EDITORIAL COMMENT

Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation
Is it Time to Slacken the Reins?*

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Drug-eluting stents (DES) were introduced in interventional practice more than 10 years ago and rapidly replaced bare-metal stents (BMS) for treatment of coronary artery disease because of their superior capability to reduce the need for restenosis-driven repeat intervention. Soon, it became obvious that besides optimal stenting technique, dual antiplatelet therapy (DAPT), which means the combination of aspirin and a P2Y12 platelet receptor inhibitor, has to be established for a prolonged time after stent implantation in order to avoid potentially catastrophic stent thrombosis (ST). In the era of first-generation DES, it turned out that premature discontinuation of DAPT, which means <3 months for sirolimus-eluting stents (SES) and <6 months for paclitaxel-eluting stents (PES), is a strong predictor of ST (1,2), and this relationship is more pronounced in patients with acute coronary syndromes receiving DES (3).

As additional safety concerns arose from reports of an increased risk of late and very late (>1 year) ST events with first-generation DES (4,5), an attitude towards “the longer, the better” DAPT therapy developed. This is reflected in current guidelines of the American societies recommending at least 12 months of DAPT with clopidogrel after DES implantation (6) and the European Society of Cardiology endorsing 6 to 12 months of DAPT treatment after DES implantation and 12 months for all patients after ACS, irrespective of revascularization strategy (7). Meanwhile, second-generation DES with durable polymers such as everolimus-eluting stents (EES) or zotarolimus-eluting stents (ZES) and third-generation DES with biodegradable polymers and abluminal coating such as biolimus-eluting stents (BES) widely replaced first-generation DES because of improved stent deliverability while exhibiting equal or superior antiproliferative efficacy, and a consistent lower rate of late or very late ST (8,9). A recent network meta-analysis presented the provocative finding that within 2 years, EES might have a lower risk of ST than BMS (10), which, unlike common perception, might be based on the possibility that polymeric coating could reduce stent thrombogenicity (11). This lower rate of ST with newer-generation DES might be attributable to better implantation technique, improved stent platform, thinner strut thickness, more biocompatible polymers, type and amount of antiproliferative drug, or a combination thereof.

Of note, in most contemporary DES trials, prolonged DAPT intake for at least 12 months was mandatory, although the optimal duration of DAPT is still lacking scientific ground.

DAPT invariably increases the risk of major bleedings (12). The bleeding risk correlates with the duration of DAPT (13), and bleeding events clearly have a negative impact on outcomes of patients after PCI (14). This raises 2 important questions, which are momentous for patients with a high likelihood for bleeding events, with the need for nondeferrable or unplanned noncardiac surgery or invasive procedures, for elderly or fragile patients, and for patients with low drug adherence: First, are there certain conditions allowing us to safely shorten DAPT to <12 months after DES implantation, and second, what are the consequences of DAPT discontinuation (temporary or permanent), in case one of these events occurs?

In this issue of the Journal, Kim et al. (15) address the first question. In the RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) trial, 2,148 patients with stable angina, unstable angina, or acute myocardial infarction (MI) undergoing elective PCI were enrolled, with 1,059 randomized to the Endeavor (Medtronic, Santa Rosa, California) zotarolimus-eluting stent (E-ZES) and 3 months of DAPT and 1,058 patients treated with standard 12-month DAPT and other DES (Resolute [Medtronic] zotarolimus-eluting stent [R-ZES], EES, or SES). Patients with significant left main disease, in-stent restenotic lesions, chronic total occlusions, or patients with acute ST-segment elevation MI (STEMI) were excluded from the trial. At 12 months, the combined endpoint of cardiovascular death, MI, ST, target vessel revascularization (TVR), or bleeding occurred in 4.7% of patients in both treatment arms (p < 0.001 for noninferiority). Overall, there was no significant difference in any of the individual components of the primary endpoint. Definite or probable ST occurred in 2 patients (0.2%) treated with E-ZES, both within the first month. Three patients (0.3%) had ST in the conventional 12 months DAPT therapy arm, all of them between 3 and 12 months. There was no significant difference in the...
primary endpoint in any of the subgroups, including patients with diabetes mellitus and those with acute MI.

Considering the RESET trial, is it now a safe strategy to implant E-ZES and limit DAPT to 3 months? Caution should be advised in interpretation of the data. First, in their power calculations, the authors assumed a 10% incidence for the primary endpoint at 12 months with a noninferiority margin of 4%, where in fact the event rate was low with 4.7%. Therefore, statistically, a much larger sample size would have been needed to prove the hypothesis. Second, the low event rate is unexpected and might in part be explained by the anatomic low-risk profile as defined in the inclusion/exclusion criteria of the trial, which makes it difficult to translate the findings to a broader all-comer population. Third, the investigators choose the E-ZES because of a supposedly better safety profile. The phospho-rycholine polymer coating of the Endeavor stent accounts for a rapid release of zotarolimus within 2 weeks, resulting in a reduced antiproliferative effect, reflected by early neo-intimal growth and higher late loss, which did not translate in clinical events in patients with a low-risk profile (16), but became evident in a more daily-practice population. The hypothesis that this E-ZES–typical feature of early neointimal growth would be protective against late ST was challenged by the SORT OUT III (Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients) trial, describing a 1.1% definite ST rate for E-ZES versus 0.3% for SES (p = 0.048) at 12 months (17), though the incidence of very late ST (>12 months) was consistently low throughout the pivotal E-ZES trials (16,18). Moreover, the follow-up time of 12 months in the RESET trial might not be long enough to detect potential safety differences. Fourth, industry has already reacted and replaced the E-ZES by its successor, the Resolute-ZES (R-ZES) with a different slow-release polymer (BioLinx) and improved antiproliferative activity. Therefore, in most catheterization laboratories, the E-ZES has disappeared from the shelves and is replaced by the R-ZES. Fifth, in the control arm, a mixture of first-generation (SES) and second-generation DES (EES, R-ZES) was used instead of the E-ZES, hindering direct comparisons, and finally, 14% of the population in the trial presented with non–STEMI, the patient group probably having the most benefit from prolonged DAPT by preventing future atherothrombotic events regardless of the stent type implanted. The OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice) trial (NCT01113372), currently randomizing 3,120 patients to 3 versus 12 months of DAPT after E-ZES implantation, will probably give us a more robust insight into the safety of this approach, although the results cannot guide catheterization laboratories that have already abandoned the E-ZES.

The work of Ferreira-González et al. (19) in this issue of the Journal engages with the topic of antiplatelet therapy discontinuation (ATD) during the first 12 months. They have extended their previous work on incidence and predictors of ATD (20) in the same population, to the consecutive risk for cardiac death and MI associated with it. DAPT nonadherence can be based on disruption because of bleeding events or noncompliance, on the recommendation of physicians (medical decision) who have felt that the patients no longer need this therapy (usually permanent), or on a guided and recommended interruption because of a surgical or invasive procedure, usually temporary and not longer than 14 days; it can be brief (<5 days), temporary or permanent. The Spanish investigators prospectively collected data on 1,622 all-comer patients undergoing implantation of at least 1 DES. The major findings are as follows: First, DAPT interruption for any reason was not infrequent and occurred in 10.6% of the patients, although in only 1 patient, ATD was observed within the first 4 weeks. Second, in the majority of the patients with ATD, the interruption was temporary, and third, the composite end-point of cardiac death or acute coronary syndrome occurred in 5.4% of all patients, but only in a minority (8%) of those patients was ATD at any time before the event noted. In multivariate analysis, ATD was not found to be predictive for future cardiac events. The authors have to be acknowledged for their thorough assessment of ATD, as most trials and registries simply collect data of patients being “on” or “off” DAPT, ignoring the dynamic nature of drug intake. The extent of ATD within the first year was high; however, in their analysis, overall premature ATD seemingly did not translate into serious consequences. This may be explained by the following issues: First, in 65% of the cases, ATD was temporary (median: 7 days), whereas it was shown that the median interval from discontinuation of thienopyridine to ST was 13.5 days for the first 6 months (1,21). Second, the temporal association between ATD and consecutive events beyond 6 months is known to be lenient (22), and twice as many patients in this study disrupted their DAPT at 6 to 12 months. Third, because the event rates were low, the power of the study is limited and the confidence intervals are wide. Fourth, the authors were well advised to do simulations of ATD in those patients who died of cardiac reasons. If in 18.8% of these cases DAPT had been interrupted before death, the association between ATD and cardiac events would have been significant. As it is difficult to receive detailed information from relatives on DAPT adherence of the deceased person, an even higher misclassification is quite conceivable. For these reasons, the data can only suggest that a brief interruption of DAPT does not have a large impact on ischemic risk. For more information on different modes of nonadherence to DAPT, subsequent outcomes, and their relation to nonadherence, we have to await the results of the observational PARIS (Patterns of Non-Adherence to Dual Anti-Platelet Regimen In Stented Patients) trial (NCT00998127) following more than 5,000 patients after stent placement over 2 years.
Are these 2 reports now suggesting that the time has come to slacken the reins in antplatelet therapy after DES? With newer-generation DES, 6 months DAPT might be sufficient, and 3 months not completely of the wall in low-risk groups. Brief interruption of DAPT beyond 4 weeks might not be associated with a dramatic risk increase. However, the patient- and device-related criteria safely allowing early DAPT withdrawal or interruption still have to be determined. Until then, we should be cautious and do our best to avoid unplanned discontinuation of DAPT.

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