EDITORIAL COMMENT

Can Coronary Stent Implantation Complexity Become an Intuitive and Useful Factor to Tailor DAPT Duration?*

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A mandatory period of dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is imperative after coronary artery bare-metal or drug-eluting stent (DES) implantation (1). The need for mandatory DAPT after DES implantation is determined by the need to protect the stented vascular segment while vascular healing and neoendothelial coverage are ongoing, a process that seems to be completed between 3 and 9 months with new-generation devices and is dependent on DES type (1). After this initial period, DAPT may be prolonged, with the aim of providing broader atherothrombotic protection from events arising outside the stented vascular segment (2).

From another point of view, percutaneous coronary intervention (PCI) for stable coronary artery disease has been associated with a mandatory DAPT period of 3 to 6 months; conversely, the consensus is that 1 year of mandatory DAPT should be administered after PCI for acute coronary syndromes (3). However, the cardiac ischemic protection achieved with intense prolonged platelet inhibition has a risk for clinically significant bleeding, which affects subsequent morbidity and possibly mortality (4).

The optimal duration of DAPT after DES has been investigated in more than 10 randomized controlled trials and several meta-analyses (3), including a very large trial focused on very late stent thrombosis.

Interpretation of the available evidence on this subject should be cautious, because indiscriminate long (or short) DAPT duration for all patients with DES would not be appropriate (3). The following 2 contradictory factors should be reconciled on the basis of the individual patient and procedure risk profile: use of long-term DAPT for secondary prevention of coronary ischemic events and use of shorter DAPT to mitigate the risk for bleeding. This difficult goal has been addressed by the recent update of DAPT guideline recommendations (3) and the development of the DAPT and PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) risk scores to inform decision making on the basis of preprocedural clinical variables (5,6).

In this issue of *JACC: Cardiovascular Interventions*, Hong et al. (7) supply new evidence to this field by publishing the results of the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions) trial (7). This was a prospective, multicenter, open-label randomized trial of 1,400 patients undergoing PCI with the new-generation everolimus-eluting stent who were randomized in a 2 × 2 factorial fashion to: 1) intravascular ultrasound (IVUS)–guided versus angiography-guided PCI; followed by 2) 6- versus 12-month DAPT with aspirin and clopidogrel. Importantly, the mandatory inclusion criterion was total stent length of at least 28 mm during the index PCI. This variable can be considered a practical (simple) way to somehow characterize more complex PCI procedures.

As its acronym indicates, this trial was primarily powered to test the superiority of IVUS-guided versus angiography-guided PCI; the comparison between the two DAPT durations was only a secondary objective of

the main study. The primary endpoint of the DAPT duration study was a composite of net clinical adverse events, including cardiac death, myocardial infarction, stroke, or Thrombolysis In Myocardial Infarction major bleeding at 1 year. At 1 year of follow-up, there were no significant differences in the occurrence of the primary endpoint between 6- and 12-month DAPT by intention-to-treat analysis. The lack of significant differences persisted by landmark analysis beyond 6 months, which was the time frame during which the 2 DAPT arms differed. Interestingly, there was a significant interaction ($p_{int} = 0.018$) according to IVUS use, with greater benefit with prolonged DAPT in patients who were not randomized to IVUS-guided PCI. From a practical point of view, "perfecting" the PCI result with intracoronary imaging in this study appears to enhance the safety of a shorter DAPT approach [7].

Despite this clinically meaningful message, some important limitations remain. First, the trial was underpowered to detect differences between DAPT duration with the observed number of events and number of patients randomized. Second, randomization occurred at hospital discharge, and (by using intention-to-treat analysis) most of the adverse events occurred within the first 6 months (i.e., when the 2 DAPT treatment arms were in fact identical). Third, the study was open label, thereby introducing the possible risk for bias. Fourth, both stent thrombosis and bleeding results may be different with prasugrel or ticagrelor rather than clopidogrel or with the inclusion of minor bleeding in the primary endpoint.

Visual inspection of the Kaplan-Meier plot suggests that the failure curves start to diverge immediately after the landmark period of 6 months, when DAPT was interrupted in the short-duration arm. Although the difference in the overall population was not statistically significant, this does not rule out any difference. In fact, the point estimate between 6 and 12 months favors the 12-month DAPT arm with a hazard ratio of 2.00 for increased harm with 6-month DAPT, albeit with a wide 95% confidence interval (0.50 to 7.98) and therefore a nonsignificant p value of 0.30. It is conceivable that a larger sample size might have enabled the documentation of a statistically significant difference.

Although this study on its own is certainly inconclusive and therefore unable to define the optimal upfront DAPT duration after complex stenting, it provides meaningful information on DAPT tailoring according to PCI complexity. First, patients who undergo complex PCI indeed have more advanced coronary atherosclerotic burden, implying a higher risk for atherothrombotic events [8]. Second, stenting of complex lesions (e.g., longer lesions, bifurcations, or highly calcified lesions) is associated with higher risk for underexpansion, malapposition, incomplete lesion coverage, and a possibly slower or nonuniform pattern of endothelialization, which may enhance the risk for platelet activation and thrombosis within the stented vascular segment [8].

In 1995, Colombo et al. [9] first reported on optimal stent implantation with IVUS guidance and high-pressure balloon inflation to avoid routine anticoagulation for the prevention of "stent occlusion," as it was then called. More than 20 years later, this concept is still operational. First, procedural complexity could be a simple and useful parameter to take into account for the practicing interventional cardiologist when making a decision on the optimal mandatory DAPT duration post-PCI. Second, efforts in optimizing intracoronary stenting to achieve proper vessel wall apposition, greater luminal diameters, and normalization of the in-stent rheology decrease the risk for periprocedural events [10] but also in averting long-term DES-related complications or obviating the necessity of extended DAPT duration for cardiac ischemic protection. Third, other measures of PCI complexity besides stent length may be investigated, such as multivessel PCI, stenting of bifurcations, or severely calcified lesions; in these cases, implementation of intracoronary imaging may be useful in optimizing procedural results and potentially enabling the avoidance of mandatory prolonged-term DAPT treatment.

Further research is needed to investigate optimal post-PCI antithrombotic therapy in terms of intensity and duration. The DAPT and PARIS risk scores provide useful tools informing which clinical risk factors most influence thrombotic and bleeding events. Nonetheless, they both do not take into account angiographic or other variables previously reported as important determinants of stent thrombosis risk [11]. Angiographic complexity and procedural success may be the next parameters to introduce in the equation to better tailor the duration and potency of DAPT after coronary stenting.

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