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Inhibiting novel mechanisms of thrombosis: next-generation antiplatelet therapy

Aspirin, which was first marketed in the 19th century, demonstrated an impressive mortality benefit in patients with myocardial infarction (MI) in the ISIS-2 trial in 1988.[1] Ever since, aspirin has formed the backbone of treatment for arterial thrombosis. Later, the platelet $P2Y_{12}$ inhibitor clopidogrel also proved to be an effective treatment for arterial thrombosis, particularly in the context of coronary artery disease, stroke and peripheral arterial disease. Patients with acute coronary syndromes (ACS) benefit from 1 year of treatment with a $P2Y_{12}$ inhibitor in combination with aspirin. In this setting, the potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel have now largely replaced clopidogrel, due to a more effective reduction in atherothrombotic events.[2] However, this comes at the expense of an increase in bleeding, which particularly limits the long-term use of $P2Y_{12}$ inhibitors.

So, where do we go from here? William Parker and Robert Storey argue that we have scope to improve on our current use of aspirin and $P2Y_{12}$ inhibitors.[3] They discuss that some patients may benefit from extended duration of $P2Y_{12}$ inhibition, as recent studies have shown benefit of long-term use of aspirin and ticagrelor in patients with diabetes and previous percutaneous coronary intervention, for example. They also highlight the novel potent $P2Y_{12}$ inhibitor selatogrel, which is administered subcutaneously and provides a rapid onset of action, thereby opening up all new possibilities for $P2Y_{12}$ inhibition. Whilst for other patients, less is more. Patients with ACS at high risk of bleeding may benefit from early discontinuation of aspirin and continuation of ticagrelor alone as this causes less bleeding. Alternatively, perhaps a lower dose of aspirin in combination with a $P2Y_{12}$ inhibitor could be the answer in the future?

The broad, potent antiplatelet effects of aspirin and $P2Y_{12}$ inhibitors inevitably interfere with haemostasis and can cause major bleeding, which has a similar impact on overall mortality as recurrent MI.[4] Therefore, the development of novel antiplatelet agents with potent antithrombotic effects, but less impact on haemostasis, offers an appealing approach to reducing overall mortality. To this end, Fawaz Alenazy describes several promising novel antiplatelet drugs (including inhibitors of platelet GPVI, PAR4 and P-selectin, amongst others) that are currently under investigation in early-phase clinical trials. In total, this review comprehensively summarises 11 antiplatelet agents currently undergoing clinical studies as well as many more not far behind at the animal model or in-vitro stage.

Maan Harbi and colleagues specifically focus on the platelet receptors GPVI and CLEC-2 as novel antiplatelet targets.[5] These particular pathways have critical roles in arterial thrombosis and inflammation-driven thrombosis respectively, with only minimal roles in haemostasis. These pathways have proven elusive to conventional small molecule inhibitors and antibody-based approaches are currently under evaluation in clinical trials. Downstream signalling of GPVI and CLEC-2 is mediated by Btk and SYK, which are also targeted by drugs that are currently used in the treatment of haematological malignancy and idiopathic thrombocytopenia. Repurposing these drugs as antithrombotic drugs therefore also offers another intriguing treatment strategy. The benefits of GPVI and CLEC-2 inhibitors could also extend beyond arterial thrombosis, with possible benefits in venous thrombo-embolism, sepsis and other inflammation-driven thrombosis.

Nithya Prasannan and Marie Scully describe the critical role of VWF and GPI in thrombosis and haemostasis.[6] In particular, they highlight the transformational impact of caplacizumab, which blocks the interaction between VWF and GPIb, in the treatment of the devastating condition thrombotic thrombocytopenic purpura. They explore whether inhibition of the VWF-GPIb axis may also be beneficial in other types of thrombosis, although the critical role of this pathway in haemostasis is likely to be a limiting factor.

These review articles demonstrates just how far antiplatelet therapy has advanced in the last few decades and highlights the many exciting new possibilities still ahead of us.

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