Antiplatelet Treatment With Dual Pathway Inhibition: A Pathway of Consistency?

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Dual pathway inhibition (DPI), consisting of low-dose aspirin and very-low-dose (VLD) Factor Xa inhibition with rivaroxaban, was investigated in a large controlled clinical trial programme in patients with vascular disease, including patients with recent acute coronary syndrome (ACS), chronic coronary syndrome/stable coronary artery disease (CAD) and peripheral artery disease (PAD), as well as patients undergoing peripheral revascularisation of the lower extremities.[1–5]

In this volume of the journal, Sibbing et al. report the results of a study-level data meta-analysis of these trials.[6] Overall, the meta-analysis showed consistency regarding the reduction of major adverse cardiovascular events (MACE) with DPI compared with aspirin alone, with an overall risk reduction of 23% for MACE. The restriction to aspirin as the antiplatelet and rivaroxaban as the anticoagulant partner drug distinguishes this meta-analysis from a previous pooled analysis in this field.[7] Thus, only a minority of patients from the ATLAS phase II and III trials were included in the analysis of Sibbing et al. because in these trials most patients were treated with a 'triple' approach using VLD rivaroxaban, aspirin and a thienopyridine. Similarly, approximately 50% of patients enrolled in the VOYAGER-PAD trial were taking thienopyridines on top of DPI and were excluded from the analysis of Sibbing et al.[5,6] Thus, the meta-analysis of Sibbing et al. was largely driven by the COMPASS trial, representing approximately 80% of the total population.

Sibbing et al. should be commended for providing a clearer picture of the efficacy and safety of this regimen in a broad spectrum of vascular diseases. Heterogeneity was low to moderate among the trials included in the analysis. However, trial differences regarding cardiovascular disease conditions assessed (CAD versus PAD), the primary safety endpoint and the duration of both follow-up and study drug treatment still need to be considered.

The results provide a basis to further discuss the timing of DPI prescription (e.g. in the more acute versus more chronic phase) because the greatest risk reductions in MI and all types of stroke were seen in patients immediately after ACS. Of note, DPI was only compared against aspirin or dual antiplatelet therapy (DAPT) with clopidogrel, and not against more potent $P2Y_{12}$ inhibitors in the ATLAS ACS trials. The added value of DPI compared with more potent DAPT in the contemporary era, at least in the early phase, and more personalised approaches, including de-escalation strategies or long-term $P2Y_{12}$ inhibitor therapy in the post-acute/long-term phase, remains uncertain.

In addition, there were distinct effects of mortality reduction across the trials and disease stages, with a reduction in cardiovascular mortality in patients with chronic coronary syndromes/stable CAD and a reduction in all-cause mortality in the COMPASS populations only. It is tempting to speculate that DPI reduces mortality in vascular patients; however, it is intriguing that this effect was only observed in CAD and not in PAD patients. The latter have exhibited a higher mortality risk in previous registries and trials, suggesting that factors other than thrombotic/vascular events impact mortality in PAD patients.[4,8,9]

The mortality effect may be partly caused by a larger benefit in patients with heart failure in the COMPASS trial, an effect that could not be reproduced in a larger randomised trial focusing on patients with recent worsening heart failure and CAD with high use of guideline-based pharmacological therapy.[10,11]

The downside of a more intense antithrombotic therapy is that it always comes at the expense of major bleeding. Overall, the meta-analysis showed a 67% increase in International Society on Thrombosis and Haemostasis major bleeding.[6] However, it is reassuring that the rate of fatal bleeding was not increased with DPI. Again, differential effects were observed across the trials, with even lower risk of major and fatal bleeding in patients with ACS in the ATLAS ACS-TIMI 51 trial and in patients with PAD. However, these differential effects need to be evaluated, considering the relatively low proportion of these patient subgroups in the overall meta-analysis.

Net clinical benefit, comprising cardiovascular death, stroke, MI, fatal bleeding or symptomatic bleeding into critical organs, was reported only in the COMPASS and ATLAS ACS-TIMI 51 trials and was 21% with DPI compared with aspirin in aggregate.[3,12] This trade-off was negatively

affected by the concomitant use of DAPT with VLD rivaroxaban in another meta-analysis.[7]

Thus, the present meta-analysis reinforces the importance of a 'sweet spot' of antithrombotic combination therapy.[6] It adds substantially to the discussion regarding the usefulness of a more personalised approach to secondary prevention, including DPI, depending on the risk, stage and location of vascular disease and to claims for further trials in cardiovascular patients at high ischaemic risk and low bleeding risk managed with contemporary guideline-adherent therapy. ❑

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