The enigmatic search for optimal DAPT duration

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Online publish-ahead-of-print 24 November 2013

This editorial refers to ‘Duration of dual antiplatelet treatment with clopidogrel and aspirin in patients with acute coronary syndrome’1, by C. Varenhorst et al., on page 969

Acute coronary syndromes are associated with injured arterial vessel walls in the setting of a highly prothrombotic state. The stimulus for thrombosis is further heightened by the frequent implantation of a foreign body (a stent) at the site of coronary artery damage. Stenting induces distinct pathological changes in platelet and fibrin deposition together with intense early inflammatory cell infiltration, followed by smooth muscle cell migration and proliferation, and finally complete or incomplete healing. Complete stent endothelialization, the most desired outcome, has been observed within a month with bare metal stent (BMS) implantation, whereas drug-eluting stent (DES) implantation has been associated with highly suppressed early healing and poor endothelial cell coverage that may persist for years.1

We know that compared with aspirin monotherapy, dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor in the non-ST-segment elevation myocardial infarction acute coronary syndrome (NSTEMI ACS) patient is effective in reducing thrombotic events but carries increased risk of bleeding.2 We also know that greater P2Y12 inhibition than derived from clopidogrel therapy in the ACS patient treated with percutaneous coronary intervention (PCI) is associated with less thrombotic event occurrence but more bleeding.3,4 However, the importance of more potent P2Y12 inhibition is a bit less clear in the medically managed ACS patient.5 In the PLATelet inhibition and patient Outcomes (PLATO) trial, the medically managed patient derived a benefit from ticagrelor therapy.3 However, in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRIALGY-ACS) trial, an investigation devoted to medical management of NSTEMI ACS, prasugrel-treated patients did not derive a similar benefit from more potent platelet inhibition than clopidogrel.5

Continuous improvements in stent technologies and PCI performance have challenged the relevance of data on the optimal duration of DAPT derived from patients studied more than even 3 years ago. The newest stents have been associated with very low early and late thrombosis rates, and recent studies have questioned the need for DAPT for longer than 3–6 months.6–10 Moreover, the accruing evidence addressing the cost and morbidity associated with bleeding during long-term DAPT has stimulated great interest in shortening the duration of DAPT.11 In this rapidly developing area, the American and European guidelines have updated recommendations for the duration of DAPT.12,13 However, the bottom line statement remains, ‘The optimal duration of DAPT after DES implantation is not known’.13 Major reasons for this statement are the absence of strong evidence from an adequately sized randomized controlled trial (RCT) to demonstrate the efficacy, particularly with respect to stent thrombosis, of a shorter duration DAPT and the lack of a dedicated trial in the ACS population.

Provocative but underpowered RCTs have attempted to address the optimal duration of DAPT in DES-treated patients. In the first reported prospective study that combined two trials where patients (n = 2701, ~60% with ACS) who were treated with DES and DAPT for 1 year and had an event-free 12 month period were randomized to DAPT or aspirin only. In this study, the primary endpoint [myocardial infarction (MI) or death] did not differ between groups. The authors rightfully concluded that their study ‘had insufficient power to allow for a conclusion regarding the safety of clopidogrel discontinuation after 12 months’.6 In the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY), 2013 patients (~75% with ACS) treated with BMS and various DES were randomized to 6 or 24 months of DAPT. At 2 years, there was a similar ~10% composite endpoint occurrence of any cause death, MI, or cerebrovascular event in both groups and a 2-fold greater risk of bleeding in the 24-month DAPT group.7 Importantly, in a pre-specified analysis that assessed device-specific outcomes relative to duration of DAPT, the occurrence of the primary endpoint was significantly lower at 6 months as compared with 24 months therapy in patients treated with a zotarolimus-eluting stent (ZES).8 In the similarly sized REAL Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation (RESET) trial (n = 2117, ~55% with ACS), the primary combined endpoint (any death, MI, or stent thrombosis) occurrence at 1 year of follow-up was non-inferior between 3-month DAPT after a ZES vs. 12-month DAPT with another DES. However,
in the latter study, the authors stated that ‘the generalized application of these results to the entire population demands careful attention’. In a recently published study, 1443 patients (~50% with ACS) treated with DES were randomly assigned to 6- vs. 12-month DAPT. The primary endpoint occurrence of cardiac death, MI, or ischaemia-driven target vessel revascularization at 12 months did not differ between groups, whereas the stent thrombosis rate tended to be higher in the 6-month DAPT group. The authors concluded that, ‘the study was underpowered for death or MI and that the non-inferiority margin was wide’. Despite the limited current evidence, the European agency gave a CE mark for only 3-month DAPT duration after treatment with the Xience Prime or the Xience V everolimus-eluting stent. In the ongoing DAPT study (NCT00977938), 20 645 patients treated with DES were randomized to 12 months vs. 30 months therapy with clopidogrel or prasugrel plus aspirin. The DAPT trial is the only adequately sized investigation to detect small but clinically meaningful differences in stent thrombosis. The DAPT trial is powered to detect an absolute 0.725% difference in death, MI, or stroke, and an absolute 0.275% difference in stent thrombosis with a non-inferiority margin of 0.8% in Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate or severe bleeding compared at an expected rate of 2.2%.

Despite being the gold standard that leads to Class I recommendations in the guidelines, there remain pitfalls of RCTs that include stringent enrolment criteria precluding generalizability (real-world experience) and high cost. The benefits of RCTs are balanced groups, limited selection bias, and well monitored follow-up including confirmation of patient compliance. Sample size and the cost of performing large-scale RCTs can be addressed by well planned registries defining pre-specified demographic, medication, and outcome variables. Although extensive measures are taken to adjust for multiple known confounders, a major limitation of registry studies is the inability to adjust for unknown confounders. An important example would be the implicit decision-making of the clinician regarding the duration of DAPT in a given patient. Other limitations include incomplete follow-up with the risk of missing important ‘silent’ endpoints and unknown patient compliance regarding study medications.

Among the most widely reported registry is the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Varenhorst et al. should be congratulated for tackling the burning issue of optimal DAPT duration in a very large ACS population. In their current study, Varenhorst et al. report findings from SWEDEHEART and other Swedish registries in 56 440 patients. Extensive measures were taken to adjust for baseline variables potentially associated with occurrence of the primary endpoint (all-cause death, stroke, or re-infarction) including revascularization. Outcomes were compared with respect to the duration of DAPT based on the number of prescribed clopidogrel tablets (3 months, 84–100 clopidogrel tablets; >3 months, >100 tablets; 6 months, 168–200 tablets; >6 months, >200 tablets). The investigators excluded patients with an ischaemic event and bleeding events during the first 3 months and 6 months for the >3 vs. 3 months and >6 vs. 6 months DAPT outcome comparisons, respectively, as these events might have influenced the decision for long-term DAPT use. Although not reported in detail, the duration of DAPT therapy was according to ‘local Swedish guidelines’. The study demonstrated a significantly lower incidence of the combined primary efficacy endpoint in patients treated with DAPT for >3 months compared with 3 months [adjusted hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.75–0.95; \( p = 0.0042 \)]. The adjusted HR (HR 0.75 with 95% CI 0.59–0.95; \( p = 0.0155 \)) was also in favour of >6 months DAPT vs. 6 months for the same endpoint. Clinically important events such as stent thrombosis and heart failure hospitalizations were not reported. Not surprisingly, a longer duration of DAPT was associated with more bleeding. The evidence from the current study deviates from that of the much smaller RCTs of 100% stented populations that included both stable and ACS patients.

Numerous factors influence the duration of DAPT. In consideration of the latter, it would be useful to take into account the recent findings of the patterns of non-adherence to antiplatelet regimens in stented patients (PARIS) registry. The PARIS registry was a prospective observational study involving 5018 patients (~40% with ACS) enrolled in the USA and Europe between 2009 and 2010 treated successfully with stenting in one or more native coronary artery and DAPT for up to 24 months. In PARIS, the influence of DAPT cessation on clinical outcomes was evaluated with respect to physician-recommended discontinuation, brief interruption (for surgery), or disruption (non-compliance or because of bleeding). In contrast to SWEDEHEART, all adverse events and episodes of DAPT cessation were independently adjudicated. Physician-guided discontinuation was the major reason (41%) for DAPT cessation and was associated with significantly lower major adverse cardiovascular events (MACEs) compared with other strategies. Also, brief interruption lasting up to 14 days was not associated with increased risk for thrombotic event occurrence, whereas disruptions due to bleeding or non-compliance were associated with significantly increased risk of MACEs that was largely attenuated after 30 days. The evidence from PARIS strongly suggested that the mode of DAPT cessation greatly influences risk.

In summary, the goal of determining an optimal duration of DAPT in an individual ACS patient is an enigma that probably will not be solved by large registry-derived information. Moreover, well conducted large-scale RCTs that use arbitrary cut-off points for DAPT duration will have challenges in being ‘definitive’. One challenge is that physicians may be reluctant to enrol their perceived high risk patients and expose them to the potential risk of DAPT cessation, thereby reducing the relevance of the study. Other challenges include interpatient variability in stent ‘healing’, in prothrombotic indices, and in vessel wall vulnerability inside and outside of the target vessel that make a uniform duration of DAPT inconsistent with underlying complex pathophysiology (Figure 1). The cautious interpretation from this very large registry-based analysis of Varenhorst et al. is that longer DAPT is better in ACS. However, how long remains unknown and is unlikely to be the same for every patient. At this time, the final decision on what is the optimal DAPT duration must be based on a complex interpretation of myriad pieces of information, in addition to guidelines.

Conflict of interest: P.A.G. reports serving as a consultant for Daiichi Sankyo, Lilly, Pozen, Novartis, Bayer, AstraZeneca, Accumetrics, Nanosphere, Sanofi-Aventis, Boehringer Ingelheim, Merck, Medtronic, Iverson Genetics, CSL, and Haemonetics; receiving grants from the National Institutes of Health, Daiichi Sankyo, Lilly, Pozen, CSL,
AstraZeneca, Sanofi-Aventis, Haemoscope, Medtronic, Harvard Clinical Research Institute, and Duke Clinical Research Institute; receiving payment for lectures, including service on speakers’ bureaus, from Lilly, Daiichi Sankyo, Nanosphere, Sanofi-Aventis, Merck, and Iverson Genetics; and receiving payment for development of educational presentations from Schering-Plough, the Discovery Channel, and Pri-Med. The other authors report no conflict of interest.

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