How long should dual antiplatelet therapy be continued following implantation of drug eluting stents?

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Drug eluting stents (DES) are now established in the treatment of coronary artery disease (1) and their development promised to improve upon limitations associated with original bare metal stents in particular that of late restenosis. Whilst restenosis rates have improved, DES have been claimed to be associated with a higher risk of late stent thrombosis (2). The administration of dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12-receptor inhibitor following implantation of DES significantly reduces the likelihood of coronary stent thrombosis (ST) due to inflammation of the stented segmented during healing (3) and for this reason is deemed mandatory in all patients following DES implantation. DAPT is also associated with additional benefits (unrelated to the stented coronary artery segment) and has been associated with a reduction in ischemic events and an improvement of clinical outcomes (4). However, these benefits are limited by a significant increase in bleeding and therefore current guidelines recommend that DAPT should be administered for 6-12 months following DES (1) with recent studies investigating the feasibility of further reducing the length of DAPT in a bid to further improve safety without exposing patients to unnecessary risks (5-7). However, the current reality is that the most effective duration of DAPT to prevent both stent thrombosis and further ischemic events (e.g., myocardial infarction) remains to be determined and the effects of prolonged DAPT beyond the currently recommended 12 months are poorly characterised.

Mauri *et al.* recently published the results of the Dual Antiplatelet Therapy study (8) that investigated the effect of prolonging DAPT beyond the currently recommended 12 to 30 months. Following completion of 12 months DAPT, following implantation of a DES, 9,961 patients were randomized to continued, (for another 18 months) thienopyridine (clopidogrel or prasugrel) (n=5,020) or placebo (n=4,941), in addition to low-dose aspirin. The primary endpoints of ST and major adverse cardiac and cerebrovascular events [MACCE; composite of death, myocardial infarction (MI), or stroke] at 12-30 months were significantly reduced with continued DAPT [stent thrombosis 0.4% *vs*. 1.4%; hazard ratio 0.29; 95% confidence interval (CI): 0.17-0.48; P<0.001; and MACCE 4.3% *vs*. 5.9%; hazard ratio 0.71; 95% CI: 0.59-0.85; P<0.001]. However, the primary safety endpoint (moderate or severe bleeding) significantly increased with continued thienopyridine (2.5% *vs*. 1.6%, P=0.001), and was greatest in individuals greater than 75 years old. Furthermore, total mortality was increased in the prolonged DAPT group although this was possibly accounted for by an increase in the number of non-cardiovascular deaths that may have been attributable to an increase in the incidence of cancer and cancer-related deaths.

Before making general conclusions on the basis of these results, there are a number of points with regards to the study that should be considered. The study recruited only patients who completed a full 12 months of DAPT, suffered no MACCE events, without bleeding complications and compliant with thienopyridine (defined as having taken 80-120% of the drug without an interruption >14 days). This resulted in the exclusion of 23% of the patients that had initially been treated with a stent and initially considered eligible. It is therefore difficult to generalise these results to individuals that suffered early events following DES implantation, and indeed this group may have most to gain from prolonged DAPT.

The efficacy results demonstrated a reduction in ST,

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MACCE and MI of which non-stent thrombosis-related MI comprised of 55% of the treatment benefit in the prolonged therapy group. Interestingly, there was an increased risk of ST in the first 3 months in the group randomized to discontinuation of thienopyridine.

Interestingly, whilst the study was not powered to identify a difference between DES implanted, in the 2,666 (26.8%) patients treated with paclitaxel eluting stents (PES) there were 10 ST (0.8%) in the continued thienopyridine group *vs.* 38 ST (3%), in the placebo group and this stent was the only one associated with a significant difference in MACCE with continued thienopyridine treatment. It may therefore be interesting to investigate the effect of prolonged DAPT if PES had been excluded.

There are other studies that have evaluated the duration of DAPT up to 12 months in patients with coronary artery disease (with or without prior revascularization procedures) (5,6,9,10) with the specific aim of investigating the efficacy of reducing the duration of DAPT in a bit to improve safety (specifically with regards to bleeding complications) whilst maintaining protection against stent thrombosis.

The clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial evaluated long term (median of 28 months) DAPT in patients with coronary artery disease and without a necessary associated invasive intervention (11). The trial was negative with regards to the primary endpoint of MI, stroke or death from cardiovascular causes (including haemorrhage) but there was a clear trend toward more severe bleeding in patients treated with long term DAPT. The PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY) trial demonstrated non-inferiority of 6-month DAPT *vs.* 24-month DAPT on the composite endpoint of MI, stroke or death following the implantation of DES or bare-metal stents (12) but again prolonged therapy was associated with a higher incidence of bleeding. The study from Park *et al*. (13) is the only previously published study that aimed to assess the efficacy of prolonging DAPT in patients that had completed 12 months of therapy and is thus is comparable to the current study. It did not show any benefit of prolonged DAPT (aspirin in combination with clopidogrel) over aspirin monotherapy however it was underpowered for this endpoint.

In conclusion, the DAPT study unequivocally demonstrates that prolonged DAPT is associated with a higher risk of bleeding in support of previous studies.

However, it is also clear that there are some patients that would benefit from prolonged DAPT following DES implantation but it is unclear which patients would most benefit from this strategy and how to best select them. The decision to prolong therapy should therefore be made on an individual basis taking into account the potential benefits against specific factors including age, prothrombotic co-morbid factors and risks of bleeding. Into the future, with the development of less thrombotic stent platforms, anti-proliferative drugs and further optimisation of procedural techniques, more compelling data are required before this strategy should be adopted into routine everyday clinical practice.

Acknowledgements

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