

Will prasugrel supersede clopidogrel for acute coronary syndromes?

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The benefits are greater efficacy and faster onset of action; the price is increased risk of bleeding...

The mainstay of antiplatelet therapy for patients with acute coronary syndromes (ACS), including those undergoing early percutaneous coronary intervention (PCI), is the combination of aspirin and clopidogrel.¹⁻³ Aspirin inhibits platelet thromboxane A₂ production and platelet activation, and reduces the relative risk of recurrent ischaemic events in patients at high risk of vascular events by about 22% (absolute risk reduction [ARR], about 2%) at the expense of an increase in the odds of major bleeding events by about 60% (absolute risk increase [ARI], about 0.5%).¹ Clopidogrel inhibits ADP-induced platelet activation by blocking the platelet P2Y₁₂ receptor. When added to aspirin therapy in patients with ACS, it reduces the risk of recurrent ischaemic events by a further 20% (ARR, about 2.1%) at the expense of an increase in major bleeding events by approximately 38% (ARI, about 1%).^{2,3}

Clopidogrel has several potential limitations, however. First, the onset of action is delayed, with a “therapeutic” level of 50% inhibition of ADP-induced platelet aggregation, as measured by light transmission aggregometry (LTA), not being reached until 4–6 hours after a 300 mg loading dose, and 2 hours after a 600 mg dose. Second, there is a “ceiling” effect — even a 900 mg dose achieves only around 60% inhibition of ADP-induced platelet aggregation. Third, laboratory testing suggests that “therapeutic” platelet inhibition is not achieved in a substantial proportion of patients because of individual variability in platelet inhibition by clopidogrel.⁴ Finally, there is uncertainty about the clinical benefit with higher loading doses of clopidogrel of 600 mg or 900 mg compared with 300 mg.^{5,6}

Prasugrel is a novel thienopyridine prodrug whose rate, magnitude and consistency of platelet ADP inhibition is greater than for

clopidogrel. It achieves more than 50% inhibition of platelet aggregation (measured by LTA) within 1 hour of a 60 mg loading dose.^{7,8} The safety and effectiveness of prasugrel have been compared with standard-dose clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel — Thrombolysis in Myocardial Infarction (TRITON-TIMI 38).⁹ A total of 13 608 patients with moderate-to-high-risk ACS scheduled for PCI were randomly assigned to receive prasugrel (60 mg loading and 10 mg daily maintenance dose) or clopidogrel (300 mg loading and 75 mg daily maintenance dose) for 6 to 15 months. Aspirin 75–162 mg daily was recommended for all patients. After a median duration of 14.5 months, the primary efficacy outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke occurred in 12.1% of patients taking clopidogrel and 9.9% of those taking prasugrel (hazard ratio [HR], 0.81; 95% CI, 0.73–0.90). Stent thrombosis was also reduced (2.4% clopidogrel v 1.1% prasugrel; HR, 0.48; 95% CI, 0.36–0.64). However, the key safety endpoint of major bleeding not related to coronary artery bypass graft (CABG) was increased (1.8% clopidogrel v 2.4% prasugrel; HR, 1.32; 95% CI, 1.03–1.68). All major bleeding (including CABG-related) was increased (1.7% v 2.5%; HR, 1.31; 95% CI, 1.16–1.50), as was fatal bleeding (0.1% v 0.4%; HR, 4.19; 95% CI, 1.6–11.1). Overall mortality did not differ significantly between treatment groups. A post-hoc subgroup analysis identified less clinical efficacy and greater bleeding among patients with a history of stroke or transient ischaemic attack, older people (age > 75 years), and those with bodyweight less than 60 kg.

It is likely that these results are externally valid. However, by design, the study drug was only given after the coronary anatomy had been defined by angiography. This does not reflect usual clinical practice where clopidogrel is given at the time of presentation with ACS. Because there is a delay in the onset of action of clopidogrel, the design was biased in favour of prasugrel. Also, the prescribed standard 300 mg loading dose of clopidogrel was lower than that now adopted by many clinicians following reports of an improved inhibition of platelet aggregation with higher loading doses of clopidogrel such as 600–900 mg in patients with PCI.⁶

These caveats aside, the data suggest that treating 1000 patients with ACS at moderate-to-high risk of vascular events with prasugrel (compared with clopidogrel at the standard approved dose) for a median duration of 14.5 months would prevent about 22 major vascular events and cause eight major haemorrhages, including three fatal bleeds.

The implications for clinicians, should prasugrel gain regulatory approval, are that it may allow cardiologists to delay their decision to administer a P2Y₁₂ inhibitor until after coronary angiography (thus avoiding the bleeding risk of clopidogrel in patients who need urgent CABG), and to use prasugrel instead of clopidogrel in the acute phase of ACS, possibly using clopidogrel for long-term maintenance therapy.

The implications of these results for researchers are that it is important to determine whether the risk of long-term bleeding with prasugrel may be reduced, without compromising efficacy, by using lower doses and by avoiding its use in those with previous stroke or low bodyweight, and older people. A lower dose of prasugrel is presently being compared with clopidogrel in the TRILOGY study, involving 10 000 patients with ACS who are treated medically. Research is also needed to evaluate the potential for individualised

antiplatelet therapy based on the results of point-of-care testing of platelet function and genetic polymorphisms. Meanwhile, large randomised trials are presently comparing: the efficacy and safety of a high loading dose and maintenance dose of clopidogrel (versus a low loading dose and maintenance dose); the oral reversible non-thienopyridine ADP receptor antagonist, AZD6140, with clopidogrel; and the parenteral reversible non-thienopyridine ADP receptor antagonist, cangrelor, with clopidogrel, all in patients with ACS treated with an early invasive strategy.

Competing interests

Graeme Hankey has received speaker fees and travel assistance from Sanofi-Aventis to attend scientific meetings.

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