REVIEW ARTICLE

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Editor's Choice

Stroke prevention with rivaroxaban in higher-risk populations with atrial fibrillation

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SUMMARY

Background: Atrial fibrillation (AF), the most common cardiac arrhythmia, is a major risk factor for stroke. Rivaroxaban, an oral factor Xa inhibitor, is approved for the prevention of stroke in patients with non-valvular AF. In the pivotal phase III trial ROCKET AF, rivaroxaban demonstrated non-inferiority compared with warfarin for reducing the risk of stroke or systemic embolism (SE) in patients with AF (intention-to-treat analysis), without an increased risk of major bleeding. Superior efficacy vs. warfarin was achieved while patients were on study medication. Other direct oral factor Xa inhibitors have completed phase III clinical trials in this indication. Compared with warfarin, apixaban (in the ARISTOTLE trial) and edoxaban (in the ENGAGE-AF trial) were shown to be superior or non-inferior, respectively, for reduction in stroke or SE risk in patients with AF. Baseline stroke risk, as indicated by $CHADS_2$ scores, was lower in patients in the ARISTOTLE and ENGAGE-AF trials than in ROCKET AF. **Objectives:** This review discusses the main findings from ROCKET AF, specifically examining recent subgroup analyses investigating rivaroxaban use across various patient types at high risk for adverse outcomes, including those with prior stroke or transient ischaemic attack, reduced renal function, prior myocardial infarction, peripheral artery disease, heart failure or patients aged ≥ 75 years and those resident in East Asia. **Conclusions:** These subgroup analyses demonstrate that the treatment effect for rivaroxaban vs. warfarin is broadly consistent across a wide range of patient groups, with respect to both efficacy and safety.

Review criteria

This review summarises findings from most of the subgroup analyses published to date from ROCKET AF (1), a phase III trial comparing rivaroxaban with warfarin for stroke risk reduction in patients with atrial fibrillation, with particular emphasis on patient subgroups at increased risk of thromboembolic or haemorrhagic events. Factors associated with intracranial haemorrhage and mortality in ROCKET AF are also reviewed.

Message for the clinic

Although the risk for thromboembolic or bleeding events varies across different patient subgroups, the relative treatment effect of rivaroxaban compared with warfarin is broadly consistent across a wide range of different patient groups with respect to both efficacy and safety – a finding that supports the use of rivaroxaban across the wide range of patients encountered in clinical practice. Nonetheless, selection of therapy must always be individualised for the particular circumstances of each patient.

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Introduction

Atrial fibrillation (AF) is thought to affect ~3 million individuals in the USA and > 6 million across Europe, with a global prevalence of ~1.5–2.0% of the general population. AF increases the risk of stroke by approximately fivefold (2–5) and accounts for approximately one in every six strokes (~15%) (6). As such, the condition imposes a significant socio-economic burden on patients and healthcare systems, and patients with AF require ongoing anticoagulant therapy to reduce the risk of stroke or systemic embolism (SE).

The novel oral anticoagulants

The well-documented limitations associated with the vitamin K antagonists (VKAs) (7–9), including an increased risk of intracranial haemorrhage (ICH) (10,11), have driven the development of novel oral anticoagulants (NOACs) that directly target specific components of the coagulation cascade and, compared with the VKAs, have been shown to have predictable pharmacology and a wider therapeutic window. These attributes permit fixed dosing without the need for routine coagulation monitoring. These NOACs include the direct thrombin inhibitor dabigatran (Pradaxa®), and the direct inhibitors of activated factor X rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Savaysa®).

Dabigatran, rivaroxaban and apixaban are approved for stroke risk reduction in patients with AF in numerous countries worldwide, including approval by the European Medicines Agency in Europe and the US Food and Drug Administration in the USA. These approvals were granted after successful phase III trials were conducted (1,12,13), using the prevailing standard of care, warfarin, as the comparator. A summary of pharmacological attributes (Table S1) and the results of the phase III trials (Table S2) are presented in Data S1.

Disclosures

HCD served as the national Principal Investigator of ROCKET AF in Germany. He received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daichii-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen-Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth and Yamanouchi. Financial support for research projects was provided by Astra Zeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of

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Key results from the phase III three trials for dabigatran, apixaban and edoxaban (Table S2) provide context for the ensuing discussion of rivaroxaban data (below). All three drugs (dabigatran, apixaban and edoxaban) were non-inferior to warfarin with regard to reduction in stroke and SE. Dabigatran (150 mg twice daily) and apixaban (5 mg twice daily) achieved statistical superiority in an intention-to-treat (ITT) analysis. In addition, all evaluated doses of all three drugs significantly reduced the incidence of ICH vs. warfarin.

Methods

The corresponding author for this paper (H-CD) was the national Principal Investigator for 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) in Germany; the remaining three authors (JLH, KF, GJH) all served on the Executive Steering Committee of ROCKET AF. As such, the authors have been intimately involved with the ongoing subanalyses of ROCKET AF.

This review assembled the efficacy and safety data for published subgroup analyses in higher-risk populations and examined the clinical implications of any treatment–comorbidity interactions (or lack thereof) to provide an overview of all data relating to the potential use of rivaroxaban for stroke risk reduction in patients with AF. In particular, this review will focus on the use of rivaroxaban in patient subgroups likely to have an elevated risk of ischaemic or bleeding events, including the relative effects of rivaroxaban vs. warfarin, to support clinical decision-making when initiating anticoagulant therapy.

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor that has been evaluated and approved for stroke risk reduction in AF. The approval was based on the results of ROCKET AF (1). Results from this phase III registration trial are presented in Data S2.

In summary, rivaroxaban, compared with warfarin, significantly reduced the incidence of haemorrhagic stroke and ICH, the most feared complication of anticoagulant therapy. These findings were consistent for all the NOACs (Table S2). The rates of stroke and SE were significantly reduced with rivaroxaban while patients were receiving study drug. The incidence of gastrointestinal (GI) bleeding was significantly increased but rates of critical-site bleeding and fatal bleeding were significantly reduced. Overall, rates of major bleeding were similar between treatment groups. These data suggest a favourable benefit–risk balance for rivaroxaban and, as a result, rivaroxaban is now approved for stroke prevention/risk reduction in patients with non-valvular AF and with one or more stroke risk factors (14).

Stroke prophylaxis with rivaroxaban among high-risk patients

The increased risk of events seen in selected patient subgroups from ROCKET AF irrespective of treatment assignment, e.g. those with particular comorbidities, is shown in Table 1. For example, prior stroke increases the risk of a recurrent stroke/SE, and renal impairment increases the risk of both ischaemic and haemorrhagic events. This paper will review key subgroup analyses from ROCKET AF to facilitate appropriate management of rivaroxaban therapy in these high-risk patient subgroups.

Patients with prior transient ischaemic attack or stroke

Patients with AF who have experienced a prior stroke or transient ischaemic attack (TIA) face increased risks of both recurrent stroke and bleeding (15,16). A prespecified subgroup analysis investigated whether the relative benefits and risks of rivaroxaban compared with warfarin differed for the 7468 (52%) patients who had a previous stroke ($n = 4907$) or TIA ($n = 2561$) compared with the 6796 (48%) patients who had no previous stroke/TIA (17). As expected, the absolute rate of stroke or SE was higher in patients with a prior stroke/TIA than in those without a prior stroke/TIA. However, the relative effect of rivaroxaban compared with warfarin was consistent among patients with a previous stroke/TIA [2.79% rivaroxaban vs. 2.96% warfarin; hazard ratio (HR): 0.94; 95% confidence interval (CI): 0.77–1.16] and those without a previous stroke/TIA (1.44% and 1.88% respectively; HR: 0.77; 95% CI: 0.58–1.01; interaction $p = 0.23$). Consistent results were obtained in an on-treatment analysis (Table 2). Among the secondary efficacy end-points evaluated, the only significant interaction between treatment and history of stroke was with regard to fatal stroke; the incidence of which, compared with warfarin, was markedly reduced with rivaroxaban among patients without prior stroke/TIA but not among those with prior stroke/TIA. Overall, rivaroxaban reduced the risk of stroke or SE to a comparable degree vs. warfarin, regardless of the history of previous stroke/TIA.

Regarding safety (Table 3), the absolute rate of major and non-major clinically relevant (NMCR) bleeding was lower among patients with prior stroke/

Table 1 Event rates observed in ROCKET AF in key patient subgroups (rivaroxaban and warfarin treatment arms combined)

	With comorbidity		Without comorbidity		With comorbidity vs. without HR (95% CI)	
	Stroke or SE	Major bleeding	Stroke or SE	Major bleeding	Stroke or SE	Major bleeding
Comorbid conditions						
Prior stroke/TIA[†] (17)	2.87	3.18	1.66	3.89	**1.70 (1.44–2.02)***	**0.81 (0.70–0.93)****
Renal impairment (CrCl 30–49 ml/min)[‡,§] (19)	2.95/3.44	4.49/4.70	1.92/2.16	3.39/3.17	NR	NR
Age ≥ 75 years[†] (23)	2.29/2.85	4.86/4.40	2.00/2.10	2.69/2.79	NR	NR
Prior MI[§] (24)	1.91	4.14	1.93	3.4	0.99 (0.77–1.28)	**1.21 (1.02–1.45)*****
Heart failure[†] (28)	1.99	NR[¶]	2.32	NR	0.94 (0.78–1.13)	NR
Baseline PAD[†] (26)	2.41	4.74	2.09	3.45	1.04 (0.72–1.50)	1.16 (0.88–1.53)
Other patient subgroups	**East Asia resident**		**Non-East Asia resident**		**East Asia vs. non-East Asia resident HR (95% CI)**	
Residence in East Asia[†] (29)	2.63/3.38	3.44/5.14	2.09/2.35	3.61/3.35	1.34 (1.00–1.80)	1.23 (0.94–1.60)

CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; SE, systemic embolism; TIA, transient ischaemic attack. Event rates are shown as per cent per year. All safety results are 'on-treatment' analyses. Results shown as X/Y are for rivaroxaban/warfarin where event rates irrespective of treatment assignment are not reported. **Results in bold** indicate significant differences. *$p < 0.0001$, **$p < 0.005$, ***$p < 0.05$. [†]Efficacy results from intention-to-treat analysis. [‡]Rivaroxaban dose of 20 mg daily in patients with CrCl ≥ 50 ml/min and 15 mg daily in patients with CrCl 30–49 ml/min. [§]Efficacy results from per protocol analysis. [¶]Data reported for major bleeding plus non-major clinically relevant bleeding. Data for major bleeding alone were not reported.

Table 2 Key efficacy results from the ROCKET AF prior stroke/TIA subanalysis (17)

	With prior stroke or TIA (*N* = 7468)			Without prior stroke or TIA (*N* = 6729)			
End-point	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value*
Stroke or SE	2.26	2.60	0.87 (0.69–1.10)	1.09	1.69	0.65 (0.47–0.90)	0.15
Any stroke	2.21	2.37	0.93 (0.73–1.19)	1.06	1.53	0.69 (0.49–0.97)	0.16
Ischaemic or unknown stroke	1.86	1.92	0.97 (0.74–1.27)	0.89	1.11	0.80 (0.55–1.16)	0.41
Haemorrhagic stroke	0.35	0.47	0.74 (0.42–1.32)	0.17	0.41	0.40 (0.19–0.87)	0.22
MI	0.89	0.86	1.04 (0.70–1.54)	0.93	1.39	0.67 (0.47–0.96)	0.11
Disabling stroke (MRS 3–5)	0.54	0.70	0.77 (0.48–1.24)	0.22	0.31	0.73 (0.35–1.53)	0.90
Fatal stroke	0.61	0.61	1.00 (0.63–1.60)	0.22	0.57	**0.39 (0.20–0.75)**	**0.02**
All-cause death	1.74	2.07	0.84 (0.64–1.10)	2.00	2.35	0.85 (0.66–1.10)	0.94

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; MRS, modified Rankin scale; SE, systemic embolism; TIA, transient ischaemic attack. On-treatment analysis in the safety population. *p-value is for the interaction between treatment effect (rivaroxaban vs. warfarin) and presence or absence of history of prior stroke or TIA. **Results in bold** indicate a significant interaction between treatment effect and presence or absence of history of prior stroke or TIA.

TIA (13.31% vs. 13.87% per year for rivaroxaban and warfarin respectively) than among patients without prior stroke/TIA (16.69% vs. 15.19% per year for rivaroxaban and warfarin respectively; HR: 1.10). No significant interactions between treatment group and history of prior stroke/TIA were identified with regard to safety outcomes evaluated, including ICH and fatal bleeding.

Table 3 Key safety results from the ROCKET AF prior stroke/TIA subanalysis (17)

	With prior stroke or TIA			Without prior stroke or TIA			
Outcome	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value*
Major plus non-major clinically relevant bleeding	13.31	13.87	0.96 (0.87–1.07)	16.69	15.19	1.10 (0.99–1.21)	0.08
Major bleeding	3.13	3.22	0.97 (0.79 –1.19)	4.10	3.69	1.11 (0.92–1.34)	0.36
ICH	0.59	0.80	0.74 (0.47–1.15)	0.39	0.68	0.57 (0.34–0.97)	0.47
Fatal bleeding	0.26	0.49	0.54 (0.29–1.00)	0.22	0.48	0.46 (0.23–0.90)	0.74

CI, confidence interval; HR, hazard ratio; ICH, intracranial haemorrhage; TIA, transient ischaemic attack. Analysis in the safety on-treatment population. *p-value is for the interaction between treatment effect (rivaroxaban vs. warfarin) and presence or absence of history of prior stroke or TIA.

These data confirm that the relative efficacy and safety of rivaroxaban and warfarin in patients with AF and prior stroke/TIA were consistent with the relative efficacy and safety in patients without prior stroke/TIA and in the overall trial population (Tables S3 and S4). These data also support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent, as well as first, stroke in patients with AF.

Patients with mild/moderate renal impairment

In the ROCKET AF study population, renal dysfunction was confirmed as a potent predictor of stroke and SE (18). In a multivariate analysis (Cox proportional hazards modelling), reduced creatinine clearance (CrCl; < 50 ml/min) was the second most important predictor of stroke and SE after prior TIA or stroke. The 2950 patients with moderate renal impairment (CrCl 30–49 ml/min) had higher absolute rates of stroke and SE and major and NMCR bleeding than the 11,277 patients with CrCl ≥ 50 ml/min, irrespective of whether they were treated with warfarin or with rivaroxaban (19). In addition, renal dysfunction has been previously recognised as a significant risk factor for major bleeding and is included in the HAS-BLED algorithm for estimating bleeding risk in patients with AF (20).

Because rivaroxaban is partially eliminated via the kidneys, its pharmacokinetics are affected by renal impairment (21). As renal function declines, rivaroxaban plasma concentrations and the area under the plasma concentration–time curve (AUC) increase. However, renal dysfunction has only a moderate effect on rivaroxaban clearance. Nonetheless, to ensure equivalent exposures in patients with and without renal impairment, pharmacokinetic modelling was performed on a simulated AF patient population (22). The results indicated approximately equivalent exposures in patients with normal renal function receiving 20 mg once-daily rivaroxaban and those with moderate renal impairment (CrCl 30–49 ml/min) receiving 15 mg once-daily rivaroxaban in terms of both AUC_{24} (AUC over 24 h) and rivaroxaban plasma concentration. Hence, patients randomised to rivaroxaban in ROCKET AF and with baseline moderate renal impairment (CrCl 30–49 ml/min) received a reduced dose of rivaroxaban of 15 mg once daily.

The relative effects of rivaroxaban vs. warfarin, in terms of the rates of stroke or SE, were consistent among patients with moderate renal impairment (2.32% per year rivaroxaban vs. 2.77% per year warfarin; HR: 0.84) and patients without moderate renal impairment (CrCl ≥ 50 ml/min; 1.57% and 2.00% per year respectively; HR: 0.78; interaction p = 0.76) while on treatment (Table 4) (19). Consistent results were also observed in an ITT analysis (19). Hence, as expected, rates of stroke/SE were mildly elevated in patients with moderate renal impairment but no interaction between treatment and renal function was detected, indicating that the treatment effect of rivaroxaban vs. warfarin was consistent in patients with and without renal impairment. Similarly, no interaction was detected for ischaemic or haemorrhagic stroke (Table 4).

Rates of major plus NMCR bleeding and rates of major bleeding were increased in patients with moderate renal impairment relative to those with CrCl ≥ 50 ml/min, but again no interaction between treatment and renal function was detected; this was also the case for ICH and for fatal bleeding (Table 4).

These results indicate that for both efficacy and safety outcomes the relative effect of rivaroxaban compared with warfarin is maintained in patients with and without moderate renal impairment. Furthermore, these results demonstrate that the reduced

Table 4 Key results from the ROCKET AF renal impairment subanalysis (19)

	Moderate renal impairment*			Mild or no renal impairment†			
End-point	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value
Stroke or SE (primary efficacy end-point)	2.32	2.77	0.84 (0.57–1.23)	1.57	2.00	0.78 (0.63–0.98)	0.76
Ischaemic stroke	1.98	1.78	1.11 (0.71–1.73)	1.20	1.34	0.90 (0.69–1.16)	0.41
Haemorrhagic stroke	0.29	0.52	0.56 (0.21–1.51)	0.26	0.42	0.62 (0.37–1.03)	0.88
Major plus NMCR bleeding (principal safety outcome)	17.82	18.28	0.98 (0.84–1.14)	14.24	13.67	1.04 (0.96–1.13)	0.45
Major bleeding	4.49	4.70	0.95 (0.72–1.26)	3.39	3.17	1.07 (0.91–1.26)	0.48
ICH	0.71	0.88	0.81 (0.41–1.60)	0.44	0.71	0.62 (0.42–0.92)	0.51
Fatal bleeding	0.28	0.74	0.39 (0.15–0.99)	0.23	0.43	0.55 (0.32–0.93)	0.53

CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; ICH, intracranial haemorrhage; NMCR, non-major clinically relevant; od, once daily; SE, systemic embolism. Efficacy analyses are in the per protocol on-treatment population. Moderate renal impairment: rivaroxaban, $N = 1474$; warfarin, $N = 1476$. For mild or no renal impairment: rivaroxaban, $N = 5637$; warfarin, $N = 5640$. *Patients with moderate renal impairment (CrCl 30–49 ml/min). Patients randomised to rivaroxaban received 15 mg od. †Patients without renal impairment (CrCl ≥ 50 ml/min). Patients randomised to rivaroxaban received 20 mg od.

rivaroxaban dose of 15 mg once daily is effective and safe in patients with AF and moderate renal impairment, thus providing an additional option for stroke prophylaxis in such patients (19).

Elderly patients

The absolute risk of stroke in patients with AF increases with age (5), as does the risk of bleeding complications with oral anticoagulation (20). Elderly patients frequently have multiple comorbidities and concomitant medications, which may be a particular concern for VKA use. It is thus essential to ensure the potential benefit of any NOAC is maintained in this important subgroup. A prespecified subgroup analysis was therefore conducted comparing the treatment effect (efficacy and safety) of rivaroxaban vs. warfarin in patients < 75 years of age with those aged ≥ 75 years (23).

In ROCKET AF, 6229 patients (44%) were aged ≥ 75 years. As expected, event rates were higher in the older age group vs. patients aged < 75 years for both stroke/SE (2.57% vs. 2.05% per year respectively; $p = 0.007$) and major bleeding (4.63% vs. 2.74% per year; $p < 0.0001$) (23). Results for the efficacy and safety of rivaroxaban vs. warfarin within the two age groups are shown in Table 5.

No effect of age on the relative efficacy of rivaroxaban vs. warfarin was noted, indicated by the lack of any significant interactions. Regarding safety, elderly patients (≥ 75 years) treated with rivaroxaban experienced a higher incidence of major plus NMCR bleeding events, compared with warfarin, whereas no significant difference was observed for younger patients (aged < 75 years), resulting in an interaction p-value of 0.009. This interaction was driven by GI bleeding which, in elderly patients, occurred more often in the rivaroxaban treatment group than in the warfarin group. However, importantly, no effect of age on treatment effect was noted for major bleeding, ICH or fatal bleeding, suggesting that the excess GI bleeding in older patients was mostly NMCR bleeding, not major bleeding.

Thus, in summary, apart from a modest increase in NMCR GI bleeding in patients aged ≥ 75 years, there was no observed effect of age on the relative effect of rivaroxaban vs. warfarin for any other evaluated efficacy or safety outcome.

Patients with prior myocardial infarction

Patients with AF often have concomitant coronary artery disease and may therefore be taking antiplatelet drugs, such as acetylsalicylic acid, which can increase the risk of bleeding. Of the patients enrolled in ROCKET AF, 17.3% had a prior myocardial infarction (MI) at baseline; a prespecified subgroup analysis was therefore conducted to evaluate results in patients with and without prior MI (24). The results of this subgroup analysis are presented in Data S3.

In summary, patients with AF and prior MI treated with rivaroxaban experienced higher NMCR bleeding compared with warfarin but, relative to warfarin, other benefits of rivaroxaban therapy (especially results for stroke/SE, ICH and fatal bleeding) were consistent with the results of the main trial and

Table 5 Key results from the ROCKET AF elderly subanalysis (23)

	Age ≥ 75 years			Age < 75 years			
End-point	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value*
Stroke or SE (primary efficacy end-point)†	2.29	2.85	0.80 (0.63–1.02)	2.00	2.10	0.95 (0.76–1.19)	0.31
Ischaemic stroke	1.71	1.95	0.88 (0.67–1.16)	1.55	1.40	1.10 (0.84–1.44)	0.24
Haemorrhagic stroke	0.34	0.49	0.70 (0.39–1.25)	0.19	0.41	0.47 (0.25–0.89)	0.37
Major plus NMCR bleeding (principal safety outcome)‡	19.83	17.55	**1.13 (1.02–1.25)**	11.58	12.43	**0.93 (0.84–1.04)**	**0.009**
Major bleeding	4.86	4.40	1.11 (0.92–1.34)	2.69	2.79	0.964 (0.78–1.19)	0.34
Intracerebral haemorrhage	0.66	0.83	0.80 (0.50–1.28)	0.37	0.68	0.54 (0.33–0.89)	0.27
Fatal bleeding	0.28	0.61	0.45 (0.23–0.87)	0.22	0.39	0.55 (0.29–1.05)	0.68

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NMCR, non-major clinically relevant; SE, systemic embolism.
*Interaction p-value refers to the interaction between treatment (rivaroxaban vs. warfarin) and age (≥ 75 years or < 75 years). **Results in bold** indicate a significant interaction between treatment effect and age (≥ 75 years or < 75 years). †Efficacy end-points are from the ITT analysis (≥ 75 years, $N = 6164$; < 75 years, $N = 8007$). ‡Safety outcomes are from the safety population (≥ 75 years, $N = 6215$; < 75 years, $N = 8021$).

were unaffected by history of MI. These results suggest that rivaroxaban is an effective alternative for stroke risk reduction in patients with AF, irrespective of MI history. However, rivaroxaban must not be used at the stroke prophylaxis dose (20 mg once daily) in patients with AF and concurrent acute coronary syndrome (14), although further clinical studies are ongoing, e.g. the PIONEER AF-PCI study (ClinicalTrials.gov NCT01830543).

Patients with peripheral artery disease

Several studies (for example that by Olesen et al. (25)) have suggested that assessment of peripheral artery disease (PAD) may have a role to play in improving stroke risk prediction for patients with AF. A *post hoc* subgroup analysis was therefore conducted in patients with a baseline diagnosis of PAD (26). The results are presented and discussed in Data S4.

Patients with or without prior VKA experience

A further prespecified subgroup analysis was conducted to evaluate the relative treatment effect of rivaroxaban vs. warfarin in patients who had received prior VKA therapy (VKA experienced) vs. those who had not (VKA naïve) (27). This analysis and its results are presented in Data S5.

Overall, the results supported the protocol used in ROCKET AF for transitioning patients from VKA to rivaroxaban therapy, which was to commence rivaroxaban and discontinue VKA when the international normalised ratio fell below 3.0. Furthermore, the results suggest that rivaroxaban may be a useful alternative to warfarin, although the individual circumstances of the patient must always be considered.

Patients with heart failure

Heart failure (HF) is a recognised risk factor for thromboembolic events in patients with AF and is included in risk scores such as $CHADS_2$. HF may also increase the risk of bleeding in patients receiving VKAs. In the light of these considerations, a subgroup analysis was conducted to assess the treatment effect of rivaroxaban vs. warfarin in patients with and without HF (28).

Of the patients enrolled in ROCKET AF, 9033 (63.7%) had HF (for this subanalysis, HF was defined as a prior history of HF or a left ventricular ejection fraction < 40%). Compared with patients without HF, patients with HF were more likely to be younger (72 vs. 74 years), to have a higher risk of stroke or SE ($CHADS_2$ score 3.7 vs. 3.2) and to have a prior MI (21% vs. 10%), but less likely to have a prior stroke or TIA (43% vs. 70%).

Event rates for both the primary efficacy end-point (composite of stroke or SE) and the principal safety outcome (composite of major or NMCR bleeding) were similar in patients with and without HF (HRs: 0.94 and 1.00, respectively), although the rate of all-cause death was significantly greater in patients with HF (5.26% vs. 3.37% per year; HR: 1.34; 95% CI: 1.17–1.55; $p < 0.0001$).

The relative treatment effect of rivaroxaban vs. warfarin was similar for both efficacy and safety

Table 6 Key results from the ROCKET AF subanalysis of patients with or without HF (28)

	With HF			Without HF			
End-point	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value*
Stroke or SE (primary efficacy end-point)	1.90	2.09	0.91 (0.74–1.13)	2.10	2.54	0.84 (0.65–1.09)	0.62
MI	1.09	1.21	0.94 (0.71–1.24)	0.69	0.72	0.94 (0.59–1.49)	0.99
All-cause death	5.05	5.46	0.93 (0.82–1.07)	3.20	3.54	0.89 (0.71–1.10)	0.68
Major plus NMCR bleeding (principal safety outcome)	14.22	14.02	1.05 (0.95–1.15)	16.12	15.35	1.05 (0.93–1.18)	0.99
ICH	0.40	0.65	0.63 (0.40–1.02)	0.64	0.89	0.72 (0.44–1.19)	0.71

CI, confidence interval; HF, heart failure; HR, hazard ratio; ICH, intracranial haemorrhage; ITT, intention-to-treat; NMCR, non-major clinically relevant; SE, systemic embolism. Efficacy analyses are ITT. With HF: rivaroxaban, $N = 4530$; warfarin, $N = 4503$. Without HF: rivaroxaban, $N = 2551$; warfarin, $N = 2587$. Safety analyses are in the on-treatment safety population. *Interaction p-values refer to the interaction between treatment (rivaroxaban vs. warfarin) and diagnosis of HF (with vs. without).

outcomes (including all-cause death and ICH), with no significant interactions between treatment groups and the presence or absence of HF (Table 6).

Among patients with HF, there were also no significant interactions between HF subgroups and the treatment effect of rivaroxaban vs. warfarin for either the primary efficacy end-point (stroke/SE) or the principal safety outcome (major plus NMCR bleeding). HF subgroups evaluated included left ventricular ejection fraction $\geq 40\%$ vs. $< 40\%$, New York Heart Association class I or II vs. class III or IV, and $CHADS_2$ score 2 vs. ≥ 3.

Collectively, these results indicate that the efficacy and safety treatment effects of rivaroxaban vs. warfarin are maintained across patients with and without HF, and across different subgroups of HF, suggesting that rivaroxaban may be an important alternative to VKA therapy for the growing population of patients with HF.

East Asian patients

There were no significant interactions between either the efficacy or safety outcomes of ROCKET AF and treatment received in terms of race or region (1). However, as there are important differences between Asian populations and other ethnic groups with regard to demographics, stroke type and approaches to the management of stroke risk, a *post hoc* analysis of the relative effects of rivaroxaban and warfarin was undertaken (29).

A total of 932 patients who took part in ROCKET AF were resident in East Asian countries (China, Korea, Taiwan and Hong Kong). This cohort had lower body weight and CrCl, was less likely to have used VKAs previously, and had a higher prevalence of prior stroke/TIA or SE compared with non-East Asian participants. Patients in this East Asian cohort received the same rivaroxaban dose as those in the main trial; 20 or 15 mg od for those with moderate renal impairment, in contrast to the reduced dose of 15 mg od (10 mg od for moderate renal impairment) approved in Japan (30) on the basis of the J-ROCKET trial (31). Key efficacy and safety results for this cohort are shown in Table 7.

The absolute event rate observed for stroke or SE was higher among East Asian compared with non-East Asian patients but the relative efficacy of rivaroxaban vs. warfarin was maintained in the East Asian cohort (2.6% and 3.4% per year; HR: 0.78; 95% CI: 0.44–1.39) compared with the non-East Asian cohort population (2.1% and 2.4% per year; HR: 0.89; 95% CI: 0.75–1.05; interaction $p = 0.666$). For the principal safety outcome of major or NMCR bleeding, the overall event rate was significantly higher among the East Asian cohort compared with the non-East Asian cohort (HR: 1.42; 95% CI: 1.25–1.62; $p < 0.0001$), irrespective of treatment assignment, but there was no impact on the relative risk for rivaroxaban compared with warfarin (20.9% vs. 20.7% per year; HR: 1.01; 95%: CI: 0.79–1.30; interaction $p = 0.867$). Consistent with the results of the overall ROCKET AF patient population, rivaroxaban treatment was associated with a reduction in critical organ bleeding in the East Asian cohort compared with warfarin (0.7% vs. 2.6% per year respectively; HR: 0.28; 95% CI: 0.10–0.75). ICH with rivaroxaban was also significantly reduced relative to warfarin (0.6% vs. 2.5% per year; HR: 0.24; 95% CI: 0.08–0.71) among East Asian patients.

Table 7 Key results from the ROCKET AF subanalysis of patients within or outside East Asia (29)

	East Asia			Non-East Asia			
End-point	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Rivaroxaban (%/year)	Warfarin (%/year)	HR (95% CI)	Interaction p-value*
Stroke or SE (primary efficacy end-point)	2.63	3.38	0.78 (0.44–1.39)	2.09	2.35	0.89 (0.75–1.05)	0.666
Ischaemic stroke	2.12	2.24	N/A	1.59	1.60	N/A	0.886
Haemorrhagic stroke	0.49	1.24	0.40 (0.13–1.27)	0.24	0.39	N/A	0.493
MI	0.99	0.99	1.00 (0.38–2.66)	1.02	1.12	N/A	0.855
All-cause death	2.58	3.57	0.73 (0.41–1.27)	4.65	5.00	N/A	0.392
Major plus NMCR bleeding (principal safety outcome)†	20.90	20.65	1.01 0.79–1.30)	14.54	14.13	1.03 (0.96–1.11)	0.867
Major bleeding	3.44	5.14	N/A	3.61	3.35	N/A	0.084
ICH	0.59	2.46‡	**0.24 (0.08–0.71)**	0.49	0.63‡	N/A	**0.044**
Fatal bleeding	0.15	1.01	0.14 (0.02–1.16)	0.25	0.45	N/A	0.223

CI, confidence interval; HR, hazard ratio; ICH, intracranial haemorrhage; MI, myocardial infarction; N/A, not available or not published; NMCR, non-major clinically relevant; SE, systemic embolism. Efficacy analyses are ITT. East Asia: rivaroxaban, $N = 468$; warfarin, $N = 464$. Non-East Asia: rivaroxaban, $N = 6613$; warfarin, $N = 6626$. Safety analyses are in the on-treatment safety population. Analyses have not been corrected for multiplicity. *Interaction p-values refer to the interaction between treatment (rivaroxaban vs. warfarin) and residence in East Asia (within vs. outside). **Results in bold** indicate a significant interaction between treatment effect and residence within or outside East Asia. †East Asia vs. non-East Asia, irrespective of treatment assignment; HR: 1.42 (95% CI: 1.25–1.62); $p < 0.0001$. ‡Among patients assigned to warfarin the rate of ICH was significantly higher in East Asian than in non-East Asian patients; HR: 3.89 (95% CI: 2.29–6.63); $p < 0.0001$.

However, there was a significant interaction between treatment assignment and residence in or outside East Asia (interaction $p = 0.044$). For patients receiving rivaroxaban there was no significant difference in rates of ICH between East Asian and non-East Asian patients (0.6% vs. 0.5% per year; $p = 0.73$). Conversely, East Asian patients receiving warfarin experienced a significantly higher rate of ICH than non-East Asian patients (2.5% vs. 0.6% per year; HR: 3.89; 95% CI: 2.29–6.63; $p < 0.0001$).

The results of this *post hoc* analysis show that despite higher thromboembolic and bleeding event rates in East Asian patients, the treatment effect of rivaroxaban relative to warfarin was maintained for both efficacy and safety. The reduction in critical organ bleeding observed with rivaroxaban, combined with an almost fourfold increase in ICH in East Asian patients compared with non-East Asian patients receiving warfarin, strongly suggests that rivaroxaban can provide a safer alternative for stroke prophylaxis than the VKAs in the East Asian population.

Other patient subgroups

In addition to those discussed above, various baseline characteristics were evaluated for any potential relationship with treatment and outcomes (1). No statistically significant interactions between treatment group (rivaroxaban or warfarin) and baseline $CHADS_2$ score, type of AF, hypertension, diabetes or geographical region were noted for either efficacy or safety outcomes.

Predictors of bleeding and mortality

Although not analysed as a specific subgroup above, patients at an increased risk of bleeding or death warrant particular consideration.

Intracranial haemorrhage

The most feared complication of anticoagulation is ICH. Approximately 50% of patients with warfarin-associated ICH die within 30 days. Although there is agreement that urgent reversal of anticoagulation is necessary, opinions differ as to how that should be achieved (32).

In ROCKET AF, rates of ICH were significantly reduced with rivaroxaban vs. warfarin (0.49% vs. 0.74% per year; HR: 0.67; $p = 0.019$) (Table S4), a finding that has also been consistently observed in other trials of NOACs vs. warfarin in patients with AF (Table S2). Significant independent predictors of ICH in the ROCKET AF cohort were shown to be race (Asian or Black), reduced serum albumin, reduced platelet count, prior stroke/TIA and

increased diastolic blood pressure (33). Conversely, randomisation to rivaroxaban and a history of HF were associated with a reduced risk of ICH.

Major bleeding

Algorithms such as HAS-BLED (20) have been developed to assess the risk of bleeding in patients with AF, although the predictive value of such schemes was lower when applied to the ROCKET AF cohort compared with the original derivation cohorts (34). However, ROCKET AF excluded patients with active internal bleeding, an increased risk of bleeding or a history of clinically significant bleeding (for example, GI bleeding within the preceding 6 months), and patients with baseline CrCl < 30 ml/min (34).

In ROCKET AF, overall rates of major bleeding were similar between the two treatment groups (3.6% vs. 3.4% per year) (Table S4). However, types of major bleeding were not equivalent between the two treatments. GI bleeding was significantly increased with rivaroxaban compared with warfarin, but critical-site bleeding and fatal bleeding were significantly reduced, in addition to the reduction in ICH (Table S4). Regarding GI bleeding, the most serious events (those requiring transfusion of ≥ 4 units) were balanced between the treatment groups. Fatal GI haemorrhages occurred in one patient in the rivaroxaban treatment group and in five patients randomised to warfarin (35).

In a recent analysis (34), factors independently associated with increased major bleeding were increasing age, baseline diastolic blood pressure ≥ 90 mmHg, history of chronic obstructive pulmonary disease, prior GI bleeding, prior acetylsalicylic acid use and anaemia. Assigned study drug was not independently associated with major bleeding, consistent with the similar incidence rates for each treatment (Table S4).

As is the case for the other novel OACs, the relatively short half-life of rivaroxaban makes it less likely that major bleeding events will require active reversal of rivaroxaban-associated major bleeding, over and above standard measures for management of bleeding, as restoration of haemostasis can be expected within 12–24 h after the last dose (36). Options for reversal are presently limited to non-specific agents such as prothrombin complex concentrates, although clinical data on their use with NOACs are sparse. However, at least one reversal agent specific for all factor Xa inhibitors is in development (a catalytically inactive recombinant form of factor Xa) (37) and has reached phase II clinical development (NCT01758432).

Mortality

In ROCKET AF, over a mean follow-up of 1.94 years, 1214 (8.6%) patients died. A preliminary analysis (38) showed that patients who died during the study had a mean age of 76 years, a mean $CHADS_2$ score of 3.6, and almost half (48%) had prior stroke or TIA. There was no difference in the rate of deaths in the two treatment arms (rivaroxaban 4.5% vs. warfarin 4.9% per year; HR: 0.92; 95% CI: 0.82–1.03; p = 0.15) (1). The strongest predictors for death in ROCKET AF were reduced renal function, chronic obstructive pulmonary disease, male sex, peripheral vascular disease and increasing age (38).

The risk factors discussed above should be considered in addition to those comprising the HAS–BLED score when assessing the likely benefit–risk balance for oral anticoagulation therapy, as well as patient subgroups shown to have a higher risk of bleeding, such as those with renal impairment (Table 4).

Discussion

This paper has summarised data from ROCKET AF for a wide range of different patient subgroups: prior stroke/TIA, renal impairment, advanced age, prior MI, history of PAD, prior VKA experience, diagnosis of HF and residence in East Asia (China, Korea, Taiwan and Hong Kong). The treatment effect of rivaroxaban vs. warfarin with regard to efficacy has been consistent across all these subgroups. With regard to safety, in those subgroups where rivaroxaban showed increased rates of bleeding relative to warfarin (advanced age, prior MI and PAD), this appears to have been driven by increases in NMCR bleeding rather than major bleeding; it is worth noting that, compared with warfarin, rivaroxaban reduced the rates of ICH, critical-site bleeding and fatal bleeding (Table S4), key findings that contribute to its favourable benefit–risk profile relative to warfarin. Nonetheless, although NMCR bleeding is unlikely to have serious or long-term sequelae, such bleeding may contribute to patients discontinuing treatment with rivaroxaban, which may result in an increased risk of thromboembolic or bleeding events, depending on which, if any, therapy is used to replace rivaroxaban for continuing stroke prophylaxis.

Rates of ICH were low and similar in East Asian and non-East Asian patients prescribed rivaroxaban, and for non-East Asian patients prescribed warfarin (Table 7). Thus the observation that rates of ICH for patients randomised to warfarin were significantly higher in East Asian patients, compared with non-East Asian patients, is of particular importance (Table 7). This finding suggests that rivaroxaban, and potentially other NOACs, may offer a significantly improved benefit–risk profile for stroke prophylaxis in this part of the world.

Major bleeding is likely to result in a temporary cessation of rivaroxaban therapy, which in turn raises the question of when rivaroxaban can be reinitiated after successful resolution of the bleeding event. Optimal timing of resumption should be individualised for each patient's particular circumstances, particularly the risk of ischaemic events vs. the risk of recurrent haemorrhage. The latter will depend on whether the source of the bleeding has been completely resolved, or removed (e.g. surgery), as well as consideration of the consequences of an ischaemic event vs. those of a recurrent bleed in the same location. When, or even if, to resume oral anticoagulation assumes even greater importance after an ICH. Heidbuchel et al. (36) have suggested that resumption can begin as soon as 10–14 days after an ICH if the risk of cardiogenic thromboembolism is high, whereas other authors have recommended delaying resumption of oral anticoagulation until 10–30 weeks after the ICH (39,40). However, these recommendations are derived from clinical experience with the VKAs; relevant clinical experience with rivaroxaban and the other NOACs is presently limited.

There is also some evidence suggesting that patients restarting warfarin therapy after a warfarin-associated ICH have, on balance, an improved survival compared with those who do not restart therapy (41), even though warfarin-associated ICH is associated with a high case fatality rate. One large cohort study reported that at hospital discharge 76% of patients with ICH had died or had severe disability compared with only 3% of those with major extracranial haemorrhage (42). Approximately half of patients experiencing a warfarin-associated ICH die within 30 days (32). In ROCKET AF, rates of fatal bleeding were low, < 1%, but were significantly less with rivaroxaban compared with warfarin, as were rates of ICH (1).

In addition to rivaroxaban, three other NOACs (the factor Xa inhibitors, apixaban and edoxaban and the direct thrombin inhibitor, dabigatran) have completed phase III clinical trials for stroke prevention in patients with AF (Table S2) (12,13,43). A fourth factor Xa inhibitor, betrixaban, has been evaluated in a phase II clinical trial (Explore-Xa) (44), but it is not known if a phase III study is planned. Both dabigatran and apixaban have been widely approved for AF-related stroke prevention. Edoxaban is approved in this indication in Japan (45) and is currently under review for approval in the EU and USA (46,47). Of these NOACs, apixaban (in the ARISTOTLE trial) and high-dose (150 mg bid) dabigatran (in the RE-LY trial) demonstrated superior efficacy in the reduction in stroke or SE compared with warfarin in an ITT analysis (apixaban vs. warfarin: HR: 0.79; 95% CI: 0.66–0.95; p = 0.01 (13); dabigatran 150 mg bid vs. warfarin: HR: 0.65, 95% CI: 0.52–0.81; p < 0.001 (12)). In ROCKET AF, rivaroxaban demonstrated superior efficacy to warfarin while patients were receiving the drug in the ITT population (HR: 0.79; 95% CI: 0.66–0.96; p = 0.02) (1). In the ENGAGE-AF trial, high-dose (60 mg od) edoxaban demonstrated superior efficacy to warfarin in the modified ITT population, i.e. patients who received at least one dose of study drug during the treatment period (HR: 0.79; 95% CI: 0.63–0.99; p = 0.02), although this was the prespecified population for non-inferiority (not superiority) analysis (43). The treatment period in this study was defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of the double-blind therapy (whichever came first), with interval censoring of events during study drug interruptions that lasted > 3 days. (Detailed efficacy results for the NOACs can be found in Tables S2 and S3). It is worth bearing in mind that in the ARISTOTLE and RE-LY trials, the patient population was at a lower baseline risk of stroke or SE than those included in the ROCKET AF trial [mean $CHADS_2$ score 2.1 (ARISTOTLE and RE-LY) vs. 3.5 (ROCKET AF)], with only approximately 20% of patients in ARISTOTLE and RE-LY having a prior history of stroke or TIA compared with 55% in the ROCKET AF trial (1,12,13). This may have contributed to the statistically superior difference in primary end-point seen with apixaban and dabigatran 150 mg bid vs. warfarin. In the ENGAGE-AF trial, patients had an intermediate baseline risk of stroke (compared with patients in ARISTOTLE/RE-LY and ROCKET AF); the mean $CHADS_2$ score at baseline was 2.8 across all treatment groups, with approximately 28% of patients having had a prior stroke or TIA (43).

Compared with warfarin, each of the NOACs demonstrated reduced rates of ICH (1,12,13,43,48) (Tables S2 and S4). Apixaban, edoxaban and low-dose dabigatran (110 mg bid) were associated with significant reductions in major bleeding, compared with warfarin (Table S2) (12,13,43).

In addition to providing information on efficacy and safety, data from the clinical trials of the NOACs have been used for the basis of cost-effectiveness analyses. A small number of papers have recently reported the relative cost-effectiveness of rivaroxaban compared with warfarin or with the other approved NOACs (Table 8) (49–54). These studies seem to show that, while all NOACs may provide improvements in quality-adjusted life-years vs. warfarin, this is associated with increased cost (49,53). Furthermore, apixaban appears to be more cost-effective

Table 8 Estimated costs of oral anticoagulation in four healthcare systems

Total lifetime costs per patient	Study details	Country (currency; year)	Warfarin	Rivaroxaban	Dabigatran	Apixaban
Canestaro et al. (49)	Markov state transition model in a US cohort of 70-year-old warfarin-eligible patients with AF initiating treatment on an OAC (warf. INR 2–3; riva. 20 mg od; dabi. 150 mg bid; apixa. 5 mg bid)	USA ($; 2012)*	49,638	84,192	88,994	87,794
		QALYs gained (+) or lost (−)	Ref.	+0.31	+0.28	+0.41
Lanitis et al. (50)	Adapted Markov model in a French cohort of patients with AF initiating treatment on an OAC [dose-adjusted warf.; riva. 20 mg od; dabi. 110 mg bid; dabi. 150 mg bid; dabi. (150 mg bid then switch to 110 mg bid at age 80 years); apixa. 5 mg bid]	France (€; 2012)	17,966	20,473	20,281–20,648†	20,281
		US$‡	21,418	24,406	24,178–24,615	24,178
		QALYs gained (+) or lost (−)	Ref.	+0.14	+0.09 to +0.12†	+0.19
Coyle et al. (51)	Markov cohort model in a Canadian cohort with NVAF, average age 72 years with no prior stroke/MI initiating treatment on an OAC (dose-adjusted warf.; riva. 20 mg od; dabi. 110 mg bid; dabi. 150 mg bid; apixa. 5 mg bid)	Canada (C$; 2011)*	18,620	22,016	21,486–22,804†	21,966
		US$‡	15,796	18,676	18,532–19,345	18,634
		QALYs gained (+) or lost (−)	Ref.	+0.06	+0.06 to +0.14†	+0.14
Pink et al. (52)	Discrete event simulation pharmacokinetics and pharmacodynamics model in a UK cohort of patients with AF, mean age 72.3 years initiating treatment on an OAC (dose-adjusted warf.; dabi. 150 mg bid; riva. 20 mg od; apixa. 5 mg bid)	UK (£; 2011)	5880	9112	8426	8437
		US$‡	8960	13,885	12,840	12,856
		QALYs gained (+) or lost (−)	Ref.	+0.10	+0.11	+0.13

AF, atrial fibrillation; apixa., apixaban; bid, twice daily; dabi., dabigatran; INR, international normalised ratio; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; od, once daily; QALY, quality-adjusted life year; ref., reference; riva., rivaroxaban; warf., warfarin. *Apixaban pricing information unavailable at time of analysis and assumed to have the same retail price as dabigatran. †Dependent on dosing regimen. ‡According to exchange rate on 05/01/2015 (www.xe.com).

than either rivaroxaban or dabigatran (49,54). However, these analyses were based on Markov models where numerous assumptions surrounding the data were made, and where outcomes data were taken from the main clinical trials in patients with AF. As alluded to earlier, there were fundamental differences between the trial populations and methodologies across these trials, and these will have impacted upon the cost-effectiveness analyses. As a result, until direct head-to-head comparisons of the agents based on extensive real-world data are available, the cost-effectiveness findings of such models are limited in their general applicability.

Overall, the findings reviewed in this paper show that rivaroxaban is an excellent alternative to warfarin for stroke prophylaxis in patients with AF, including most patient comorbidities likely to be encountered in routine practice. In the light of the limitations associated with warfarin therapy, these findings raise the question of whether patients with AF receiving warfarin should be transferred to rivaroxaban therapy. In this regard, patients who are well controlled on warfarin, with a stable international normalised ratio maintained within the therapeutic range (2.0–3.0), may prefer to remain on warfarin, although the increased risk of ICH relative to the NOACs should be considered. In addition, rivaroxaban should not be considered for comorbidities where regulatory approval is lacking, including severe renal dysfunction (CrCl < 15 ml/min), or in patients with prosthetic heart valves or with a requirement for concomitant medication that is not recommended for use with rivaroxaban, such as ketoconazole. Warfarin should continue to be used for stroke prophylaxis in such patients. Rivaroxaban, at any dose, should also not be used in patients being treated with ticagrelor or prasugrel after an acute coronary syndrome (14).

Conclusions

Rivaroxaban, an oral factor Xa inhibitor, has demonstrated consistent benefits vs. warfarin across a wide range of patient subgroups at increased risk of stroke or major bleeding, including those most likely to be encountered in clinical practice. Specifically, the treatment effect of rivaroxaban vs. warfarin was consistent for patients with or without prior stroke, and for those with or without HF. Similar results were seen for patients with moderate renal impairment even though renal dysfunction is a risk factor for major bleeding and patients with moderate renal impairment received a reduced dose of rivaroxaban. Some patient subgroups receiving rivaroxaban experienced increases in NMCR bleeding compared with those receiving warfarin. These included patients aged ≥ 75 years, and those with prior MI or PAD. It is important that these factors are considered when selecting the optimal therapy for individual patients, but not at the cost of offsetting important reductions in other adverse clinical outcomes.

Thus, the overall evidence indicates that rivaroxaban can be considered a safe and efficacious alternative to warfarin in these patient subgroups.

Author contributions

Professor Hans-Christoph Diener drafted the first version of the manuscript. Professor Jonathan L. Halperin contributed to revisions of the text. Professor Keith Fox revised the manuscript. Professor Graeme J. Hankey wrote the section on the subgroup of patients with prior stroke or TIA and reviewed the first and final versions of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. The novel oral anticoagulants.
Data S2. Rivaroxaban – ROCKET AF.
Data S3. Patients with prior myocardial infarction.
Data S4. Patients with peripheral artery disease.
Data S5. Patients with or without prior vitamin K antagonist experience.
Table S1. Pharmacologic properties of apixaban, dabigatran, edoxaban and rivaroxaban.
Table S2. Characteristics and key results of phase III trials of NOACs in patients with AF.
Table S3. Efficacy results of ROCKET AF (4).
Table S4. Safety results of ROCKET AF (4)
Table S5. Key results from the ROCKET AF subanalysis of patients with or without prior MI (5).
Table S6. Key results from the ROCKET AF subanalysis of patients with or without baseline PAD (7).
Table S7. Key results from the ROCKET AF subanalysis of patients with or without prior VKA experience (8).

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