patients with valvular disease (such patients were not included in previous placebo-controlled studies of warfarin therapy); those with transient AF caused by a reversible disorder; increased haemorrhagic risk; or planned cardioversion. Full details are presented in the ROCKET study design publication[10]
- The study sought to include a substantial proportion of VKA-naïve patients

Endpoints

- Primary efficacy: composite of all-cause stroke and non-CNS systemic embolism
- Primary safety: composite of major and clinically relevant non-major bleeding events
  - Major bleeding is defined by any of the following: a fatal outcome; involvement of a critical site (i.e. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal bleeding); or clinically overt (≥2 g/dl fall in haemoglobin, or requiring the transfusion of ≥2 units of packed red blood cells or whole blood)
  - Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study drug, pain, or impairment of daily activities

Statistical power

- The study is powered to show non-inferiority of rivaroxaban to warfarin for the prevention of stroke and non-CNS systemic embolism (primary efficacy endpoint)
- To obtain a 95% power with a one-sided α of 0.025 and a non-inferiority margin of 1.46 for the risk ratio (rivaroxaban/warfarin), 363 events are required in the per-protocol population. However, the number of events was increased to 405 to provide robust evaluation of all subgroups
  - Allowing for a 14% dropout rate, it was estimated that 14,000 patients would need to be randomized to observe 405 events
- The primary efficacy analysis (non-inferiority) will be undertaken in the per-protocol population (all randomized patients who have received study drug, except those with major protocol violations before a primary endpoint event). If this non-inferiority criterion is satisfied, superiority for the primary efficacy endpoint will be tested in the intention-to-treat population

Results

Study progress

- 14,269 patients at 1,100 study sites across 45 countries were randomized between December 2006 and June 2009
- This event-driven trial is expected to run for ~40 months

Patient characteristics

- Preliminary characteristics of the ROCKET AF cohort compared with other VKA-controlled studies for stroke prevention in AF are given in Table 1; further characteristics of the ROCKET AF cohort can be found in Table 2
- More than half of all patients had a history of stroke, TIA or non-CNS systemic embolism
  - This subgroup will provide much needed secondary prevention data for patients at high risk of stroke
- Approximately one-quarter of patients had moderate renal impairment (creatinine clearance 30–49 ml/min)
  - Rivaroxaban was given at the reduced dose of 15 mg od, based on pharmacokinetic/pharmacodynamic modelling of rivaroxaban clearance in the setting of moderate renal impairment
- More than one-third of patients were VKA naïve at baseline
  - Such patients may be expected to show a more variable response to VKAs compared with those who had been managed with VKAs before enrolment
- Substantially more patients in ROCKET AF had a $CHADS_2$ score ≥3 (high risk) compared with those in RE-LY,[11] AMADEUS,[12] SPORTIF V[13] or ACTIVE W[14]
- In ROCKET AF, <1% of patients in had a $CHADS_2$ score of 0–1 compared with 25–41% of patients in RE-LY,[11] AMADEUS[12] and SPORTIF V[13]
  - The current guidelines[15,16] recommend acetylsalicylic acid (ASA) for patients with a $CHADS_2$ score of 0, or a choice between either ASA or VKA for patients with a $CHADS_2$ score of 1

Table 1. Baseline patient demographics: comparison of ROCKET AF with VKA-controlled randomized trials for stroke prevention in atrial fibrillation

	ROCKET AF	RE-LY[11]	ACTIVE W[14]	AMADEUS[12]	SPORTIF V[13]
Patients randomized (n)	14,269	18,113	6,706	4,576	3,922
Investigational regimen	Rivaroxaban	Dabigatran	Clopidogrel + ASA	Idraparinux	Ximelagatran
Comparator regimen	Warfarin (INR 2–3)	Warfarin (INR 2–3)	Warfarin (INR 2–3)	VKA (INR 2–3)	Warfarin (INR 2–3)
Patient characteristics					
Age at randomization (years)	73	72	70	70	72
Female (%)	40	36	33	34	31
Moderate renal impairment (%)*	21	NA	NA	16	NA
AF diagnosed within the last year (%)	26	NA	20 (range 6 months to 2 years)	NA	16
ASA use prior to randomization (%)	38	40	28	NA	18
VKA use prior to screening (%)†	62	50	77	76	84
$CHADS_2$ score (%)					
0–1	<1	32		41	25
2	13	36	Median 2.0	32	31
≥3	86	32		27	44
Risk factors (%)					
CHF or LVEF ≤35%	63	32	30	23	39
Hypertension	90	79	82	77	81
Age ≥75 years	44	–	–	31	42
Diabetes mellitus	40	23	21	10‡	19§
Prior stroke, TIA or non-CNS systemic embolism	55	20	15	24	18

*Moderate renal impairment: creatinine clearance 30–49 ml/min. †Defined as vitamin K antagonist use for ≥6 weeks at the time of screening in ROCKET AF. However, the definition varied between these five trials. ‡Diabetes mellitus and age 65–75 years. §Diabetes mellitus and age ≥65 years. Percentages may not add up to 100% due to rounding. AF, atrial fibrillation; ASA, acetylsalicylic acid; $CHADS_2$, Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, previous Stroke or TIA; CHF, congestive heart failure; CNS, central nervous system; LVEF, left ventricular ejection fraction; NA, not available; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Table 2. ROCKET AF patient characteristics at baseline and procedures received during the trial

	Total*
Patients randomized (n)	14,269
Race (%)	
White	83.3
Black	1.3
Asian	12.5
Other	2.9
Creatinine clearance (%)	
30–49 ml/min	20.9
50–79 ml/min	45.9
≥80 ml/min	33.1
Procedures performed during the trial (%)	
Percutaneous intervention	0.7
Cardioversion	1.4
AF ablation	0.4

*Rivaroxaban and warfarin groups combined. AF, atrial fibrillation.

Conclusions

- ROCKET AF is a large, robust trial involving >14,000 patients with AF at risk of stroke
- The preliminary baseline characteristics of the ROCKET AF cohort demonstrate that this population includes a greater proportion of patients at higher risk of stroke than those involved in other VKA-controlled trials (RE-LY, AMADEUS, SPORTIF V, ACTIVE W)
  - A greater proportion of the ROCKET AF cohort is representative of those patients receiving anticoagulation in the real-world setting
- Many of the risk factors for anticoagulant-related bleeding (e.g. advanced age, uncontrolled hypertension, previous myocardial infarction or ischaemic heart disease and cerebrovascular disease) are the same as for stroke. Consequently, individual patient stroke risk may be proportionally related to the risk of adverse bleeding events[17–19]
  - The ROCKET AF cohort includes a substantial proportion of patients with these risk factors
- In randomized, warfarin-controlled trials evaluating the safety and efficacy of new oral anticoagulants for stroke prevention in AF, patient populations at greater risk of stroke, in both arms, can therefore be expected to show:
  - Higher rates of thrombotic events
  - Higher rates of bleeding and/or more serious bleeding
- Renal impairment may increase bleeding risk in patients receiving anticoagulants that are excreted renally
  - ROCKET AF includes a substantial proportion of patients with moderate renal impairment (creatinine clearance 30–49 ml/min), and is not only the first stroke prevention in AF study, but also the first rivaroxaban-specific study, to evaluate dose reduction for these patients
  - This trial will ascertain the possible value of treating patients with moderate renal impairment and AF with a reduced dose of rivaroxaban
- Finally, in ROCKET AF, warfarin, the comparator drug, was given double blind, whereas in RE-LY warfarin was given open label
  - This is an important difference in study design because an analysis of SPORTIF V vs III indicated that warfarin may perform better in terms of stroke prevention and INR control when given double blind rather than open label, respectively[20]

References

1. Finisterer J, Stölberger C. *Neth J Med* 2008;66:327–333.
2. Wolf PA *et al. Stroke* 1991;22:983–988.
3. Wolf PA *et al. Arch Intern Med* 1987;147:1561–1564.
4. Hart RG *et al. Ann Intern Med* 2007;146:857–867.
5. Nieuwlaat R *et al. Eur Heart J* 2006;27:3018–3026.
6. Eriksson BI *et al. N Engl J Med* 2008;358:2765–2775.
7. Kakkar AK *et al. Lancet* 2008;372:31–39.
8. Lassen MR *et al. N Engl J Med* 2008;358:2776–2786.
9. Turpie AGG *et al. Lancet* 2009;373:1673–1680.
10. The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators. *Am Heart J* 2010;159:340–347.
11. Connolly SJ *et al. N Engl J Med* 2009;361:1139–1151.
12. Amadeus Investigators. *Lancet* 2008;371:315–321.
13. Albers GW *et al. JAMA* 2005;293:690–698.
14. ACTIVE Writing Group of ACTIVE Investigators. *Lancet* 2006;367:1903–1912.
15. Fuster V *et al. Circulation* 2006;114:257–354.
16. Singer DE *et al. Chest* 2008;133:546S–592S.
17. Hughes M, Lip GY. *QJM* 2007;100:599–607.
18. Hylek EM *et al. Circulation* 2007;115:2689–2696.
19. Kakar P *et al. Chest* 2006;130:1296–1299.
20. Hylek EM *et al. Stroke* 2008;39:3009–3014.

Disclosure of conflict of interest
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