Balancing ischaemia and bleeding with dual antiplatelet therapy: a resolute endeavour

Gregg W. Stone*

Columbia University Medical Center, New York-Presbyterian Hospital, and the Cardiovascular Research Foundation, New York, NY, USA

Online publish-ahead-of-print 21 March 2014

This editorial refers to ‘Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type’, by E. Camenzind et al., on page 1932 and ‘Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following Resolute zotarolimus-eluting stent implantation’, by S. Silber et al., on page 1949.

The most devastating complication after stent implantation is sudden, thrombotic coronary occlusion, which results in myocardial infarction (MI) in 80–90% of patients and death in 20–30%. Dual antiplatelet therapy (DAPT) with aspirin and an ADP receptor antagonist is the foundation to prevent stent thrombosis (ST). Whereas drug-eluting stents (DES) are more effective than bare metal stents (BMS) in preventing restenosis and recurrent ischaemia, DES susceptibility to ST is increased by delayed endothelialization, polymer hypersensitivity, and other mechanisms, necessitating prolonged DAPT. Long-term DAPT may have additional benefits by preventing atherothrombotic events in patients with vascular disease. However, DAPT increases major bleeding, the occurrence of which is strongly associated with subsequent mortality.

Striking the right balance between ischaemic and bleeding complications by fine-tuning the potency and duration of DAPT is essential to optimize DES outcomes.

First-generation paclitaxel-eluting stents and sirolimus-eluting stents (SES) were approved based on the basis of double-blind randomized trials in which DAPT was used for 3–6 months. Thereafter, reports of late ST resulted in recommendations for DAPT for 1 year or longer, without randomized evidence to support this endorsement. These guidelines have been carried forward to newer generation DES, despite randomized trials demonstrating enhanced safety and effectiveness with these devices compared with their earlier counterparts. What is the appropriate duration of DAPT with contemporary DES? Two recent reports tackle this issue head on.

The PROTECT trial randomized 8709 patients to Cypher SES vs. Endeavor zotarolimus-eluting stents (E-ZES). There was no significant difference in the primary endpoint of ST at 3 years (1.8% vs. 1.4%, respectively, P = 0.22). However, ST rates were greater with E-ZES between 30 days and 1 year (when most patients were on DAPT), but greater with SES between 1 and 3 years (after DAPT had been discontinued in the majority). These findings are further clarified by Camenzind and colleagues who report that very late ST (>1 year) with SES was increased relative to E-ZES only in those patients in whom DAPT had been previously discontinued. However, the duration of DAPT use was not randomized, and selection bias is evidenced by the fact that patients remaining on DAPT had paradoxically higher absolute ST rates than those in whom DAPT was discontinued. Nonetheless, this report strongly suggests that the varying ST propensity of different DES is a temporally related phenomenon which in some (but not all) stents may be modulated by DAPT duration.

In the second report, Silber and colleagues examined the outcomes of 4896 patients treated with Resolute ZES (R-ZES), among whom DAPT was discontinued for >1 day in 1069 (21.8%). Increased 1-year ST rates were observed in patients with DAPT discontinuation within 1 month, but not between 1 and 12 months, compared with those remaining on DAPT for 12 months (3.6% vs. 0.1% vs. 0.8%, respectively). DAPT adherence for the full year was also associated with increased bleeding. These findings are consistent with a recent large-scale study in 8583 DES-treated patients reporting that high platelet reactivity on clopidogrel was strongly related to ST before but not after 30 days, and was protective from bleeding. However, premature DAPT discontinuation after R-ZES was not randomized. The impact of measured and unmeasured confounders are again evident in the surprisingly higher ST rates among patients never discontinuing DAPT compared with those with discontinuation after 1 month. DAPT may be prematurely discontinued for social or economic reasons; because patients are doing well; for drug-related or other complications; or prior to necessary procedures. DAPT disruption associated with states of increased platelet
reactivity, such as major bleeding, trauma, or surgery, may confer increased ST risk, and too few patients were present with these conditions. While many high-risk patients were included, these same investigators have shown that even ‘all-comers’ studies are not wholly representative of all patients receiving stents. Finally, the number of patients with premature DAPT discontinuation in the potentially high-risk 1–3 month ($n = 92$) and 3–6 month ($n = 171$) periods is insufficient to foster high confidence. Nonetheless, while this study cannot be used to support a universal recommendation for 1-month DAPT after R-ZES, these data do provide some level of reassurance of safety for patients in whom DAPT must be or has been prematurely discontinued beyond 1 month.

Importantly, the findings from these reports must be considered in the context of the specific DES studied, as the underlying stent platform, polymer, and drug type, dose, and kinetics may affect vascular healing. In this regard, the SES (no longer manufactured) was a thick-strut stainless steel closed-cell design, was not very deliverable or conformable, and its polymer was inflammatory. Conversely E-ZES and R-ZES both have rounded thin struts made from a malleable cobalt–chromium alloy. However, while both elute similar amounts of zotarolimus, their polymers and drug release kinetics vary greatly. Rapid zotarolimus elution from E-ZES results in substantially more neointimal hyperplasia than with the extended drug release from R-ZES. Emerging metallic DES using bioabsorbable polymers, polymer-free systems, and fully bioresorbable vascular scaffolds may have distinctive early, late, and very late ST risks. Thus the risk–benefit ratio of shortening or extending DAPT duration is device specific, and cannot be generalized to the class.

These caveats notwithstanding, at least eight large-scale, randomized trials are investigating the optimal DAPT duration after DES, whether abbreviated (3–6 months), 1 year, or prolonged (2 years or greater). While all published trials to date (Figure 1) have been underpowered for low frequency safety events such as ST, several themes have emerged. Three trials collectively support the safety of 3–6 months of DAPT compared with a more prolonged course with E-ZES, R-ZES, and fluoropolymer-based everolimus-eluting stents, while two trials of DAPT prolongation to 2 years have reported excess bleeding without reduced rates of ST, MI, or death. However, only one trial (recruited, currently undergoing follow-up) has been adequately powered to determine whether prolonged DAPT (2.5 years vs. 1 year) might improve late outcomes by reducing stent-related and/or non-stent-related cardiovascular events, but its interpretation might be confounded by inclusion of numerous different types of DES and antiplatelet agents. Thus, based on current randomized and observational data (pending the results of future studies), 6 months of DAPT is reasonable after current best-in-class DES implantation in patients with stable coronary artery disease, whereas at least 1 year of DAPT is recommended after DES (or BMS) in acute coronary syndromes, as randomized

![Figure 1](https://example.com/figure1.png)

**Figure 1** Cardiac event and bleeding rates in published randomized trials of different durations of dual antiplatelet therapy after drug-eluting stent implantation. Randomization was performed at baseline in EXCELLENT and OPTIMIZE and at 30 days in PRODIGY, and reported results include the early period during which all patients were on dual antiplatelet therapy (DAPT). In DES LATE, randomization occurred at 12–18 months, and results represent a landmark analysis from that point forward for an additional 24 months. In DES LATE, extended follow-up to 48 months after randomization demonstrated increased bleeding with long-term DAPT (hazard ratio 1.49, $P = 0.026$). MI, myocardial infarction; NS, non-significant.
trials have demonstrated incremental suppression of ischaemic events with more potent platelet ADP receptor inhibition during this period. 1 Finally, these guidelines should be individualized based on each patient’s relative risk of atherothrombosis and bleeding. 2 ‘Resolute’ attention to stent pharmacotherapy is essential to optimize patient outcomes—a most laudable ‘endeavour’.

Conflict of interest: in the last 36 months G.W.S. has served as a consultant to Abbott Vascular, Boston Scientific, Medtronic, Reva, Daiichi Sankyo, Eli Lilly, Bristol-Meyers-Squibb, and Astra Zeneca.

References