

# Antiplatelet therapy after percutaneous coronary intervention: is less more (more or less)?

Trisha Singh, Rong Bing 

In an era of incremental gains in preventative cardiology, the ongoing pursuit of reduction in ischaemic events has led to advances in the antiplatelet armamentarium that is available for use after percutaneous coronary intervention (PCI). The protection offered by antithrombotic may be enhanced by extending their duration of use, or through the application of more potent drugs—longer, stronger or both. The corollary, of course, is the potential for increased bleeding, which may carry significant associated morbidity and mortality. What combination and duration of aspirin, clopidogrel, ticagrelor or prasugrel is optimal in a given patient? This is a nuanced question that is pertinent in both acute and chronic coronary syndromes. Current guidelines broadly recommend the use of dual antiplatelet therapy (DAPT) for at least 12 months in patients undergoing PCI for an acute coronary syndrome (ACS) and at least 6 months in chronic coronary syndrome, with the proviso that shorter duration DAPT may be considered in patients at high risk of bleeding.<sup>1 2</sup> Within these boundaries, clinicians must gauge the ischaemic and bleeding risk of an individual patient in order to optimise their DAPT regime.

The advent of potent P2Y12 inhibitors and iterative improvements in drug-eluting stents (DES), the latest of which have thinner struts, improved drug delivery and are associated with lower rates of stent thrombosis and restenosis, have raised the possibility of a shorter duration of DAPT after PCI, with the goal of minimising bleeding while offering non-inferior protection from ischaemic events. Multiple randomised trials have studied various combinations of drugs and DAPT duration, including short-term DAPT followed by aspirin monotherapy and short-term DAPT followed by P2Y12 inhibitor monotherapy.<sup>3–5</sup> Although somewhat heterogenous, collectively, these data suggest that short-term DAPT may

be considered as a safe option in selected individuals. The authors of the current paper conducted one such contemporary randomised trial, the Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) trial. This was a multicentre, open-label, non-inferiority randomised trial performed in patients undergoing PCI with DES for stable angina or ACS at 33 Korean sites, which demonstrated that P2Y12 inhibitor monotherapy after 3 months of DAPT was non-inferior to 12 months of DAPT for the primary endpoint of major adverse cardiac and cerebrovascular events, and was associated with a lower rate of bleeding.<sup>6</sup>

Of note, 77% (n=2312) of patients in SMART-CHOICE were treated with clopidogrel, as opposed to ticagrelor (n=552, 18%) or prasugrel (n=129, 4%); importantly, this choice was made at the discretion of the treating clinician. Given concerns regarding the onset of action and variability in platelet inhibition induced by clopidogrel, a clinically relevant question is whether this agent is appropriate for shortened DAPT regimes. Kim and colleagues provide further insight into this issue with a prespecified secondary analysis of SMART-CHOICE.<sup>7</sup>

The authors compared 3 months of DAPT followed by P2Y12 inhibitor monotherapy to 12 months of DAPT in the subgroup who were prescribed clopidogrel, as well as those receiving more potent P2Y12 inhibitors (prasugrel or ticagrelor). There were clear baseline differences between the clopidogrel subgroup and the potent P2Y12 subgroup, with the former being older with a higher prevalence of previous revascularisation and stroke. Approximately half of those prescribed clopidogrel had a clinical presentation of stable angina, in contrast to only 9% of those prescribed potent P2Y12 inhibitors. However, characteristics within each group were well balanced between the P2Y12 monotherapy and 12-month DAPT treatment arms. The investigators demonstrate comparable rates of major adverse cardiovascular and cerebrovascular events

between P2Y12 monotherapy and standard DAPT arms at 12 months in the clopidogrel group on intention-to-treat analysis (3.0% vs 3.0%; hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.64 to 1.65). There was no difference in the rates of Bleeding Academic Research Consortium (BARC) type 2–5 bleeding (2.1% vs 2.9%, HR 0.71, 95% CI 0.42 to 1.21). In the smaller ticagrelor/prasugrel subgroup, there was similarly no difference in the primary outcome—although with a low absolute number of events—between treatment allocations (2.4% vs 0.7%, HR 3.37, 95% CI 0.77 to 14.78), but a lower prevalence of BARC types 2–5 bleeding with P2Y12 monotherapy (1.5% vs 5.0%, HR 0.33, 95% CI 0.12 to 0.87).

The investigators have undertaken a valuable analysis that recapitulates the results from the primary analysis and provides important insights into P2Y12 inhibitor therapy that are contemporary and of practical and clinical relevance. This examination of the large subgroup of SMART-CHOICE that were prescribed clopidogrel is also salient as, despite the advent and uptake of prasugrel and ticagrelor, clopidogrel is a cheap, widely available P2Y12 inhibitor that remains in routine use. Of course, the standard caveat that this is a subgroup analysis for which the trial was not powered applies here. This is notably evidenced by the low number of events in the potent P2Y12 inhibitor subgroup (n=8 and n=2 major adverse cardiac and cerebrovascular events for P2Y12 inhibitor monotherapy and 12 month DAPT respectively) with consequent uncertainty around the hazard ratio point estimate. However, the findings reported here—that the rate of ischaemic events with a shorter period of DAPT followed by P2Y12 monotherapy is comparable with 12 months of DAPT, with clopidogrel as well as ticagrelor or prasugrel—are congruent with the wider body of literature, lending credence to these observations. Whether there is a definite benefit in terms of reduced bleeding is less certain from these subgroup data, but again, in the context of the wider evidence base, it is likely that the observed bleeding reduction with shorter DAPT in the ticagrelor/prasugrel subgroup is a real effect.

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Another consideration is the comparison arm—12 months of DAPT. More than 50% of the clopidogrel arm presented with stable angina, a population in whom 6 months of DAPT is routinely used.<sup>2</sup> We largely agree with the authors' interpretation that if 3 months of DAPT followed by clopidogrel is non-inferior with regards to ischaemic events when compared with 12 months of DAPT, this should also hold true when compared with 6 months of DAPT. The clinical presentation and indication for PCI is an important factor, one that this analysis (and indeed the main trial) is not designed or powered to examine, since PCI in the acute setting may entail substantial differences in procedural and patient characteristics, with attendant variation in downstream ischaemic and bleeding risk. This is highlighted by the Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes (SMART-DATE) randomised trial, which found that the rate of myocardial infarction was increased with 6 months of DAPT compared with 12 months of DAPT (80% clopidogrel use) in Korean patients undergoing PCI for ACS.<sup>8</sup>

Other seminal randomised trials such as Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 (STOP-DAPT-2) and Ticagrelor with Aspirin or Alone in High-Risk Patient After Coronary Intervention (TWILIGHT) enrolled both stable and acute patients. In this regard, the currently recruiting Duration of Dual Anti-Platelet Therapy in Acute Coronary Syndrome (DUAL-ACS) randomised trial (NCT03252249), which is comparing 3 months of DAPT to 12 months of DAPT in patients with ACS (with or without PCI), may be informative.

The authors also appropriately raise the limited generalisability of SMART-CHOICE to non-Asian populations, given the well-documented genetic differences and possibly divergent ischaemic and bleeding risks between patients of Asian and Caucasian ethnicities. Indeed, clopidogrel monotherapy after short-term DAPT following PCI has only been evaluated in Asian populations (Korean and Japanese in SMART-CHOICE and STOPDAPT-2, respectively). Again, in this regard, DUAL-ACS, which is enrolling in the UK and New Zealand and will therefore be likely to recruit a preponderance of Caucasian patients, will be of value. Finally, although it may be tempting on initial perusal to compare outcomes between clopidogrel and potent P2Y<sub>12</sub> inhibitors in this analysis, confounding by indication largely invalidates inferences drawn from such a comparison.

The authors have added to the growing evidence base that supports the use of a shorter duration of DAPT, with the use of clopidogrel as well as more potent P2Y<sub>12</sub> inhibitors, after PCI in selected patients. Individual assessment of risk and benefit remains essential; after all, an individual patient who experiences an adverse event is not consoled by a low overall risk across thousands of patients in a clinical trial. In contemporary cardiology, with ever more potent preventative therapies that incrementally reduce the risk of ischaemic events at the expense of bleeding, it is not amiss to consider that, on balance, less may often be more.

**Contributors** TS drafted the manuscript. TS and RB edited the final version.

**Funding** This work was supported by the Medical Research Council (MR/T029153/1) and the British Heart Foundation (PG/19/40/34422).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; externally peer reviewed.

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**To cite** Singh T, Bing R. *Heart* 2021;**107**:1028–1029.

Published Online First 13 May 2021



► <http://dx.doi.org/10.1136/heartjnl-2020-318821>

*Heart* 2021;**107**:1028–1029.

doi:10.1136/heartjnl-2021-319126

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