The Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

Chasing a Mirage*

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The optimal treatment duration of aspirin and a P2Y12 receptor antagonist after percutaneous coronary intervention (PCI) has vexed cardiologists since the introduction of drug-eluting stents (DES) approximately a decade ago. A short (2- to 4-week) course of aspirin and a thienopyridine after elective implantation of a bare-metal stent became the standard of care by default from randomized trials that observed subjects for only a short period after PCI (1, 2), not from studies that compared different treatment durations. An ongoing hazard of late stent thrombosis was observed when thienopyridine therapy was withdrawn beyond 3 to 6 months after implantation of first-generation DES (3), and histopathological studies linked these events to the presence of inflammation, delayed endothelialization, and neoatherosclerosis (4, 5). The current consensus, codified by the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guidelines, is to treat DES patients with at least 12 months of dual antiplatelet therapy (DAPT), unless the risk of morbidity from bleeding outweighs the anticipated benefit afforded by continued P2Y12 inhibitor therapy (6). From a philosophical perspective, the unnerving experience with first-generation DES shifted the priorities of the interventional cardiologist at the time of discharge from treating the patient to treating the stent.

The second-generation DES are associated with better endothelial healing, likely due to differences in strut design, polymer quantity and composition, use of rapamycin analogues, and drug-release kinetics (7). Network meta-analysis and post-randomization analyses of varying durations of thienopyridine treatment suggest that late stent thrombosis is also less frequent with the newer DES, raising the question of whether a 12-month regimen of aspirin and a P2Y12 antagonist is still required in patients with stable coronary artery disease undergoing stent implantation (8). Although several trials have attempted to assess the safety of more abbreviated courses of a thienopyridine after implantation of second-generation DES, these trials are hampered by lack of power and open-label designs. The results of the DAPT (Dual Antiplatelet Therapy) study added further confusion for many practitioners (9). This large, placebo-controlled trial, which included both first- and second-generation DES, found that continued administration of a thienopyridine beyond the consensus 12-month duration reduced the risk of stent thrombosis and spontaneous myocardial infarction (MI) but was associated with an increased risk of bleeding.

In this issue of the Journal, Giustino et al. (10) address this confusion with a meta-analysis of the effects of different durations of DAPT on ischemic and bleeding outcomes after DES implantation. The investigators included a total of 10 studies involving

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32,135 patients. Among those studies, the duration of “short” DAPT ranged from 3 to 12 months, and the duration of “longer” DAPT ranged from 12 to 48 months. The investigators found that short DAPT was associated with a significantly higher rate of stent thrombosis (odds ratio: 1.71; 95% confidence interval: 1.36 to 2.32) but with less clinically significant bleeding (odds ratio: 0.63; 95% confidence interval: 0.52 to 0.72). Pooling the data from the trials demonstrated that for every episode of stent thrombosis prevented by longer DAPT, ~2.4 clinically significant episodes of bleeding would occur. Second-generation DES substantially attenuated the increased risk of stent thrombosis with short DAPT, and therefore, the authors warn that “the prevention of a single episode of late stent thrombosis will require exposing a greater number of patients with a second-generation DES to potentially serious bleeding harm.”

With this sobering admonition regarding the practical implications of adopting extended P2Y12 inhibition in the current era of second-generation DES, the investigators cast doubt on the appropriate application of the DAPT trial findings, in which the risk reduction in ischemic events beyond 1 year of thienopyridine therapy was consistent across stent type (9). However, there are several issues with the current study that make the validity of its findings uncertain. First, the included trials are clinically and methodologically heterogeneous, suggesting that they are not poolable. The trials can be broadly divided into 2 groups with different purposes: those that were designed to test whether the duration of DAPT could be safely shortened (e.g., 3 to 6 months vs. 6 to 12 months) and those that were performed to investigate whether DAPT beyond the consensus duration could improve outcomes (12 months vs. 30 months). The significant interaction between the 2 clinical groupings and the treatment effect of DAPT duration supports the presence of such heterogeneity and suggests that pooling may have diluted the protective effect of extended thienopyridine therapy. The comparison between stent generations is fraught with even more uncertainty, as the DAPT trial is the only study included in the analysis that examined the benefit of continued thienopyridine treatment beyond 12 months with both generations of DES. Therefore, the meta-analysis cannot provide greater insight than the DAPT trial alone regarding the risk and benefit of extended therapy with second-generation DES. Sensitivity analyses further suggest that the meta-analysis findings are not robust: after excluding the DAPT trial, the effects of different treatment durations on stent thrombosis and on mortality were of borderline significance and neutral, respectively. Finally, the investigators perform an elegant analysis by using standardized incident ratios to quantify the trade-off between a reduction in stent thrombosis and increased “clinically significant” bleeding with continued DAPT. However, this approach was limited in 2 respects: first, it assumed that the clinician and patient view these events with equal weight, and second, the calculation ignored the protection from spontaneous MIs unrelated to the index DES, which in the DAPT trial accounted for more than one-half the ischemic reduction associated with continued thienopyridine therapy beyond 12 months.

Despite these limitations, several important conclusions can be drawn from the efforts of Giustino et al. (10). The analysis of abbreviated duration of DAPT support the hypothesis that it is reasonably safe to treat second-generation DES with a 12-month or briefer (3- to 6-month) course of DAPT, if required, with the caveat that the safety of noncardiac surgery early after discontinuation was not evaluated. The influence of anatomic complexity and clinical characteristics are unknown, and evidence from a meta-analysis is not as robust as that from a large randomized clinical trial. However, an adequately powered randomized trial will be difficult to complete, as exemplified by the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial, which was prematurely halted due to slow recruitment and lower-than-expected event rates (11).

Treating patients who have received a newer DES with extended therapy beyond 12 months reduces stent-related and non-stent-related ischemic events but at the cost of more bleeding. The net balance between these events for the individual patient is the conundrum that has yet to be convincingly answered. Although the current study (10) may have overestimated the degree to which second-generation DES attenuates the clinical benefit of extended DAPT, the totality of data strongly suggests that the risk of late stent thrombosis is substantially lower with these stents, which will narrow the therapeutic window for extended P2Y12 antagonism even if it reduces the relative risk reduction of stent thrombosis consistently across DES type (9). The magnitude of the reduction in non-stent-related ischemic events is therefore a major contributor to the risk/benefit calculus for the particular patient treated with extended therapy. The existence of a non-stent-related ischemic reduction is supported by CREDO (Clopidogrel for the Reduction of Events During Observation) (12), a post-hoc analysis of the CHARISMA
(Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial (13), the DAPT trial (9), and now PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) (14). The next hurdle is to quantify the ischemic benefit unrelated to the stent for the particular DES patient, which will likely depend on a spectrum of clinical, demographic, and possibly genetic characteristics. In addition, targeted P2Y12 inhibition within a range that reduces ischemia but mitigates bleeding remains a tantalizing, yet unproven, approach to enhance long-term safety (15). Once these challenges are overcome, interventional cardiologists will be able to stop treating the stent and begin (again) to treat the patient.

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