Primary and key secondary results from the ROCKET AF trial, and their implications on clinical practice

Rohan Shah and Manesh R. Patel

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Abstract

Background: The safety and efficacy of the oral anticoagulant rivaroxaban were studied in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF trial). A number of subanalyses of the ROCKET AF trial have subsequently analyzed the use of rivaroxaban in special patient populations.

Methods: The outcomes of the ROCKET AF trial were reviewed. The use of rivaroxaban in higher risk populations, as determined by the presence of co-morbidities included in the CHADS2 criteria, was analyzed. Requirements for dose adjustment in patients with renal impairment and in East Asian patients were described. Finally, clinical management challenges, including interruptions in therapy, drug discontinuation, management of bleeding events, drug interactions, and management of patients requiring cardioversion/ablation were reviewed.

Results: Rivaroxaban is efficacious in high-risk populations, including elderly patients, patients with diabetes, heart failure, history of stroke, prior myocardial infarction, or peripheral arterial disease (PAD). Patients with PAD have a higher risk of bleeding with rivaroxaban compared with warfarin. East Asian populations do not require a dose adjustment for rivaroxaban, while a reduced dose of 15 mg daily is required for patients with moderate renal impairment. Rivaroxaban remains effective with temporary interruptions in therapy and in patients requiring cardioversion/ablation. Rates of major bleeding and subsequent outcomes were similar in patients on warfarin and rivaroxaban, although rates of gastrointestinal bleeding were higher with rivaroxaban. Concurrent use of antiarrhythmic therapy was not associated with adverse outcomes.

Conclusions: Rivaroxaban represents an efficacious alternative to warfarin in high-risk patients with AF. Dose adjustment is required for patients with moderate renal impairment. Rivaroxaban can be used safely in a number of challenging clinical management scenarios although the concurrent use of amiodarone requires more study.

Keywords: atrial fibrillation, rivaroxaban, warfarin

Introduction

Rivaroxaban is a direct factor Xa inhibitor that represents an alternative to the more conventional vitamin K antagonist (VKA) warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). While VKAs are highly effective for stroke prevention, they often require frequent dose adjustments due to the multitude of food and drug interactions associated with warfarin [Hart *et al.* 1999, 2007; Singer *et al.* 2004;

Albers *et al.* 1996; Go *et al.* 1999; Piccini *et al.* 2009]. Rivaroxaban was studied with the hope of providing more predictable anticoagulation than warfarin, eliminating the need for frequent dose adjustments [Kubitza *et al.* 2005b, 2008]. The safety and efficacy of rivaroxaban, compared with warfarin, in patients with nonvalvular AF, were studied extensively in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke

Correspondence to:
Manesh R. Patel, MD
Duke Clinical Research
Institute, Division of
Cardiology, Department of
Medicine, Duke University
Medical Center, PO Box
17969, 2400 Pratt St,
Durham, NC 27715, USA
manesh.patel@duke.edu

Rohan Shah, MD
Duke Clinical Research
Institute, Durham, NC,
USA

and Embolism Trial in AF (ROCKET AF trial) [Patel *et al.* 2011; ROCKET AF Study Investigators, 2010].

The ROCKET AF trial was a multicenter, randomized, double-blind trial that was conducted at 1,178 participating sites in 45 countries around the world. In the ROCKET AF trial, patients with nonvalvular AF documented on electrocardiography, who were at moderate to high risk for stroke based on a CHADS2 score of 2 or more, were randomly assigned to receive a fixed dose of rivaroxaban 20 mg once daily [or 15 mg daily if creatinine clearance (CrCl) was 30–49 ml/min] or dose-adjusted warfarin. Patients were excluded from the ROCKET AF trial if they had a recent stroke or systemic embolism event, were at risk for bleeding, had prosthetic heart valves, hemodynamically significant mitral stenosis, or a CrCl <30 ml/min [ROCKET AF Study Investigators, 2010].

The primary efficacy endpoint analyzed in the ROCKET AF trial was the composite of stroke and systemic embolism. The secondary efficacy endpoints analyzed included a composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular causes, or myocardial infarction (MI); and individual components of the composite endpoints. The primary safety endpoint analyzed was a composite of major and nonmajor clinically relevant (NMCR) bleeding events.

A total of 14,264 patients were enrolled in the ROCKET AF trial. Rivaroxaban was found to be non-inferior to warfarin for the prevention of stroke and systemic embolism in patients with AF, with the primary endpoint occurring in 1.7% of patients on rivaroxaban and 2.2% of patients on warfarin ($p < 0.001$ for non-inferiority). In terms of safety, there was no major difference between the groups in rates of major and NMCR bleeding [14.9% per year in rivaroxaban group *versus* 14.5% per year in the warfarin group, hazard ratio (HR) 1.03, 95% confidence interval (CI) 0.96–1.11; $p = 0.44$] although rates of intracranial bleeding (0.5% *versus* 0.7%; $p = 0.02$) and fatal bleeding (0.2% *versus* 0.5%; $p = 0.003$) were lower in the group of patients randomized to rivaroxaban.

Rates of death and MI, both key secondary outcomes analyzed in the main ROCKET AF trial, were similar across both groups. The composite

of stroke, systemic embolism and vascular death was lower in patients on rivaroxaban (HR 0.86; 95% CI 0.74–0.99; $p = 0.034$) compared with patients on warfarin.

The ROCKET AF trial directly compared the safety and efficacy of rivaroxaban and warfarin for stroke prevention and was the major trial to firmly establish and enable the use of rivaroxaban in patients with AF around the globe. A number of secondary analyses of the ROCKET AF trial detailing the use, safety and efficacy of rivaroxaban in a variety of specialized populations have been subsequently carried out. For the purpose of this paper, we reviewed these pertinent secondary analyses of the ROCKET AF trial. The results of these analyses have been summarized in this review (Table 1).

The use of rivaroxaban in populations with higher risk of stroke

The following patient populations may be regarded as patients at higher risk for stroke owing to their age or the presence of other co-morbidities that are included in the CHADS2 criteria [Gage *et al.* 2001; Keogh *et al.* 2011]. The use of anticoagulation in these groups is of particular interest as these patients are more likely to develop the embolic complications associated with AF. From a clinical standpoint, knowing the relative efficacy as well as the relative safety of rivaroxaban in each group can help physicians make individualized decisions about the use of rivaroxaban in these patient populations.

Elderly patients

The prevalence of nonvalvular AF increases with age and is a major cause of disability in the elderly [Miyasaka *et al.* 2006; Gombert-Maitland *et al.* 2006]. A variety of reasons including polypharmacy, sensitivity to warfarin and comorbidities may make it difficult for the elderly to maintain stable anticoagulation [Singer *et al.* 2009; DiMarco *et al.* 2005]. Thus, the use of novel oral anticoagulants (NOACs) that do not require frequent monitoring and have fewer interactions may be beneficial in this population.

The use of rivaroxaban in elderly patients has been studied by Halperin and colleagues [2014] in a prespecified analysis of the ROCKET AF trial. Patients were analyzed in groups based on age <75 years or age ≥75 years at entry. Of the

Table 1. Summary of analyses reviewed.

Study authors	Subgroup studied	Pre-specified analysis or not	Efficacy ^a of rivaroxaban versus warfarin in subgroup population	Safety of rivaroxaban versus warfarin in subgroup population	Notes
			HR (95% CI), <i>p</i> value ^b	HR (95% CI), <i>p</i> value ^a	
Halperin <i>et al.</i> [2014]	Elderly patients (age >75 years)	Pre-specified	0.80 [0.63–1.02], <i>p</i> = 0.3131	1.11 [0.92–1.34], <i>p</i> = 0.34 ^c	Results similar for EF >40 and EF <40
van Diepen <i>et al.</i> [2013]	Heart failure	Pre-specified	0.91 [0.74–1.13], <i>p</i> = 0.62	1.05 [0.95–1.15], <i>p</i> = 0.99 ^d	
Bansilal <i>et al.</i> [2015]	Diabetes	Pre-specified	0.82 [0.63–1.08], <i>p</i> = 0.53	0.98 [0.88–1.10], <i>p</i> = 0.17 ^d	
Hankey <i>et al.</i> [2012]	Previous stroke or TIA	Pre-specified	0.94 [0.77–1.16], <i>p</i> = 0.23	0.96 [0.87–1.07], <i>p</i> = 0.08 ^d	
Mahaffey <i>et al.</i> [2014]	Prior MI	Pre-specified	0.61 [0.37–0.99], <i>p</i> = 0.25	1.21 [1.03–1.43], <i>p</i> = 0.04 ^d	
Jones <i>et al.</i> [2014]	PAD	<i>Post-hoc</i>	1.19 [0.63–2.22], <i>p</i> = 0.34	1.40 [1.06–1.86], <i>p</i> = 0.04 ^d	Trend to improved CV outcomes with rivaroxaban if prior MI. Limited data on DAPT use
Fox <i>et al.</i> [2011]	Renal impairment	Pre-specified	0.84 [0.57–1.23], <i>p</i> = 0.76	0.98 [0.84–1.14], <i>p</i> = 0.45 ^d	
Wong <i>et al.</i> [2014]	East Asian patients	<i>Post-hoc</i>	0.78 [0.44–1.39], <i>p</i> = 0.67	1.01 [0.79–1.30], <i>p</i> = 0.87 ^d	Limited data on DAPT use
Sherwood <i>et al.</i> [2014]	Temporary interruptions in therapy	<i>Post-hoc</i>	0.74 [0.36–1.50], <i>p</i> = 0.40	1.12 [0.85–1.47], <i>p</i> = 0.43 ^d	
Patel <i>et al.</i> [2013]	Drug discontinuation	<i>Post-hoc</i>	1.21 [0.81–1.81], <i>p</i> = 0.35	0.79 [0.54–1.16], <i>p</i> = 0.23 ^c	CrCI 30–49 mL/min. rivaroxaban dose reduced to 15 mg
Piccini <i>et al.</i> [2009]	Major bleeding	<i>Post-hoc</i>	0.89 [0.42–1.88], <i>p</i> = 0.51	0.79 [0.54–1.16], <i>p</i> = 0.23 ^c	
Piccini <i>et al.</i> [2013]	Cardioversion or catheter ablation	<i>Post-hoc</i>	Rate 1.88% versus 1.86% ^e	Rate 18.75% versus 13.04% ^e	Risk of bleeding with rivaroxaban at end of study higher (HR 3.62) Higher rates of GI bleeding on rivaroxaban
Steinberg <i>et al.</i> [2014]	Antiarrhythmic therapy	<i>Post-hoc</i>	1.71 [0.80–3.65], <i>p</i> = 0.06 ^f	1.35 [0.94–1.92], <i>p</i> = 0.3 ^{d,f}	
CI, confidence interval; CrCI, creatinine clearance; CV, cardiovascular; DAPT, dual antiplatelet therapy; EF, ejection fraction; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; NMCR, non-major clinically relevant; PAD, peripheral artery disease; TIA, transient ischemic attack.					
^a Efficacy outcome reported is the composite of stroke or systemic embolism.					
^b <i>p</i> value reported for interaction of treatment and subgroup population.					
^c Safety data for major bleeding.					
^d Safety data for major or NMCR bleeding.					
^e Data for treatment and outcomes interaction reported by authors in terms of rates only. No HR, CI or <i>p</i> value reported.					
^f Data reported by authors for amiodarone and treatment interaction only. Other antiarrhythmic drugs not included in this calculation.					

CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; DAPT, dual antiplatelet therapy; EF, ejection fraction; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; NMCR, non-major clinically relevant; PAD, peripheral artery disease; TIA, transient ischemic attack.

^aEfficacy outcome reported is the composite of stroke or systemic embolism.

^b*p* value reported for interaction of treatment and subgroup population.

^cSafety data for major bleeding.

^dSafety data for major or NMCR bleeding.

^eData for treatment and outcomes interaction reported by authors in terms of rates only. No HR, CI or *p* value reported.

^fData reported by authors for amiodarone and treatment interaction only. Other antiarrhythmic drugs not included in this calculation.

Figure 1. Clinical benefit of rivaroxaban compared with warfarin in elderly *versus* younger patients with AF. AF, atrial fibrillation. Source: Halperin *et al.* [2014].

14,171 patients in the ROCKET AF trial intention to treat (ITT) population, 6,164 patients (43%) were aged ≥ 75 years at entry. Elderly patients had a higher mean CHADS₂ score (3.7 *versus* 3.3) and were found to have higher rates of stroke/systemic embolism (2.57% *versus* 2.05%/100 patient-years; $p = 0.0068$) and bleeding (4.63% *versus* 2.74%/100 patient-years; $p < 0.0001$) compared with younger patients. However, the efficacy ($p = 0.313$ for interaction of age and treatment) and safety ($p = 0.336$ for interaction) of rivaroxaban compared with warfarin did not differ with age. When considering the net clinical benefit based on the avoidance of ischemic stroke, severe bleeding and all-cause mortality, the benefit of rivaroxaban compared with warfarin was more pronounced in elderly patients than younger patients (Figure 1).

Given that the safety and efficacy of rivaroxaban *versus* warfarin did not differ with age, this analysis supports the use of rivaroxaban in the elderly. However, it should be noted that the seventy-fifth percentile for patient age in this analysis was 82 years. As such, these results should be used with caution and in patients well above this age. It is also important to consider the drop in CrCl as patients age and to dose rivaroxaban appropriately based on CrCl in elderly patients.

Patients with heart failure

AF occurs in 12–41% of patients with heart failure (HF) and the presence of AF correlates with severity of HF [Maisel and Stevenson, 2003;

Adams *et al.* 2005; Nieminen *et al.* 2006; Owan *et al.* 2006]. Although VKAs are recommended in patients with both AF and HF [Fuster *et al.* 2006; Singer *et al.* 2004; Dries *et al.* 1998], HF is a recognized risk for reduction of time in the therapeutic range with VKAs, and these patients may be predisposed to reduced efficacy of anticoagulation and increased bleeding [Rose *et al.* 2010; Lip *et al.* 2011; DiMarco *et al.* 2005; Witt *et al.* 2009, 2010]. Rivaroxaban, with its predictable pharmacokinetic profile, thus theoretically represents a possible alternative to warfarin in patients with both AF and HF.

The safety and efficacy of rivaroxaban in patients with AF and HF has been studied by van Diepen and colleagues [2013] in a prespecified subgroup analysis of the ROCKET AF trial. A total of 9,033 (63.7%) of the patients in the ROCKET AF trial had HF. Patients with HF had a higher mean CHADS₂ score (3.7 *versus* 3.1). The efficacy of rivaroxaban compared with warfarin was similar in patients with HF and without HF ($p = 0.62$ for interaction of presence of HF and treatment), as was the risk of major or NMCR bleeding with and without HF ($p = 0.99$ for interaction). Among patients with HF, the efficacy of rivaroxaban was similar irrespective of ejection fraction (EF) $< 40\%$ or $\geq 40\%$ ($p = 0.38$ for interaction), New York Heart Association class I–II *versus* III–IV ($p = 0.68$ for interaction), or HF with preserved *versus* reduced EF ($p = 0.35$ for interaction). Since there was no difference in the safety and efficacy of rivaroxaban compared with warfarin in HF patients, rivaroxaban can be used in patients with both preserved or reduced EF and in mild or severe HF.

Patients with diabetes mellitus

Diabetes mellitus (DM) and AF often co-occur in the same patient and the presence of DM leads to an increased risk of stroke and poorer outcomes in AF patients [Benjamin *et al.* 1994; Murphy *et al.* 2007; Movahed *et al.* 2005; Iguchi *et al.* 2008]. The safety and efficacy of rivaroxaban in patients with and without DM was reported by Bansilal and colleagues [2015] in a prespecified analysis. A total of 5,695 (40%) of the patients in ROCKET AF had DM. Adjusted analyses from Bansilal and colleagues suggested that the 2-year risk of stroke, vascular mortality and MI was 1.3-, 1.5- and 1.9-fold higher respectively in AF patients with diabetes compared with AF patients without DM [Bansilal *et al.* 2015].

Figure 2. Kaplan-Meier plot showing time to primary outcome (stroke or systemic embolism) for AF patients with and without prior stroke or TIA on rivaroxaban or warfarin. AF, atrial fibrillation; TIA, transient ischemic attack. Source: Hankey *et al.* [2012].

The relative efficacy of rivaroxaban compared with warfarin for the prevention of stroke or systemic embolism was similar with and without DM. The safety of rivaroxaban compared with warfarin with respect to major bleeding, major or NMCR bleeding and intracranial haemorrhage (ICH) was independent of DM status. These results support the use of rivaroxaban in AF in both patients with and without DM. It should be noted, however, that the analysis did not include the degree of glycemic control in patients. As such, we are unable to assess whether the degree of glycemic control affects ischemic or bleeding risks in these patients.

Patients with previous stroke or transient ischemic attack

A prior history of stroke or a transient ischemic attack (TIA) is a major risk factor for future strokes in patients with AF [Stroke in AF Working Group, 2007]. The benefits and risks of warfarin have been reported to be consistent in patients with and without previous stroke/TIA [European AF Trial Study Group, 1993;

Morocutti *et al.* 1997; Saxena and Koudstaal, 1995; Hart *et al.* 2007]. Given the differences in risks between the two patient populations, it is important to analyze the safety and efficacy of rivaroxaban across them.

The effects of rivaroxaban in AF patients with and without previous stroke/TIA were investigated by Hankey and colleagues [2012] in a pre-specified subgroup analysis. 7,468 patients (52%) of the ROCKET AF population had a previous stroke or TIA. As would be expected, patients with prior history of stroke or TIA had higher rates of stroke/systemic embolism (Figure 2). However, the efficacy of rivaroxaban compared with warfarin remained similar in both patients with and without prior stroke/TIA for the prevention of stroke/systemic embolism ($p = 0.23$ for interaction of prior stroke/TIA and treatment). There was no difference in safety of rivaroxaban compared with warfarin regardless of prior stroke/TIA ($p = 0.08$ for interaction). Thus rivaroxaban can be used to prevent initial strokes, as well as recurrent strokes in patients with AF at high risk for these events.

Patients with prior myocardial infarction

The prevalence of coronary artery disease (CAD) is common in patients with AF [Schmitt *et al.* 2009]. Management of patients with AF and CAD includes the use of antiplatelet and anticoagulant agents [ACCF/AHA Task Force, 2011, 2012; European Heart Rhythm Association, 2010; Guyatt *et al.* 2012; Faxon *et al.* 2011]. However, the benefit of multiple antiplatelet and anticoagulant agents needs to be balanced with the increased risk of bleeding in these patients [Paikin *et al.* 2010; Lamberts *et al.* 2012; Wong *et al.* 2002].

The effects of rivaroxaban *versus* warfarin in AF patients with and without established CAD, as defined by prior MI were investigated by Mahaffey and colleagues [2014] in a prespecified subgroup analysis. A total of 2,468 (17%) of the patients in the trial had a prior MI at the time of enrollment. The primary efficacy outcome analyzed was cardiovascular death, MI or unstable angina. Rates of the primary efficacy outcome were higher in patients with prior MI compared with those with no prior MI (6.68 *versus* 2.19 events/100 patient-years; HR 3.04; 95% CI 2.59–3.56) and tended to be lower in patients assigned to rivaroxaban *versus* warfarin (2.70 *versus* 3.15 events/100 patient-years; HR 0.86; 95% CI 0.73–1.00; $p = 0.0509$). There was no difference in incidence of stroke/systemic embolism between rivaroxaban and warfarin regardless of prior MI ($p = 0.25$ for interaction). However, patients with prior MI did tend to have higher rates of bleeding with rivaroxaban *versus* warfarin (HR 1.21; 95% CI 1.03–1.43; $p = 0.0352$).

While data for prior MI exists, there is a paucity of data for rivaroxaban use in the context of dual antiplatelet therapy (DAPT). Only a minority of patients in the Mahaffey and colleagues study were on DAPT, though a higher proportion (36.5%) were on aspirin only. This limited analysis noted that DAPT was associated with higher event rates. This lack of data on DAPT and anticoagulant use should be considered in patients with a prior MI.

Given the trend towards improved cardiovascular outcomes, no difference in stroke/systemic embolism outcomes and slight increase in bleeding for patients with prior MI on rivaroxaban compared with warfarin, decisions about the final management should be made on a case-by-case basis after a thorough risk–benefit analysis.

Patients with peripheral arterial disease

The presence of vascular disease, as defined by prior MI, aortic atherosclerotic plaque, or PAD is a risk factor for stroke in patients with AF and has been incorporated into an updated risk score (CHA2DS2-VASc) for stroke [Lip *et al.* 2010; Aguilar *et al.* 2012; Goto *et al.* 2008; Winkel *et al.* 2010; Olesen *et al.* 2012]. Furthermore, patients with PAD may be on antiplatelet therapy, especially if symptomatic [Rooke *et al.* 2011; Antithrombotic Trialists' Collaboration, 2002; Berger *et al.* 2009] and thus may be at higher risk of bleeding with anticoagulation.

The safety and efficacy of rivaroxaban compared with warfarin in patients with PAD was investigated in a *post-hoc* analysis by Jones and colleagues [2014]. In ROCKET AF, a total of 839 (5.9%) of patients had PAD. Patients with and without PAD had similar rates of stroke/systemic embolism and major or NMCR bleeding. The efficacy of rivaroxaban compared with warfarin was similar for patients with and without PAD ($p = 0.34$ for interaction of PAD and treatment). There was a significant interaction for major or NMCR bleeding in patients with PAD treated with rivaroxaban *versus* warfarin (21.02 events/100 patient-years *versus* 15.12 events/100 patient-years; HR 1.40; 95% CI 1.06–1.86) compared with those without PAD (14.59 events/100 patient-years *versus* 14.48 events/100 patient-years; HR 1.03; 95% CI 0.95–1.11) with a $p = 0.037$ for interaction. Thus, while the efficacy of rivaroxaban remained unchanged, it did have a higher risk of bleeding *versus* warfarin in patients with PAD compared with patients without PAD.

It should be noted however that a higher proportion of PAD patients were on aspirin, clopidogrel or dipyridamole at the beginning of the study (41.2% *versus* 37.3%) and at 1 year (28% *versus* 18.7%) compared with patients without PAD and this may account for some of the increased risk of bleeding seen in these patients. As such, similar to patients with prior MI on antiplatelet therapy, a patient specific risk–benefit analysis with a complete review of medications, is suggested in patients with AF with PAD in whom rivaroxaban is being considered.

Questions around dose adjustment*Patients with moderate renal impairment*

Rivaroxaban has a dual clearance pathway, renal and hepatic [Kubitza *et al.* 2005a, 2005b]. As

such, AF patients with renal dysfunction face higher risks of both thromboembolism and bleeding with anticoagulation [Fang *et al.* 2011; Pisters *et al.* 2010; Vazquez and Sanchez-Perales, 2011]. Reliable anticoagulation in patients with renal impairment is challenging given the risks associated with it.

In the ROCKET AF trial, patients with moderate renal insufficiency (CrCl of 30–49 ml/min) were given a dose of 15 mg rivaroxaban daily, compared with 20 mg daily in subjects with CrCl $\geq$ 50 ml/min, based on extensive pharmacokinetic data and modeling. Patients with an initial CrCl $<$ 30 were excluded from the trial. There were no further dose adjustments unless CrCl fell below 30 ml/min at which point rivaroxaban was discontinued.

The safety and efficacy of rivaroxaban in patients with moderate renal impairment was reported in a prespecified analysis by Fox and colleagues [2011]. The 2,950 (20.7%) of patients in ROCKET AF with a CrCl of 30–49 ml/min had higher rates of stroke and bleeding irrespective of study treatment compared with patients with normal renal function. However, there was no difference in efficacy of rivaroxaban (adjusted for CrCl) compared with warfarin between patients with and without renal impairment ($p = 0.76$ for interaction of renal impairment and treatment, Figure 3A). Similarly, there was no difference in safety of rivaroxaban (adjusted for CrCl) *versus* warfarin between patients with and without renal impairment ($p = 0.45$ for interaction, Figure 3B). In patients with moderate renal impairment, rivaroxaban must be dose reduced to 15 mg daily. At this dose, there is appropriate prevention of stroke and systemic emboli without increase in bleeding risk.

East Asian patients

The ROCKET AF trial was carried out at multiple sites across the globe including 73 sites from four regions in East Asia (China, Korea, Taiwan and Hong Kong). Differences between Asian populations compared with other ethnic groups that may affect optimal dosing of anticoagulants include body weight and body mass index, higher proportion of hemorrhagic strokes in Asian populations compared with White populations, and increased sensitivity to warfarin [Wang *et al.* 2011; Thrift *et al.* 2001; Zhang *et al.* 2003; Zhao *et al.* 2004; Yuen *et al.* 2010]. A sep-

arate trial of rivaroxaban *versus* warfarin in patients with nonvalvular AF called the J-ROCKET AF trial was also conducted in Japan with a lower 15 mg daily dose of rivaroxaban given in line with Japanese clinical practice guidelines [Hori *et al.* 2012]. J-ROCKET AF demonstrated non-inferiority for the principal safety outcome of major or NMCR bleeding and a strong trend for a reduction in stroke/systemic embolism for rivaroxaban *versus* warfarin (HR 0.49; $p = 0.050$).

As a result of these differences, the relative effects of rivaroxaban *versus* warfarin in East Asian and non-East Asian populations were analyzed by Wong and colleagues [2014]. A total of 932 patients (6.5%) of the ROCKET AF trial population formed the East Asian cohort. The East Asian patients had lower weight, lower CrCl and higher prevalence of prior stroke at baseline. The absolute event rates for both primary efficacy outcomes and safety outcomes were higher in the East Asian cohort compared with the non-East Asian cohort for both warfarin and rivaroxaban. However, the relative efficacy of rivaroxaban 20 mg daily *versus* warfarin for stroke/systemic embolism remained consistent among East Asians and non-East Asians ($p = 0.666$ for interaction of ethnicity and treatment), as did the relative safety of rivaroxaban *versus* warfarin ($p = 0.867$ for interaction). Thus there is no need to reduce the dose of rivaroxaban in East Asian patients provided renal function is normal. It should be noted, however, that in this analysis, the overall number of East Asian patients was low and not all countries in East Asia were represented.

Clinical management challenges

The use of anticoagulation medication poses a number of practical challenges for physicians. As with any medication, patients may experience interruptions in their regimen or may discontinue the medication. The patient may also experience adverse effects that require critical evaluation of the medication or the patient may be on other therapy that could affect treatment. These clinical management issues have been addressed in this section.

Temporary interruption of therapy

A large number of AF patients experience temporary interruption (TI) of their anticoagulation for

Figure 3. (A) Efficacy endpoints in the on treatment population for patients with and without renal impairment. (B) Safety endpoints in the on treatment population for patients with and without renal impairment. CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; MI, myocardial infarction; mg, milligrams; PE, pulmonary embolism; pt/years, patient-years. Source: Fox *et al.* [2011].

invasive procedures, illnesses or bleeding events [Douketis *et al.* 2012]. Bridging therapy in these patients may be pursued based on clinical risk–benefit analysis [Douketis *et al.* 2012; Korte *et al.* 2011]. The outcome of TI with rivaroxaban is thus of clinical benefit to aid physicians in making decisions regarding management.

Sherwood and colleagues [2014] report the impact of TIs on outcomes in the ROCKET AF trial in a *post-hoc* analysis. TI was defined as cessation of the study drug for ≥3 days, without transition to an open-label anticoagulant, with resumption within 30 days. Of the 14,236 patients who received at least one dose of the study drug, 4,692 patients experienced at least one TI with a total of 7,555 TIs. Overall, 40%

of TIs were for surgical/invasive procedures and 25% were for nonbleeding adverse events. A total of 8.2% of TI incidents on rivaroxaban received bridging therapy compared with 4.9% of TI incidents on warfarin. The predominant type of bridging therapy low molecular weight heparin (LMWH) and median duration (6 days) were similar across both groups. Rates of stroke/systemic embolism during the at-risk period were similar for rivaroxaban *versus* warfarin (0.30% *versus* 0.41% per 30 days; HR 0.74; 95% CI 0.36–1.50; *p* = 0.40) as were the rates of major bleeding during the at-risk period (0.99% *versus* 0.79% per 30 days; HR 1.26; 95% CI 0.80–2.00; *p* = 0.32). These results support the use of rivaroxaban in patients who experience TIs. It should be noted however

that this was a *post-hoc* analysis and that utilization of bridging therapy was not randomized.

Drug discontinuation

Due to the challenges with continuous monitoring, intolerability and adverse effects almost one quarter of patients started on warfarin discontinued therapy within the first year [Fang *et al.* 2010; Hylek *et al.* 2007]. Although they do not need continuous monitoring, AF patients on rivaroxaban may discontinue the drug for a variety of reasons as well. Concerns regarding a potential risk of increased thrombotic events and stroke after discontinuation of rivaroxaban led the United States Food and Drug Administration to require a boxed warning on the drug [United States Food and Drug Administration, 2011].

To better understand this risk, Patel and colleagues investigated TIs of ≥ 3 days, early permanent study drug discontinuation and end-of-study transition to open-label therapy in a *post-hoc* analysis of the ROCKET AF trial [Patel *et al.* 2013]. Stroke/systemic embolism occurred at similar rates for rivaroxaban *versus* warfarin after TIs (6.20 *versus* 5.05/100 patient-years; HR 1.28; 95% CI 0.49–3.31; $p = 0.62$) and after early permanent discontinuation (25.60 *versus* 23.28/100 patient-years; HR 1.10; 95% CI 0.71–1.72; $p = 0.66$). Patient transitioning to open-label therapy at the end of the trial had more strokes on rivaroxaban compared with warfarin (6.42 *versus* 1.73/100 patient-years; HR 3.72; 95% CI 1.51–9.61; $p = 0.0044$). However, patients on rivaroxaban took longer to reach a therapeutic international normalized ratio (INR) while transitioning to open-label therapy at the end of the trial (essentially being uncovered for a period of time) compared with patients already on warfarin who continued to receive prophylaxis with no uncovered period at the end of the trial. This was largely a factor of regional variation in early warfarin initiation and management post trial.

As highlighted, the risk of stopping anticoagulation is significant and the increased risk of stroke or systemic embolism in rivaroxaban patients at the end of the trial highlights the importance of therapeutic anticoagulation during transition of therapy.

Management of major bleeding events

While newer anticoagulation agents have several advantages, they also are associated with a risk of

bleeding. There continue to be concerns about the management and outcomes of patients treated with these newer agents, including questions about reversal agents or the use of coagulation products in these patients [Siegal and Crowther, 2013].

Piccini and colleagues analyzed the outcomes and management of patients with major bleeding in ROCKET AF [Piccini *et al.* 2014] in a *post-hoc* analysis. Major bleeding was defined and adjudicated by a blinded clinical events committee using the International Society on Thrombosis and Haemostasis criteria [Schulman and Kearon, 2005]. Over a median follow-up period of 1.9 years, 779 patients (5.5%) experienced major bleeding (3.52 events/100 patient-years) with a similar rate in the rivaroxaban and warfarin arms (see Table 2 for location of major bleeds). Factors associated with major bleeding include age, male sex, prior bleeding and diastolic blood pressure among others [Goodman *et al.* 2014]. Rates of gastrointestinal (GI) bleeds were noted to be higher in patients on rivaroxaban. The median number of transfused packed red blood cells per episode was similar across rivaroxaban and warfarin but the use of fresh frozen plasma was lower in those on rivaroxaban ($n = 45$ *versus* 81; odds ratio 0.43; 95% CI 0.29–0.66; $p < 0.0001$). Outcomes after major bleeding including stroke/systemic embolism and all cause death were similar between patients on rivaroxaban *versus* warfarin ($p = 0.51$ and 0.11 for interaction of outcome and treatment respectively).

As discussed above, GI bleeds occurred in both patients on rivaroxaban and warfarin. The incidence and outcomes of patients in ROCKET AF with GI bleeds was further investigated by Nessel and colleagues [2012] and Sherwood and colleagues [2015]. The composite of GI bleeds (upper, lower, rectal) occurred more frequently in patients on rivaroxaban than on warfarin (3.61 *versus* 2.60 events/100 patient-years; HR 1.39; 95% CI 1.19–1.61) with higher individual rates of both major and NMCR GI bleeding. The most severe GI bleeding events, measured by transfusion of >4 units, were similar between treatment groups ($n = 49$ for rivaroxaban and $n = 47$ for warfarin). Absolute fatality rate was very low with fewer patients on rivaroxaban developing fatal GI bleeding compared with warfarin ($n = 1$ *versus* $n = 5$). Thus, clinicians should advise patients that there are higher GI bleeding events on rivaroxaban.

Table 2. Location of major bleeds in ROCKET AF by randomized treatment.^a

Characteristic	Rivaroxaban (n = 431)	Warfarin (n = 409)
Number of major bleeds ^b		
1	361 (91.4%)	359 (93.5%)
2	32 (8.1%)	25 (6.5%)
>2	2 (0.5%)	0 (0.0%)
Bleeding details		
Bleeding associated with cardiac surgery (including CABG)	0 (0.0%)	2 (0.5%)
Bleeding associated with noncardiac surgery	19 (4.4%)	27 (6.6%)
Epistaxis	14 (3.2%)	14 (3.4%)
GI (Upper)	164 (38.1%)	105 (25.7%)
GI (Lower)	51 (11.8%)	33 (8.1%)
Gingival	1 (0.2%)	2 (0.5%)
Hematoma	13 (3.0%)	26 (6.4%)
Hemoptysis	5 (1.2%)	4 (1.0%)
Increased or prolonged menstrual or abnormal vaginal bleeding	3 (0.7%)	1 (0.2%)
Intra-articular	16 (3.7%)	21 (5.1%)
Intracranial	55 (12.8%)	84 (20.5%)
Intramuscular (with compartment syndrome)	2 (0.5%)	1 (0.2%)
Intramuscular (without compartment syndrome)	2 (0.5%)	4 (1.0%)
Intraocular/retinal	19 (4.4%)	27 (6.6%)
Macroscopic (gross) hematuria	27 (6.3%)	21 (5.1%)
Pericardial	0 (0.0%)	1 (0.2%)
Puncture site	2 (0.5%)	4 (1.0%)
Rectal	28 (6.5%)	8 (2.0%)
Retroperitoneal	1 (0.2%)	3 (0.7%)
Skin (ecchymosis other than instrumented site)	2 (0.5%)	3 (0.7%)
Subconjunctival or other ocular	0 (0.0%)	1 (0.2%)
Other	7 (1.6%)	19 (4.6%)

CABG, coronary artery bypass graft; GI, gastrointestinal; 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; VKA, vitamin K antagonist.

^aDenominator is based on the number of bleeds, which may be more than the number of subjects with major bleeds.

^bDenominator for just this row is based on the number of patients with major bleeds.

Source: Piccini *et al.* [2014].

However, there is no difference in most severe GI bleeding events between rivaroxaban and warfarin, and the absolute fatality rate is very low.

Patients having undergone cardioversion or catheter ablation

Cardioversion or catheter ablation represents an important option for symptom control in patients with AF [Wann *et al.* 2011]. Given the increased risk of thrombotic events following return of sinus rhythm, the periprocedural use of oral anticoagulation represents an important management challenge in AF patients [Nagarakanti *et al.* 2011].

Piccini and colleagues reported the incidence of electrical cardioversions (ECVs), pharmacological cardioversions (PCVs) or AF ablations and subsequent patient outcomes in a *post-hoc* analysis of the ROCKET AF population [Piccini *et al.* 2013]. The overall incidence of ECVs, PCVs and AF ablations was similar across both rivaroxaban and warfarin (1.46 *versus* 1.45 events/100 patient-years). There was an increase in the crude rates of stroke and death in the first 30 days after cardioversion or ablation. However, after adjusting for baseline differences, no difference was observed in the long-term incidence of stroke or systemic embolism, cardiovascular death or all-cause death before and after cardioversion or ablation.

Hospitalizations increased after cardioversion or ablation (HR 2.01; 95% CI 1.51–2.68) but the effect was similar across both rivaroxaban and warfarin ($p = 0.58$ for interaction) as were the efficacy and safety outcomes.

These results are similar to those observed in the X-VerT trial comparing the use of rivaroxaban with warfarin in patients with AF undergoing elective cardioversion [Cappato *et al.* 2014]. In the X-VerT trial, no significant difference was observed between rivaroxaban and warfarin for the efficacy outcome of the composite of stroke, TIA, MI, systemic embolism and cardiovascular death or for the safety outcome of major bleeding.

Patients on antiarrhythmic therapy

Antiarrhythmic drugs (AADs) represent an important component of medical therapy in patients with AF. Given the concerns with concurrent antiarrhythmic and warfarin therapy in these patients [Guerin *et al.* 2013], it is important to know the effect of concurrent antiarrhythmic therapy and rivaroxaban in AF patients.

As reported by Steinberg and colleagues [2014], in a *post-hoc* analysis of the 14,264 patients in the ROCKET AF trial, 1681 (11.8%) were treated with an AAD. Of the 1681 patients on an AAD, 1144 were on amiodarone and 537 were on other AADs (primarily sotalol, propafenone and flecainide). Time in therapeutic range was lower in patients on warfarin receiving amiodarone compared with those not on AADs (50% *versus* 58%; $p < 0.0001$). Compared with no AAD, neither amiodarone nor the other AADs were associated with increased mortality, embolic or bleeding outcomes. The efficacy and safety of rivaroxaban compared with warfarin was not significantly different for amiodarone use or no AAD use.

However, it should be noted that treatment with AADs was not randomized and the population represented only a fraction of the overall ROCKET AF population. As such, the authors suggest that further study is required on the interaction of rivaroxaban and amiodarone.

Conclusion

The ROCKET AF trial represents a landmark trial establishing the use of rivaroxaban as an effective and well-tolerated alternative oral anti-coagulant to warfarin in patients with AF. Recent

analyses have reinforced the robustness of the results of the ROCKET AF trial and suggest that the results hold up well in real life clinical practice [Martinez-Rubio *et al.* 2014; Baron-Esquivias *et al.* 2015]. The results from the ROCKET AF trial parallel those from other major trials establishing the use of NOACs in AF patients [Connolly *et al.* 2009; Granger *et al.* 2011; Giugliano *et al.* 2013]. A recent systematic review by Ruff and colleagues combining results from all four major NOAC trials further affirms the safety and efficacy of NOACs in AF patients [Ruff *et al.* 2014].

The subanalyses of the ROCKET AF trial presented here have important implications for clinical practice and the use of rivaroxaban in challenging patient populations. These analyses demonstrate that rivaroxaban remains an efficacious alternative to warfarin in high-risk populations including elderly patients, and those with HF, diabetes, history of stroke/TIA, prior MI and PAD. The safety profile of rivaroxaban is also maintained across these patient groups except for patients with PAD who had higher rates of bleeding with rivaroxaban. These analyses also note that East Asian populations do not require a dose reduction for rivaroxaban. However, patients with moderate renal impairment do require a dose reduction and a dose of rivaroxaban to 15 mg daily in patients with moderate renal impairment yielded results consistent with the overall ROCKET AF trial.

Rivaroxaban also remains a feasible alternative to warfarin in patients who experience TIs in therapy or permanently discontinue anticoagulation. It must be noted, however, that adequate therapeutic coverage is essential during a transition from rivaroxaban to open-label therapy to counter the increased risk of stroke/systemic embolism. Despite an increase in hospitalizations in patients undergoing ECV, PCV or AF ablation, rivaroxaban can be safely used compared with warfarin in these patients. While the overall use of AADs was not associated with increased morbidity or mortality in ROCKET AF, the use of amiodarone with rivaroxaban required more study.

As noted in the main trial, the rates of major bleeding are similar for rivaroxaban and warfarin with similar outcomes after bleeds in both groups. Rivaroxaban does have lower rates of intracranial and fatal bleeding but higher rates of GI bleeding as seen in the subanalyses above. Even in this case

however, the rate of fatal bleeding was lower than for warfarin.

Although more research needs to be done to assess the impact of rivaroxaban as discussed above, the results from these studies represent valuable information that may allow physicians to tailor the use of rivaroxaban to individual patients with their particular set of co-morbidities. This should give physicians increased confidence in the use of rivaroxaban in challenging patient populations, especially given the advantage of once daily administration of the drug. It should be noted, however, that while most of these analyses did not find a significant difference between rivaroxaban and warfarin with respect to safety and efficacy, this could be due to under-powering of some of these analyses, as is always a concern in retrospective studies. As the use of rivaroxaban and other NOACs continues to expand, we shall continue to learn more about the real-world use of these medications, which in turn can help guide the direction of future research.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

- ACCF/AHA Task Force. (2011) Focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Circulation* 123: e269–e367.
- ACCF/AHA Task Force. (2012) Focused update on the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 60: 645–681.
- Adams, K., Fonarow, G., Emerman, C., LeJemtel, T., Costanzo, M., Abraham, W. *et al.* (2005) Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (AHDRE). *Am Heart J* 149: 209–216.
- Aguilar, E., Garcia-Diaz, A., Sanchez Munoz-Torrero, J., Alvarez, L., Piedecausa, M., Arnedo, G. *et al.* (2012) Clinical outcome of stable outpatients with coronary, cerebrovascular or peripheral artery disease, and atrial fibrillation. *Thromb Res* 130: 390–395.
- Albers, G., Yim, J., Belew, K., Bittar, N., Hattemer, C., Phillips, B. *et al.* (1996) Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med* 156: 2311–2316.
- Antithrombotic Trialists' Collaboration. (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324: 71–86.
- Bansilal, S., Bloomgarden, Z., Halperin, J., Hellkamp, A., Lokhnygina, Y., Patel, M. *et al.* (2015) Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial). *Am Heart J* 170: 675–682.
- Barón-Esquivias, G., Fernández-Avilés, F., Atienza, F., Pueyo, P., Toro, R. and Fernández, M. (2015) Efficacy and safety of rivaroxaban in real-life patients with atrial fibrillation. *Exp Rev Cardiovasc Ther* 13: 341–353.
- Benjamin, E., Levy, D., Vaziri, S., D'Agostino, R., Belanger, A. and Wolf, P. (1994) Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA* 271: 840–844.
- Berger, J., Krantz, M., Kittelson, J. and Hiatt, W. (2009) Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA* 301: 1909–1919.
- Cappato, R., Ezekowitz, M., Klein, A., Camm, A., Ma, C., Le Heuzey, J. *et al.* (2014) Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 35: 3346–3355.
- Connolly, S., Ezekowitz, M., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A. *et al.* (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361: 1139–1151.
- DiMarco, J., Flaker, G., Waldo, A., Corley, S., Greene, H., Safford, R. *et al.* (2005) Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 149: 650–656.
- Douketis, J., Spyropoulos, A., Spencer, F., Mayr, M., Jaffer, A., Eckman, M. *et al.* (2012) Perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 141: e326S–e350S.
- Dries, D., Exner, D., Gersh, B., Domanski, M., Waclawiw, M. and Stevenson, L. (1998) Atrial

fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol* 32: 695–703.

European AF Trial Study Group. (1993) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 342: 1255–1262.

European Heart Rhythm Association. (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 31: 2369–2429.

Fang, M., Go, A., Chang, Y., Borowsky, L., Pomernacki, N., Udaltsova, N. *et al.* (2010) Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 3: 624–631.

Fang, M., Go, A., Chang, Y., Borowsky, L., Pomernacki, N., Udaltsova, N. *et al.* (2011) A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol* 58: 395–401.

Faxon, D., Eikelboom, J., Berger, P., Holmes, D., Bhatt, D., Moliterno, D. *et al.* (2011) Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective. *Circ Cardiovasc Interv* 4: 522–534.

Fox, K., Piccini, J., Wojdyla, D., Becker, R., Halperin, J., Nessel, C. *et al.* (2011) Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 32: 2387–2394.

Fuster, V., Rydén, L., Cannom, D., Crijns, H., Curtis, A., Ellenbogen, K. *et al.* (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: executive summary. *Circulation* 114: 700–752.

Gage, B., Waterman, A., Shannon, W., Boechler, M., Rich, M. and Radford, M. (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 285: 2864–2870.

Giugliano, R., Ruff, C., Braunwald, E., Murphy, S., Wiviott, S., Halperin, J. *et al.* (2013) Once-daily edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 369: 2093–2104.

Go, A., Hylek, E., Borowsky, L., Phillips, K., Selby, J. and Singer, D. (1999) Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Ann Intern Med* 131: 927–934.

Gomberg-Maitland, M., Wenger, N., Feyzi, J., Lengyel, M., Volgman, A., Petersen, P. *et al.* (2006) Anticoagulation in women with nonvalvular atrial fibrillation in the Stroke Prevention Using an Oral Thrombin Inhibitor (SPORTIF) trials. *Eur Heart J* 27: 1947–1953.

Goodman, S., Wojdyla, D., Piccini, J., White, H., Paolini, J., Nessel, C. *et al.* (2014) Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 63: 891–900.

Goto, S., Bhatt, D., Rother, J., Alberts, M., Hill, M., Ikeda, Y. *et al.* (2008) Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 156: 855–863.

Granger, C., Alexander, J., McMurray, J., Lopes, R., Hylek, E., Hanna, M. *et al.* (2011) Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 365: 981–992.

Guyatt, G., Akl, E., Crowther, M., Gutterman, D. and Schuünemann, H. (2012) Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 141: 7S–47S.

Guerin, A., Lin, J., Jhaveri, M., Wu, E., Yu, A., Cloutier, M. *et al.* (2013) Outcomes in atrial fibrillation patients on combined warfarin & antiarrhythmic therapy. *Int J Cardiol* 167: 564–569.

Halperin, J., Hankey, G., Wojdyla, D., Piccini, J., Lokhnygina, Y., Patel, M. *et al.* (2014) Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 130: 138–146.

Hankey, G., Patel, M., Stevens, S., Becker, R., Breithardt, G., Carolei, A. *et al.* (2012) Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 11: 315–322.

Hart, R., Benavente, O., McBride, R. and Pearce, L. (1999) Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 131: 492–501.

Hart, R., Pearce, L. and Aguilar, M. (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 146: 857–867.

Hori, M., Matsumoto, M., Tanahashi, N., Momomura, S., Uchiyama, S., Goto, S. *et al.*; J-ROCKET AF Study

- Investigators. (2012) Rivaroxaban versus warfarin in Japanese patients with atrial fibrillation: the J-ROCKET AF study. *Circ* 76: 2104–2111.
- Hylek, E., Evans-Molina, C., Shea, C., Henault, L. and Regan, S. (2007) Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 115: 2689–2696.
- Iguchi, Y., Kimura, K., Aoki, J., Kobayashi, K., Terasawa, Y., Sakai, K. *et al.* (2008) Prevalence of atrial fibrillation in community dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. *Circ* 72: 909–913.
- Jones, W., Hellkamp, A., Halperin, J., Piccini, J., Breithardt, G., Singer, D. *et al.* (2014) Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and nonvalvular atrial fibrillation: insights from ROCKET AF. *Eur Heart J* 35: 242–249.
- Keogh, C., Wallace, E., Dillion, C., Dimitrov, B. and Fahey, T. (2011) Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. *Thromb Haemost* 106: 528–538.
- Korte, W., Cattaneo, M., Chassot, P., Eichinger, S., von Heymann, C., Hofmann, N. *et al.* (2011) Peri-operative management of antiplatelet therapy in patients with coronary artery disease: joint position paper by members of the working group on perioperative haemostasis of the society on thrombosis and haemostasis research (GTH), the working group on perioperative coagulation of the Austrian society for anesthesiology, resuscitation and intensive care (OGARI) and the working group thrombosis of the European society for cardiology (ESC). *Thromb Haemost* 105: 743–749.
- Kubitza, D., Becka, M., Roth, A. and Mueck, W. (2008) Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin* 24: 2757–2765.
- Kubitza, D., Becka, M., Voith, B., Zuehlsdorf, M. and Wensing, G. (2005a) Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 78: 412–421.
- Kubitza, D., Becka, M., Wensing, G., Voith, B. and Zuehlsdorf, M. (2005b) Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct factor Xa inhibitor—after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 61: 873–880.
- Lamberts, M., Olesen, J., Ruwald, M., Hansen, C., Karasoy, D., Kristensen, S. *et al.* (2012) Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 126: 1185–1193.
- Lip, G., Frison, L., Halperin, J. and Lane, D. (2011) Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 57: 173–180.
- Lip, G., Nieuwlaat, R., Pisters, R., Lane, D. and Crijns, H. (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 137: 263–272.
- Mahaffey, K., Stevens, S., White, H., Nessel, C., Goodman, S., Piccini, J. *et al.* (2014) Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial. *Eur Heart J* 35: 233–241.
- Maisel, W. and Stevenson, L. (2003) Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 91: 2D–8D.
- Martínez-Rubio, A., Dan, G. and Kaski, J. (2014) Rivaroxaban and stroke prevention in patients with atrial fibrillation: new evidence. *Expert Rev Cardiovasc Ther* 12: 933–947.
- Miyasaka, Y., Barnes, M., Gersh, B., Cha, S., Bailey, K., Abhayaratna, W. *et al.* (2006) Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 114: 119–125.
- Morocutti, C., Amabile, G., Fattannoposta, F., Nicolosi, A., Matteoli, S., Trappolini, M. *et al.*; for the SIFA (Studio Italiano Fibrillazione Atrial) Investigators. (1997) Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. *Stroke* 28: 1015–1021.
- Movahed, M., Hashemzadeh, M. and Jamal, M. (2005) Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 105: 315–318.
- Murphy, N., Simpson, C., Jhund, P., Stewart, S., Kirkpatrick, M., Chalmers, J. *et al.* (2007) A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart* 93: 606–612.
- Nagarakanti, R., Ezekowitz, M., Oldgren, J., Yang, S., Chernick, M., Aikens, T. *et al.* (2011) Dabigatran versus warfarin in patients with atrial fibrillation:

- an analysis of patients undergoing cardioversion. *Circulation* 123: 131–136.
- Nessel, C., Mahaffey, K., Piccini, J., Pan, G., Patel, M., Becker, R. *et al.* (2012) Incidence and outcomes of gastrointestinal hemorrhage in patients with atrial fibrillation treated with rivaroxaban or warfarin: results from the ROCKET AF trial. *Chest* 142: 84A.
- Nieminen, M., Brutsaert, D., Dickstein, K., Drexler, H., Follath, F., Harjola, V. *et al.* (2006) EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients—description of population. *Eur Heart J* 27: 2725–2736.
- Olesen, J., Lip, G., Lane, D., Kober, L., Hansen, M., Karasoy, D. *et al.* (2012) Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med* 125: e13–e23.
- Owan, T., Hodge, D., Herges, R., Jacobsen, S., Roger, V. and Redfield, M. (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 355: 251–259.
- Paikin, J., Wright, D., Crowther, M., Mehta, S. and Eikelboom, J. (2010) Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. *Circulation* 121: 2067–2070.
- Patel, M., Hellkamp, A., Lokhnygina, Y., Piccini, J., Zhang, Z., Mohanty, S. *et al.* (2013) Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 61: 651–658.
- Patel, M., Mahaffey, K., Garg, J., Pan, G., Singer, D., Hacke, W. *et al.* (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365: 883–891.
- Piccini, J., Garg, J., Patel, M., Lokhnygina, Y., Goodman, S., Becker, R. *et al.*; ROCKET-AF Investigators. (2014) Management of major bleeding events in patients treated with rivaroxaban versus warfarin: results from the ROCKET-AF trial. *Eur Heart J* 35: 1873–1880.
- Piccini, J., Hernandez, A., Zhao, X., Patel, M., Lewis, W., Peterson, E. *et al.* (2009) Quality of care for atrial fibrillation among patients hospitalized for heart failure. *J Am Coll Cardiol* 54: 1280–1289.
- Piccini, J., Stevens, S., Lokhnygina, Y., Patel, M., Halperin, J., Singer, D. *et al.* (2013) Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol* 61: 1998–2006.
- Pisters, R., Lane, D., Nieuwlaat, R., de Vos, C., Crijns, H. and Lip, G. (2010) A novel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138: 1093–1100.
- ROCKET AF Study Investigators. (2010) 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* 159: 340–347.
- Rooke, T., Hirsch, A., Misra, S., Sidawy, A., Beckman, J., Findeiss, L. *et al.* (2011) ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 58: 2020–2045.
- Rose, A., Hylek, E., Ozonoff, A., Ash, A., Reisman, J. and Berlowitz, D. (2010) Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *J Thromb Haemost* 8: 2182–2191.
- Ruff, C., Giugliano, R., Braunwald, E., Hoffman, E., Deenadayalu, N., Ezekowitz, M. *et al.* (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 383: 955–962.
- Saxena, R. and Koudstaal, P. (1995) Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 1: CD000185.
- Schmitt, J., Duray, G., Gersh, B. and Hohnloser, S. (2009) Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 30: 1038–1045.
- Schulman, S. and Kearon, C. (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 3: 692–694.
- Sherwood, M., Douketis, J., Patel, M., Piccini, J., Hellkamp, A., Lokhnygina, Y. *et al.* (2014) Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 129: 1850–1859.
- Sherwood, M., Nessel, C., Hellkamp, A., Mahaffey, K., Piccini, J., Suh, E. *et al.* (2015) Gastrointestinal bleeding in patients with atrial fibrillation treated

- with rivaroxaban or warfarin. *J Am Coll Cardiol* 66: 2271–2281.
- Siegel, D. and Crowther, M. (2013) Acute management of bleeding in patients on novel oral anticoagulants. *Eur Heart J* 34: 489–498.
- Singer, D., Albers, G., Dalen, J., Go, A., Halperin, J. and Manning, W. (2004) Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126(Suppl): 429S–456S.
- Singer, D., Chang, Y., Fang, M., Borowsky, L., Pomernacki, N., Udaltsova, N. *et al.* (2009) The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 151: 297–305.
- Steinberg, B., Hellkamp, A., Lokhnygina, Y., Halperin, J., Breithardt, G., Passman, R. *et al.* (2014) Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: results from the ROCKET AF trial. *Heart Rhythm* 11: 925–932.
- Stroke in Atrial Fibrillation Working Group. (2007) Independent predictors of stroke in atrial fibrillation: a systematic review. *Neurology* 69: 546–554.
- Thrift, A., Dewey, H., MacDonell, R., McNeil, J. and Donnan, G. (2001) Incidence of the major stroke subtypes initial findings from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 32: 1732–1738.
- United States Food and Drug Administration. (2011) *XARELTO (Rivaroxaban) Tablets*. Risk Evaluation and Mitigation Strategy (REMS). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000RiskR.pdf
- van Diepen, S., Hellkamp, A., Patel, M., Becker, R., Breithardt, G., Hacke, W. *et al.* (2013) Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ Heart Fail* 6: 740–747.
- Vazquez, E. and Sanchez-Perales, C. (2011) The HAS-BLED score and renal failure. *Chest* 139: 1248–1249.
- Wang, D., Li, Y., Lee, S., Wang, L., Fan, J., Zhang, G. *et al.* (2011) Ethnic differences in body composition and obesity related risk factors: study in Chinese and white males living in China. *PLoS One* 6: e19835.
- Wann, L., Curtis, A., Ellenbogen, K., Estes, M., Ezekowitz, M., Jackman, W. *et al.* (2011) ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 57: 1330–1337.
- Winkel, T., Hoeks, S., Schouten, O., Zeymer, U., Limbourg, T., Baumgartner, I. *et al.* (2010) Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg* 40: 9–16.
- Witt, D., Delate, T., Clark, N., Martell, C., Tran, T., Crowther, M. *et al.* (2009) Warfarin Associated Research Projects and other Endeavors (WARPED) Consortium. Outcomes and predictors of very stable INR control during chronic anticoagulation therapy. *Blood* 114: 952–956.
- Witt, D., Delate, T., Clark, N., Martell, C., Tran, T., Crowther, M. *et al.*; Warped Consortium. (2010) Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users. *J Thromb Haemost* 8: 744–749.
- Wong, K., Hu, D., Oomman, A., Tan, R., Patel, M., Singer, D. *et al.* (2014) Rivaroxaban for stroke prevention in East Asia patients from the ROCKET AF trial. *Stroke* 45: 1739–1747.
- Wong, C., White, H., Wilcox, R., Criger, D., Califf, R., Topol, E. *et al.* (2002) Management and outcome of patients with atrial fibrillation during acute myocardial infarction: the GUSTO-III experience. *Heart* 88: 357–362.
- Yuen, E., Gueorguieva, I., Wise, S., Soon, D. and Aarons, L. (2010) Ethnic differences in the population pharmacokinetics and pharmacodynamics of warfarin. *J Pharmacokinet Pharmacodyn* 37: 3–24.
- Zhang, L., Yang, J., Hong, Z., Yuan, G., Zhou, B., Zhao, L. *et al.*; Collaborative Group of China Multicenter Study of Cardiovascular Epidemiology. (2003) Proportion of different subtypes of stroke in China. *Stroke* 34: 2091–2096.
- Zhao, F., Loke, C., Rankin, S., Guo, J., Lee, H., Wu, T. *et al.* (2004) Novel CYP2C9 genetic variants in Asian subjects and their influence on maintenance warfarin dose. *Clin Pharmacol Ther* 76: 210–219.