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**Antithrombotic therapy after 1 year of dual antiplatelet therapy following acute coronary syndrome: what to do?**

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The benefits of antithrombotic, and in particular antiplatelet, therapy in patients with atherosclerotic cardiovascular disease are well established, the accumulated evidence now stretching back well over three decades. What has been more difficult to pin down is the optimal intensity as well as duration of such therapy in different clinical situations, since the balance between the undoubted benefits (in terms of prevention of thrombotic complications) have to be balanced against the harms (and in particular bleeding complications) that come with it. In primary prevention, the weight of evidence suggests that there is little to be gained by antiplatelet therapy, since the relatively small thrombotic risk is matched (or even exceeded) by the bleeding risk; whereas by contrast, following acute coronary syndrome, a situation where re-thrombotic risk is high, the benefit gained by one year of dual antiplatelet therapy (DAPT) with aspirin combined with a potent P2Y<sub>12</sub> inhibitor greatly outweighs the risk from bleeding (although, in patients considered at especially high bleeding risk, there is reason to reduce the intensity and/or length of DAPT). These considerations are reflected in the most recent international guidelines, including from the European Society of Cardiology [1] and the American College of Cardiology / American Heart Association [2].

In the context of stable disease, the PEGASUS-TIMI 54 trial showed that, in patients who had experienced a myocardial infarction 1-3 years previously and were receiving aspirin, addition of low dose (60 mg twice daily) and standard dose (90 mg twice daily) ticagrelor both reduced the composite outcome of cardiovascular death, myocardial infarction (MI) or stroke, with an increase in TIMI major bleeding, as compared with placebo; and although the increased bleeding risk was numerically but not significantly lower in the 60 mg group, the lower dose was associated with reduced side effects, in particular dyspnea [3]. In the COMPASS trial,

patients with a history of peripheral artery disease of the lower extremities, of the carotid arteries or coronary artery disease treated with aspirin who also received rivaroxaban 2.5 mg twice daily (so called dual pathway inhibition, DPI) exhibited a reduction in the composite of cardiovascular death, MI or stroke compared with those receiving placebo, with a relatively small increase in bleeding [4]. There is therefore a strong argument to suggest that a more intensive antithrombotic strategy than aspirin alone, consisting of the addition of low-dose ticagrelor or rivaroxaban, in patients who have received their full one year of DAPT may give rise to added net clinical benefit.

In this issue of the *International Journal of Cardiology*, Cesaro *et al.* have interrogated the START-ANTIPLATELET registry to investigate the proportion of patients in a real world setting, namely those admitted for acute coronary syndrome (ACS) in seven Italian cardiology centers, who by PEGASUS and/or COMPASS trial enrolment criteria would be eligible for prolongation of dual antithrombotic therapy (with either ticagrelor or rivaroxaban) following their standard year of DAPT [5]. Of those who completed one year of DAPT, the study found that approximately two thirds of patients were eligible for such prolongation (with similar percentages in the PEGASUS-like and COMPASS-like groups). In the PEGASUS-like group, net adverse clinical events (NACE, defined as all cause death, MI, stroke and major bleeding) were almost doubled compared with the reference group (those not eligible for either PEGASUS or COMPASS); and in the COMPASS-like group, although NACE were numerically higher, this was small in magnitude and non-significant. Major adverse cardiovascular events (MACE, defined as a composite of MI, stroke and all cause death) were also doubled in the PEGASUS-like group, and not different in the COMPASS-like group.

In the PEGASUS-like patients, age 64 years or greater was the most common eligibility criterion by a considerable margin, followed by chronic kidney disease (eGFR < 60 ml/min), diabetes mellitus, multivessel disease and (least common) recurrent MI. In the COMPASS-like patients, the presence of two or more cardiovascular risk factors was the most common eligibility criterion, followed closely by age 64 years or greater, with disease in two vascular beds trailing considerably behind.

What does this tell us about how patients post-ACS should be treated following their one year of DAPT? It is clear from the literature that routinely prolonging DAPT beyond one year in all patients post-ACS is not the answer, being associated with no net benefit or indeed possible harm from bleeding outweighing the incremental reduction in thrombosis [6]. However, it is also clear from PEGASUS that there is a sub-population where continuation of DAPT, albeit with low dose ticagrelor, does indeed result in net benefit; and the present study underlines that such patients are at increased risk of both MACE and NACE. The outstanding question which arises from the present data is whether such patients would benefit from even more intensive antithrombotic therapy, whether that be more intensive (e.g. triple) antiplatelet therapy or addition of an anticoagulant (e.g. rivaroxaban); and whether that should form part of their treatment at an even earlier stage. The present study also demonstrates that the COMPASS-like population are at lower risk than PEGASUS-like patients, and that DAPT seems to do the job well in these patients. The question for them is whether they should continue on DAPT over the longer term or switch to DPI.

In a sense, therefore, this study raises more questions than it answers, although it is undoubtedly is an important and valuable contribution to the literature. What it most

certainly highlights is the high prevalence of patients who are at high risk of further thrombotic complications, in whom long term dual antithrombotic therapy (either DAPT or DPI, tailored to patients' individual characteristics) should be considered more routinely than happens at present.

**Disclosure of conflicts of interest**

The author declares no conflicts of interest.

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