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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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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

LETTERS

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

The intriguing phenomenon of the smokers' paradox in relation to $P2Y_{12}$ 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 $P2Y_{12}$ receptor has been found to be upregulated in smokers, which may explain the enhanced effect of $P2Y_{12}$ 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 $P2Y_{12}$ 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-analysis** [5]

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

4. Gurbel PA, Bliden KP, Logan DK, Kereiakes DJ, Lasseter KC, White A, et al. The influence of smoking status on the pharmacokinetics and pharmacodynamics of clopidogrel and prasugrel: the PARADOX study. J Am Coll Cardiol 2013;62:505-12.
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Preoperative investigations

As an anaesthetist, I read the article 'Preoperative assessment: a cardiologist's perspective' (Aust Prescr 2014;37:188-91) with much interest. The statement that 'risk assessment before surgery aims to minimise potential perioperative complications' is likely correct, although there is regrettably little evidence to substantiate this claim. However, I dispute the authors' view that for emergency surgery 'preoperative assessment uncommonly alters the course or outcome'.

The 2014 American College of Cardiology/American Heart Association guidelines recommend that, even for emergency surgery, clinical risk stratification should be undertaken, and that patients' morbidity and mortality risk can be estimated with the use of validated tools (www.riskcalculator.facs.org and www.riskprediction.org.uk/pp-index.php). Discussion of morbidity and mortality risk enables shared decision making, including the possibility that patients may decline surgery.

High-risk surgical patients have been described as those with a predicted postoperative mortality of greater than 5%.[1] A 2011 report from the UK National Confidential Enquiry into Patient Outcome and Death suggests that high-risk surgical patients should be carefully considered for postoperative high-dependency or intensive care.[2]

Disturbingly, in Australia (unlike New Zealand) good data on system-wide postoperative mortality are not collected and publicly reported. Clearly, not all postoperative morbidity and mortality is cardiac.

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Austin Ng and Leonard Kritharides, the authors of the article, comment:

We stand by our statement that 'for emergency non-elective surgery, preoperative risk assessment uncommonly alters the course or outcome of the operation as the urgency of the surgery takes precedence'. However, we did not intend for the statement to suggest not conducting preoperative assessments for emergency non-elective surgery. As stated by Dr Sutherland and in our article, 'identifying high-risk conditions such as class IV congestive heart failure, unstable coronary syndromes, or severe valvular heart disease (by conducting a preoperative assessment) can impact upon perioperative and postoperative management' from a cardiologist's perspective. Moreover, we agree that using validated surgical risk assessment tools will identify other non-cardiac high-risk factors. An appropriate risk assessment can then be presented to the patient or relatives for an informed decision. More research is clearly needed as the evidence behind preoperative assessment remains poor.

Data informs debate

The editorial 'Data informs debate' (Aust Prescr 2015;38:38-9) describes the uncertainties around the efficacy and safety of new medicines entering the market. It outlines the role that increased access to clinical trial data may have in informing assessments about the appropriate place of new drugs in clinical practice.

Just as it is important to consider new drugs, it is also important to consider the use of currently available drugs in new markets, or new populations. Populations vary, for a variety of reasons, in their response to specific drug therapies.[1,2]

Australia has a unique population in its Aboriginal and Torres Strait Islander people. This population may not have been included in clinical trials, so further analysis of trial data will often not be informative. Substantial uncertainty exists regarding