Controversy Surrounding ROCKET-AF: A Call for Transparency, But Should We Be Changing Practice?

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Prior to the emergence of novel oral anticoagulants (NOACs), nearly all patients were prescribed vitamin K antagonists for thromboembolic prophylaxis in non-valvular atrial fibrillation (AF). Rivaroxaban (Xarelto, Bayer/Johnson & Johnson), an oral factor Xa inhibitor, is now one of the most frequently prescribed NOACs used for this indication.^{1,2}

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), published in the *New England Journal of Medicine* in 2011, demonstrated the non-inferiority of rivaroxaban compared with warfarin for the primary prevention of stroke or systemic embolism in patients with AF. This double-blinded randomised trial, which included 14,264 patients across 45 countries, also showed no significant difference in the risk of major bleeding between these two groups.³

Rivaroxaban use in AF has become widespread since the publication of this trial and US Food and Drug Administration (FDA) approval. Two additional Factor Xa inhibitors, apixaban and edoxaban, have also been evaluated in similar randomised trials and have demonstrated non-inferiority to warfarin for stroke or systemic embolism prophylaxis in patients with non-valvular AF with no significant difference in major bleeding.^{4,5}

In recent months, the results of ROCKET-AF have come into question after the FDA issued a recall notice for the device used to obtain International Normalised Ratio (INR) measurements in the warfarin control group. The FDA found that lower INR values were seen with the 'point-of-care' INRatio Monitor System (Alere) compared with a plasma-based laboratory in patients with certain medical conditions.² These conditions included abnormal haemoglobin levels, abnormal bleeding and abnormal fibrinogen levels.⁶ Since the FDA recall of this device, there has been widespread concern that falsely low INR readings in ROCKET-AF may have led to warfarin overdosing. Inappropriately high warfarin dosing could have increased bleeding rates in the control group and therefore made the rivaroxaban arm appear falsely favourable.⁷ This point-of-care device recall also highlighted a lack of transparency of the specifics of devices used in large clinical trials.

In response, the authors from ROCKET-AF released a correspondence in February 2016, citing the FDA recall. They also provided a *post hoc* analysis of patients who may have been affected by the recall. They found that major bleeding was greater in patients with conditions affected by the recall, but, reassuringly, the bleeding risk was greater in those who were on rivaroxaban and not warfarin.⁶

Despite this *post hoc* analysis, concern has arisen regarding the generalisability of ROCKET-AF given the faulty point-of-care INR readings. There has been a call for complete transparency of the data from this trial and a better explanation of the mechanism of the incorrect INR measurements.⁷

Once published, the data supporting an FDA-approved treatment should be available for independent analysis. One issue is that rivaroxaban was approved in the US prior to 1 January 2014, before a new transparency policy on clinical trial data sharing was approved by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA).² Drug companies are refusing to share any data on pharmaceuticals approved before 2014.

A device malfunction in a large clinical trial also should raise concern, especially when that trial has altered clinical practice for millions of patients. On review of Patel et al's correspondence regarding the point-of-care malfunction, there is inadequate explanation of the mechanism of these faulty readings. Why are they only seen only in patients with abnormal haemoglobin and fibrinogen levels? How

inaccurate could the readings be – within 0.1 or 1.0 of a gold standard value? Most alarming is the revelation that the manufacturer had evidence of faulty readings in similar models dating back to 2002.²

Despite legitimate concerns regarding the absence of data transparency and the faulty point-of-care device, rivaroxaban need not be removed from clinical practice for AF patients. In ROCKET-AF, the drug demonstrated non-inferiority to warfarin in preventing thromboembolic events. In addition, data has shown that patients potentially affected by the faulty point-of-care device actually bled more on rivaroxaban than warfarin.⁶ Therefore, the original risk–benefit ratio presented in ROCKET-AF remains true.

There are other, albeit smaller, randomised trials with shorter follow-up times that compare rivaroxaban and warfarin for thromboembolic prophylaxis.^{8,9} For example, Cappato et al in 2014, randomised 1,504 patients to show that oral rivaroxaban was non-inferior to warfarin in preventing a composite endpoint of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction and cardiovascular death in patients with AF undergoing cardioversion. Major bleeding rates in the rivaroxaban and warfarin arms were similar (0.6 % versus 0.8 % respectively).⁸

The prospective observational trial XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) followed 6,784 patients on rivaroxaban for AF during a mean time of 329 days at 311 different hospitals. Major bleeding occurred in 128 patients (2.1 events/100 patient years) and 43 patients (0.7 events/100 patient years) suffered a stroke. These numbers are more reassuring than those seen in ROCKET-AF, though the patient population had a lower risk profile, with an average CHADS₂ score of 2.0 compared with 3.5 in ROCKET-AF.¹⁰

To further mitigate concern regarding inaccuracies of bleeding rates in the ROCKET-AF control group, it is helpful to compare bleeding rates in the warfarin arms of the other major NOAC trials. The RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial, had a warfarin-arm major bleeding rate of 3.4%/year.¹¹ The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, had a warfarin-arm major bleeding rate of 3.1%/year.⁴ The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, had a warfarin-arm major bleeding rate of 3.4 %/year.⁵ The warfarin arm of ROCKET-AF had a 3.4 %/year major bleeding rate, comparable to the other studies. Furthermore, the ROCKET-AF patients are known to be at higher risk for stroke and bleeding; their average CHADS₂ score was highest among these studies (3.5 compared with 2.1–2.8).³ In addition, ROCKET-AF had a very high percentage of patients with a HAS-BLED score ≥3 (62 %) compared with the other studies (23 % in ARISTOTLE and 51 % in ENGAGE AF-TIMI 48).^{12–14}

Several large randomised trials have compared the safety and efficacy of rivaroxaban versus warfarin for venous thromboembolic disease. The warfarin arm of the EINSTEIN-PE trial (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Pulmonary Embolism), which randomised patients with pulmonary embolism to warfarin or rivaroxaban, had a major bleeding rate of 2.2 %. The bleeding rate was lower in the rivaroxaban arm (1.1 %) and notably patients received a higher loading dose of rivaroxaban for the first 3 weeks (15 mg twice daily) compared with the daily 20 mg daily in ROCKET-AF.¹⁵

The recent uncertainties surrounding ROCKET-AF demonstrate the need for widespread data transparency for major trials with the capability of so greatly affecting patients' lives. These are complicated issues both for the companies' manufacturing products and the clinical trial organisations who carry out these studies and analyse the data. Ultimately the goal of full transparency to allow increased confidence in trial results should be sought. In this instance there is no compelling evidence of imminent danger of excessive bleeding with rivaroxaban. We should take notice of the recent findings, but there is no need to change practice. ■

- Kubitza D, Becka M, Wensing G, et al. 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* 2005;**61**:873–80. PMID: 16328318
- Cohen D. Rivaroxaban: can we trust the evidence? *BMJ* 2016;**352**:i575. DOI: 10.1136/bmj.i575; PMID: 26843102
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91. DOI: 10.1056/NEJMoa1009638; PMID: 21830957
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92. DOI: 10.1056/NEJMoa1107039; PMID: 21870978
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104. DOI: 10.1056/NEJMoa1310907; PMID: 24251359
- Patel MR, Hellkamp AS, Fox KA, et al. Point-of-care warfarin monitoring in the ROCKET AF Trial. *N Engl J Med* 2016;**374**:785–8. DOI: 10.1056/NEJMc1515842; PMID: 26839968
- Mandrola J. Rivaroxaban: It's not time to cut the rope, yet. Medscape. 9 February 2016. Available at: www.medscape.com/viewarticle/858648 (accessed 6 May 2016).
- Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–55. DOI: 10.1093/eurheartj/ehu367; PMID: 25182247
- Cappato R, Marchlinski FE, Hohnloser SH, et al. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J* 2015;**36**:1805–11. DOI: 10.1093/eurheartj/ehv177; PMID: 25975659
- Camm AJ, Amarencu P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145–53. DOI: 10.1093/eurheartj/ehv466; PMID: 26330425
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51. DOI: 10.1056/NEJMoa0905561; PMID: 19717844
- Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial. *J Am Coll Cardiol* 2015;**66**:2271–81. DOI: 10.1016/j.jacc.2015.09.024; PMID: 26610874
- Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet* 2012;**380**:1749–58. DOI: 10.1016/S0140-6736(12)60986-6; PMID: 23036896
- Eisen A, Giugliano RP, Ruff CT, et al. Edoxaban vs warfarin in patients with nonvalvular atrial fibrillation in the US Food and Drug Administration approval population: An analysis from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. *Am Heart J* 2016;**172**:144–51. DOI: 10.1016/j.ahj.2015.11.004; PMID: 26856226
- EINSTEIN-PE Investigators, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;**366**:1287–97. DOI: 10.1056/NEJMoa1113572. PMID: 22449293