In search of a better platelet ADP-receptor blocker

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The second-generation antiplatelet agents – the inhibitors of the ADP receptor – have proven important in the management of acute coronary syndromes with or without coronary intervention. For patients suffering from non-ST-elevation acute coronary syndromes, clopidogrel has shown to bring down the risk of recurrent ischaemic events by 20% with an acceptable safety.¹ Also patients undergoing intervention in that trial benefited both before and after coronary intervention.² In ST-elevation myocardial infarction treated with fibrinolysis, clopidogrel has been registered for the prevention of recurrent ischaemic events. The mechanism involved is probably the reduction of re-occlusion.³ Also in patients with STEMI not receiving reperfusion therapy, clopidogrel reduces recurrent ischaemic events.⁴ But clopidogrel found by far its greatest popularity in the prevention of stent thrombosis in patients undergoing stent implantation for coronary disease.⁵

One of the downsides of clopidogrel is its slow onset of action. Therefore, nowadays loading doses up to 600 mg are given to patients before percutaneous coronary intervention, but still the platelet response to clopidogrel is insufficient in many patients at the moment of balloon inflation and stent implantation. Better drugs with a faster onset action and a more predictable ADP-receptor blockade on the platelet have been developed and evaluated. Prasugrel, which is not metabolised in the liver but in the plasma, has a faster onset of action and a stronger platelet binding than clopidogrel,⁶ which translated into a better outcome in patients with acute coronary syndrome treated with PCI.⁷ The disadvantage of prasugrel is the increased risk of bleeding including fatal bleeding in the latter trial. Recently, the fast-acting but reversible oral

platelet ADP-receptor blocker ticagrelor has been tested against clopidogrel in a dose-finding study and found to be effective and relatively safe.⁸ Ticagrelor is currently being evaluated in the huge PLATO trial in patients with acute coronary syndromes, the results of which will be available mid-2009.

A clear alternative to oral loading with a faster-acting thienopyridine than clopidogrel is the use of intravenous ADP blocker cangrelor. In today's issue of *Netherlands Heart Journal*, Bouman et al. present results of an elegant *in vitro* study showing that cangrelor offers additional reduction of ADP-induced platelet aggregation in patients already treated with clopidogrel.⁹ This strongly suggests that cangrelor is a better platelet inhibitor than clopidogrel in PCI. The authors used classical light transmission aggregometry but even with this rather rough method, they did not only find better platelet inhibition than with clopidogrel but also a more predictable result. Needless to say, intravenous injection of an immediately acting ADP-receptor blocker has large advantages over the slow-acting and less predictable clopidogrel. Moreover, cangrelor is a reversible ADP blocker, which makes its duration of action very short. This may be advantageous in patients developing major bleeding, or those in need of urgent CABG.

Whether these favourable findings will result in better procedural outcome has to be established by the two large trials which are nearly finished. In CHAMPION PCI, intravenous cangrelor is compared with front-loaded clopidogrel in high-risk patients undergoing PCI and in CHAMPION PLATFORM cangrelor is compared with placebo in low-risk patients not up-loaded with clopidogrel. If positive, these trials will open the way to a new, partly reversible and fast-acting double antiplatelet strategy in PCI. ■

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