Atrial fibrillation and prior MI: searching for balance in ischaemic and bleeding events in patients treated with factor-specific anticoagulants

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This editorial refers to ‘Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial†, by K.W. Mahaffey et al., on page 223

Patients with both atrial fibrillation (AF) and prior myocardial infarction (MI) represent a unique and potentially high risk population. Strategies for managing these patients using the newer factor-specific oral anticoagulants are somewhat limited, as these patients represent a small fraction of the overall cohorts studied and only limited results have been published previously.1,2

Mahaffey et al., investigators from the 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) trial,3 now report on the prevalence of prior MI in that study; the incidence of new cardiovascular (CV) events; and the treatment effect of rivaroxaban, a direct factor Xa inhibitor, compared with warfarin on the risk of new CV events in those with and without a history of MI.

In the ROCKET AF trial, 17% of patients had prior MI at enrolment (n = 2468/14 264).3 These subjects were significantly more likely to have other co-morbidities and risk factors, notably more heart failure, diabetes, and peripheral arterial disease. Additionally, concomitant aspirin (47% vs. 34%) and thienopyridine (3.4% and 2.1%) were more common in this subgroup. Patients with and without prior MI had similar rates of stroke and systemic embolism during a median 2 years of follow-up, but recurrent CV events and mortality were more frequent in the prior MI cohort, with a three-fold increase in the key efficacy outcome for these analyses, a composite of CV death, MI, or unstable angina [unadjusted hazard ratio(HR) 3.04, 95% confidence interval (CI) 2.59–3.56; P < 0.0001]. Bleeding was also higher in the prior MI subgroup.

It is still debatable as to how much of an increased risk having a prior MI independently confers in this AF population. After including potential confounders in the model, the adjusted HR for a history of MI was about half the unadjusted estimate (adjusted HR 1.64, 95% CI 1.21–2.24; P = 0.002). Given the large number of differences in baseline co-morbidities and risk factors as well as concomitant therapies among those with vs. without prior MI, it is not surprising that this association was greatly reduced. In addition, there were probably even more unidentified confounders that were unaccounted for in the analysis.

There was no evidence of a treatment–subgroup interaction for the primary efficacy endpoint of stroke or systemic embolism, suggesting a consistent treatment effect with rivaroxaban on that endpoint regardless of a prior MI. However, there was an interaction for the principle safety endpoint of major and non-major clinically relevant (NMCR) bleeding events. The results suggested increased bleeding with rivaroxaban in the prior MI cohort. There was also an interaction for all-cause mortality; rivaroxaban was associated with less of an effect on mortality relative to warfarin (i.e. mortality was similar between the rivaroxaban and warfarin groups) in patients with a history of MI, whereas in patients without prior MI rivaroxaban was associated with a 25% reduction in death compared with warfarin.

While the data presented are intriguing, the authors did not present data on a net clinical composite outcome to help evaluate these counterbalancing effects. When managing patients with AF, clinicians seek to find a balance between efficacy and safety. The outcomes in patients with a history of MI for rivaroxaban vs. warfarin are clearly described for the endpoints of stroke, CV events, and bleeding individually, but it is critical also to evaluate net composite outcomes that combine ischaemic and bleeding events, such as a composite of CV death, stroke, MI, or life-threatening bleeding.

Data are limited in subjects with a prior MI from other large studies of the newer factor-specific oral anticoagulants. In the RE-LY trial, there was no interaction observed for either dose of dabigatran with prior coronary artery disease for thrombotic events, ischaemic...
events, or major bleeding.\textsuperscript{1} Likewise, in the ARISTOTLE trial with apixaban, there was no interaction between treatment, prior coronary artery disease, and the outcomes of stroke/systemic embolic events or major bleeding.\textsuperscript{2} Unfortunately, neither trial has reported on the prior MI cohort specifically, only the broader category of prior coronary artery disease.

Another unanswered question is: what are the appropriate concomitant therapies to use in patients with AF managed with a factor-specific anticoagulant who have a history of MI? Some guidelines for management of patients with AF and MI recommend antplatelet and anticoagulant therapy for up to 12 months, followed by anticoagulant alone.\textsuperscript{3} Acute coronary syndrome (ACS) guidelines, however, recommend lifelong aspirin in most patients following MI.\textsuperscript{4,5} It was somewhat surprising to see that fewer than half of the patients with prior MI were being treated with aspirin, and thienopyridine was rarely (3.4%) used. While treatment with multiple antplatelet and anticoagulant agents may be necessary to prevent additional ischaemic and thrombotic events, the optimal combination that avoids excessive bleeding reported with triple antithrombotic therapy\textsuperscript{6} remains elusive. The study of Mahaffey et al.\textsuperscript{3} only reported major bleeding rates in patients with and without baseline use of aspirin or a thienopyridine (4.59 per 100 patient-years vs. 3.73 per 100 patient-years for patients with prior MI), but did not report the rates further stratified by warfarin or rivaroxaban within those groups. Additionally, future studies are needed to establish the impact of more potent oral P2Y\textsubscript{12} inhibitors in this population.

Clarity is also needed regarding the appropriate therapies for patients with AF on factor-specific oral anticoagulants who develop ACS. In patients with an ST-segment elevation MI, should fibrinolytic therapy be contraindicated, avoided, or might it be safe in a selected group of patients at low risk for bleeding (e.g. age \(<65\) years, \(>12\) h since last dose) in whom primary percutaneous coronary intervention (PCI) is not immediately available? While only 22 patients in the study of Mahaffey et al. received fibrinolytic therapy for new MIs, none had an intracranial haemorrhage within 5 days. Although primary PCI may be the logical choice, only two subjects underwent primary PCI for new MIs in ROCKET-AF. If primary PCI is available, what concomitant medical therapy should be used to prevent stent thrombosis and minimize bleeding? Should i.v. antplatelet agents be avoided? Should dual antplatelet therapy be initiated after patients are stabilized, and, if so, for how long? These questions and others need to be addressed as clinicians move toward factor-specific oral anticoagulants to manage complex patients with AF.\textsuperscript{7}

In conclusion, patients with a history of MI and AF represent a challenging cohort for physicians. Clinicians must juggle the need to prevent secondary coronary ischaemic events with the primary prevention of thrombo-embolic events, while minimizing bleeding. In the present study of patients with AF and prior MI, rivaroxaban demonstrated similar efficacy compared with warfarin, but possibly more bleeding. More data are needed to determine the optimal treatment with the newer factor-specific oral anticoagulants alone or in combination with antplatelets for this complex group of patients.

Conflict of interest: R.P.G. reports receiving consulting fees from Daiichi-Sankyo, Janssen, and Sanofi-Aventis; lecture fees from Bristol-Myers Squibb, Daiichi-Sankyo, Merck, and Sanofi Aventis; and grant support through his institution from Merck and Daiichi-Sankyo. S.A.M. reports receiving grant support through her institution from Merck, Janssen, and Daiichi-Sankyo.

References
\begin{enumerate}
\item Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. \textit{CMAJ Open} 2013;\textbf{1}:1 in press.
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