Combined antiplatelet and novel oral anticoagulant therapy after acute coronary syndrome: is three a crowd?

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This editorial refers to ‘New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis’1, by J. Oldgren et al., on page 1670.

The past 20 years have seen substantial advances in the short- and long-term outcomes for patients after acute coronary syndromes (ACS). Improvements in therapy and adherence to guidelines have resulted in a reduction in hospital mortality from 10.4% in 1994 to 6.3% in 2006.1 Despite this, ~17% of patients surviving an ACS event would experience recurrent events without secondary prophylaxis, and even with the newer antithrombotics there remains an ~10% risk of recurrence over 12 months.2,3 The high rates of recurrence highlight the need for more effective secondary prevention strategies. Besides novel antiplatelet therapies, novel anticoagulants have also been developed. They have first been tested in atrial fibrillation and shown to be effective in stroke prevention.6 Given the positive results obtained with warfarin on top of aspirin after myocardial infarction published > 10 years ago,7,8 they have also been tested on a large scale after ACS.9,10

A meta-analysis about the use of the new-generation oral anticoagulant agents on top of single or dual antiplatelet therapy after ACS has now been published.11 Properly randomized controlled trials are lumped together for the evaluation of efficacy against the usual endpoints (cardiovascular) death, (re)infarction, or stroke. Also, the safety with these new agents on top of the standard of dual antiplatelet therapy has been evaluated. As expected, bleeding is increased by adding a second antithrombotic strategy on top of dual antiplatelet therapy. However, efficacy is increased as well; but here the trials clearly are heterogeneous in outcome. The strength of the paper is the large number of ACS patients included. The weakness is that it is just a meta-analysis, and that all types of trial designs have been included: phase II dose-finding studies as well as phase III registration trials. Especially in phase II trials the safety of the agent tested is more carefully scrutinized than its efficacy, whereas in phase III trials efficacy is the primary outcome for ischaemic endpoints, which is subsequently mirrored against the expected increase in bleeding. Doses of the novel anticoagulants with excessive bleeding, that never made it to phase III evaluation, have been included, which has overestimated the bleeding risk in this meta-analysis. Therefore, only the phase III trials APPRAISE-29 and ATLAS-210 should have been included. The former trial has been stopped prematurely because of excess bleeding. Apparently, the dose of apixaban was too high and in fact similar to the dose successfully applied in stroke prevention in atrial fibrillation.12 In ATLAS-2, only a quarter or half of the dose used in stroke prevention in atrial fibrillation13 was tested, and found to be successful, albeit with more bleeding.

Secondly, the comparator in this meta-analysis is either dual or single antiplatelet therapy, the former being the standard of care in patients who have survived an ACS whether it has been treated invasively or conservatively, or whether a stent has been implanted or not. Therefore, only the components of the phase III trials with dual antiplatelet therapy exclusively should have been included.

The 15% relative risk reduction in cardiovascular death, myocardial infarction, and stroke in the two phase II trials is also accompanied by a reduction in stent thrombosis seen with both rivaroxaban and apixaban (Table 1), which is comparable with the reduction seen with, for example, the novel antiplatelet agent ticagrelor when compared with clopidogrel.13 This remarkable finding has not been seen before with anticoagulants and suggests a role for the coagulation cascade in the pathogenesis of stent thrombosis formerly thought to be a platelet activation-derived phenomenon. Interestingly, triple antiplatelet therapy with aspirin, clopidogrel, and vorapaxar for ACS did not reduce stent thrombosis when compared with clopidogrel and aspirin alone.14

Unfortunately, the meta-analysis is not based on individual patient data. So, which ACS patients are eligible for a novel oral anticoagulant on top of dual antiplatelet therapy after ACS?
Basically, all patients randomized in ATLAS-2 are eligible in that their acute event occurred at least 4 days earlier, that they should not have experienced a previous stroke while on dual antiplatelet agents, and that they are on low-dose rather than high-dose aspirin. Clearly, the novel antiplatelet agents ticagrelor and prasugrel have not been tested in combination with rivaroxaban. Though more effective than clopidogrel, both antiplatelet agents increase short- and long-term bleeding, and as of now should not be used in conjunction with a novel oral anticoagulant, at least not in the acute phase of ACS.

Table I  Stent thrombosis in the APPRAISE-2 and ATLAS-2 studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>f/u (m)</th>
<th>n</th>
<th>Reported stent thrombosis (%/year)</th>
<th>HR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NOAC</td>
<td></td>
<td></td>
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<tr>
<td>APPRAISE-2</td>
<td>8</td>
<td>7392</td>
<td>0.9</td>
<td>1.3</td>
<td>0.73 (0.47–1.12)** 250</td>
</tr>
<tr>
<td>ATLAS-2*</td>
<td>13</td>
<td>15 526</td>
<td>1.1</td>
<td>1.5</td>
<td>0.69 (0.51–0.93)** 250</td>
</tr>
</tbody>
</table>

\*Both doses of rivaroxaban.

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References

Patients with cardiogenic shock who require mechanical circulation support may profit from more effective, less invasive devices. Panel A shows the first-in-man use of biventricular percutaneous support with impeller devices (Abiomed Impella, Danvers, MA, USA). The 54-year-old patient presented with acute myocardial infarction and shock due to biventricular pump failure. When angioplasty of the RCA, intravascular volume optimization, and high-dose inotropes failed to stabilize the patient, a percutaneous left ventricular-assist device was implanted. Pulmonary oedema resolved, but severe right heart failure with multi-organ failure (liver, kidney) persisted despite nitric oxide therapy. Additional percutaneous device implantation in the right heart led to circulatory stabilization and progressive organ function recovery, with successful device weaning on Day 8. Echocardiography on Day 44 showed a normal right ventricular function. Panel B shows the pump head and Panel C the topology of the devices.