Road mapping ATLAS ACS 2: are we there yet?

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The interface between recurrent thrombotic arterial events and the potential bleeding hazards of antithrombotic treatment after an acute coronary syndrome (ACS) occupies a central position in the practice of contemporary cardiovascular medicine. Although substantial progress has occurred in modelling the likelihood of recurrent events in this setting, it is somewhat ironic that the very characteristics, i.e. advanced age, female sex, low body weight, and chronic kidney disease, that presage negative ischaemic outcomes commonly co-exist in models predicting the risk of bleeding from antiplatelet/anticoagulant therapy.

Nonetheless, tenacious pursuit of novel therapies directed towards platelet-mediated vascular events has resulted in the recent approval of two novel antiplatelet agents, prasugrel and ticagrelor. Whereas each has proven superior when compared with clopidogrel in percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS) patients receiving background aspirin therapy, both therapies extracted a price in the form of excess major bleeding.1,2 Somewhat remarkably, ticagrelor also increased fatal intracranial bleeding, yet had a beneficial overall impact on cardiovascular death: this favourable efficacy/safety profile facilitated recent regulatory approval.

In parallel with these advances in inhibiting platelet function has been the search for novel anticoagulants that are alternatives to warfarin either by directly inhibiting thrombin or, most recently, through the inhibition of factor Xa (FXa). Dabigatran was the first thrombin inhibitor approved as an alternative to warfarin, initially as prophylaxis for deep venous thrombosis, and most recently for patients with non-valvular atrial fibrillation. The latter development was based on a reduction in the risk of systemic embolism or stroke produced by dabigatran as compared with warfarin.3 While the risk of haemorrhagic stroke was also lower, there was more gastrointestinal bleeding with the use of dabigatran and a trend towards more myocardial infarction. Its future role in other thrombotic disease settings such as the ACS population remains to be defined. Apixaban, an anti-FXa agent tested in a dose of 5 mg b.i.d., had a significantly beneficial effect, including a reduction in mortality in patients with non-valvular atrial fibrillation as compared with warfarin. In sharp contrast, the same apixaban dose administered to patients after ACS proved not only ineffective as compared with conventional antiplatelet therapy, but hazardous because of excess bleeding and intracranial haemorrhage.4,5 On the other hand, rivaroxaban, another direct anti-FXa inhibitor, in a dose of 20 mg daily was shown to be non-inferior but not superior to warfarin in atrial fibrillation.6 Remarkably, however, when tested in much lower doses (i.e. 2.5 and 5 mg b.i.d.) in the recent ATLAS ACS 2 trial, rivaroxaban demonstrated superior efficacy in ACS compared with placebo on a background of standard post-ACS antiplatelet therapy.7

Our purpose here is to reflect further on what we can learn from ATLAS ACS 2, define those areas where our knowledge is deficient, and explore the potential future implications of oral anti-FXa inhibitor therapy in patients convalescing from ACS. Based on an extensive phase II dose-finding study of four doses tested, as both a once- and twice-daily regimen, the ATLAS investigators selected the 2.5 and 5 mg doses of rivaroxaban in a b.i.d. schedule for phase III testing.8 It seems clear that the lower 2.5 mg b.i.d. rivaroxaban dose in the ACS population studied was preferable to the 5 mg b.i.d. dose since it significantly reduced cardiovascular death by 34% (i.e. from 4.1 to 2.7% P = 0.002). Although this dose produced a significant increase in both major and intracranial bleeding, there was no excess of fatal bleeding. The mechanism whereby low dose rivaroxaban reduced mortality and why this benefit appears to widen over time is unclear given the lack of any effect of this dose on reducing the frequency of myocardial infarction. However, the evidence for persisting thrombin activation after an acute coronary event could point towards a sustained impact on coronary thrombotic events mediating a reduction in sudden death as a possible mechanism worth pursuing.9 Although there was little reduction in myocardial infarction with the low rivaroxaban dose, the higher 5 mg b.i.d. dose achieved a surprising and significant 21% reduction in infarction, yet no effect on mortality. Perhaps this relates at least in part to the 4.5-fold increase in major bleeding and a 3.7-fold increase in intracranial haemorrhage with the higher dose. We need to learn much more from ATLAS ACS 2 and specifically: (i) whether prior PCI and coronary artery bypass graft (CABG) performed in the 60% of patients in conjunction with the index event affected the outcome; (ii) to what extent there was recovery from the non-fatal excess intracranial haemorrhages in the treatment arm; and (iii) how to better evaluate the risk of intracranial

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The road map ahead for this form of antithrombotic therapy may discover even more potential for benefit, given that approximately one-third of the events post-ACS would have been expected to occur prior to the median time of 4.7 days when rivaroxaban therapy was begun in ATLAS ACS. These are exciting times for clinicians interested in providing therapies with additional benefit to their patients who have had an ACS event. Yet much remains to be understood, including the optimal dosing of these combinations, the duration of therapy for various subsets of patients, and even the combination schedule (i.e. antiplatelet therapy early followed by later anticoagulant therapy). All of these questions will require investigation, including outcomes trials as well as studies positing mechanistic studies to better unravel the complexities of interfering with the natural balance of thrombosis and haemostasis.

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