

Letters to the Editor

Antiplatelet drugs and the smokers' paradox

The review on the new antiplatelet drugs (Aust Prescr 2014;37:182-6) was very useful and timely. However, one important aspect not mentioned was the influence of smoking status on drug efficacy. Smokers have an enhanced response to clopidogrel – the so-called smokers' paradox.¹

A recent meta-analysis concluded that the clinical benefit of clopidogrel in reducing cardiovascular events was seen primarily in smokers (25% risk reduction compared to controls), with little benefit in non-smokers (8% reduction).²

Prasugrel and ticagrelor were 47% and 36% more effective respectively than clopidogrel in smokers. However, in non-smokers the risk reduction was a modest 15% and 18% respectively compared with controls.²

It would be helpful if the authors could comment on the clinical significance of these findings and

their implications for drug selection and dosing. For example, is clopidogrel a suitable choice for non-smokers and should they receive larger doses to improve efficacy? Should prasugrel and ticagrelor replace clopidogrel in smokers who quit? Are smokers at higher risk of major bleeds from these antiplatelet drugs?

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Colin Mendelsohn has received payments for consultancy, educational presentations, travel and related expenses from Pfizer Australia, GlaxoSmithKline and Johnson & Johnson Pacific.

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Praveen Indraratna and Christopher Cao, the authors of the article, comment:

The intriguing phenomenon of the smokers' paradox in relation to P2Y₁₂ inhibitors refers to their apparent higher efficacy in patients who smoke. It has been proposed that induction of the cytochrome P450 (CYP) 1A2 enzyme may enhance the conversion of the prodrug clopidogrel into its active metabolite.¹ Also, the P2Y₁₂ receptor has been found to be upregulated in smokers, which may explain the enhanced effect of P2Y₁₂ inhibitors in these people.²

Unlike clopidogrel and prasugrel, ticagrelor does not appear to be affected by the smokers' paradox according to retrospective data from a recent study.³ On the other hand, the PARADOX study found that platelet aggregation was inhibited more strongly at a cellular level for both clopidogrel and prasugrel in smokers than in non-smokers, but clinical outcomes were not reported.⁴ Overall, the clinical significance of the smokers' paradox remains controversial.²

As Dr Mendelsohn pointed out, a meta-analysis noted differing relative risk reductions between smokers and non-smokers (see Table).⁵

This analysis included patients with both acute coronary syndrome and stable coronary artery disease, whereas our recent systematic review and meta-analysis focused on patients who presented with acute coronary syndrome.⁶

Another meta-analysis combined the two major trials for prasugrel in acute coronary syndrome (TRILOGY ACS and TRITON TIMI 38).⁷ Post hoc analysis found that prasugrel was superior to clopidogrel in reducing cardiovascular events only in smokers, and that the two drugs were similar in efficacy among non-smokers. A sub-study of the pivotal PLATO study comparing ticagrelor and clopidogrel did not find any significant difference in a reduction of cardiovascular outcomes between smokers and non-smokers. Additionally, the benefits

of ticagrelor over clopidogrel were found in both smokers and non-smokers.³

It should be acknowledged that such analyses of smoking status and cardiovascular events do have limitations, and speculative findings should be interpreted with caution. Patients within these trials were not randomised into smoking and non-smoking arms, and the data were analysed retrospectively. Baseline characteristics between the two comparative groups may have differed and cigarette exposure (heavy vs occasional smoking) was often not quantified. It was also unclear whether patients continued to smoke or stopped when they started antiplatelet therapy. Without such data, a clear advantage of one antiplatelet drug over the other is difficult to establish. Furthermore, little is known about the influence of smoking on bleeding risk with antiplatelet drugs, and available data are conflicting.^{3,5}

At this stage, we would not use smoking status as a determinant of drug selection until additional prospective data are available. Premature cessation or non-compliance with antiplatelet therapy is the strongest risk factor for stent thrombosis.⁸ After acute coronary syndrome, in addition to smoking cessation, we would always recommend dual antiplatelet therapy regardless of smoking status in patients who are treated either with percutaneous coronary intervention or medical therapy. This is in line with Australian and New Zealand guidelines (www.csanz.edu.au). The role of P2Y₁₂ inhibitors following coronary artery bypass grafting remains controversial.

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Table The effect of P2Y12 inhibitors on cardiovascular events in smokers and non-smokers: a meta-analysis⁵

Drug	Cardiovascular events	
	Relative risk reduction in smokers	Relative risk reduction in non-smokers
Clopidogrel	25%	8%
Prasugrel	29%	18%
Ticagrelor	17%	15%

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