JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 12, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.05.008

EDITORIAL COMMENT

DAPT Duration After Drug-Eluting Stent Implantation

No News Is Good News*

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This year, percutaneous coronary intervention (PCI) is living its 40th anniversary, which indicates the coming of age of a technique that has achieved low procedural risks and excellent clinical outcomes, providing similar (if not superior) results as compared with conventional coronary bypass surgery in many patient/lesion subsets.

The advent of coronary stents greatly contributed to make the results of PCI predictable, satisfactory, and durable. The risk of thrombotic stent occlusion led to the development of dual antiplatelet therapy (DAPT), which was originally conceived as a dedicated treatment regimen to prevent stent thrombosis (ST), a serious limitation of stent implantation.

Twenty years after the first study ascertained the efficacy of DAPT for ST prevention (1), and roughly 10 years after durable DAPT was mandated by consensus to avert the risks of very-late ST (2), DAPT investigations have reached a mature state, to which the 2-year results of the ITALIC (Is There a Life for Drug Eluting Stent (DES) After Discontinuation of Clopidogrel) study nicely contributes (3). The current evidence shows that there can be safe drug-eluting stent (DES) implantation without prolonged DAPT and that there is value for prolonged DAPT in some cases of DES implantation (**Table 1**).

Trials have explored the potential to safely reduce DAPT duration to 3 to 6 months and showed the noninferiority of this approach compared with 12 months DAPT (4). Recently, in high bleeding-risk patients, even 1-month DAPT was shown to be safe and effective after new-generation DES implantation as compared with bare-metal stents (5,6). By contrast, other randomized clinical trials have shown benefits, even if at greater bleeding risk, of a DAPT regimen longer than 12 months (ranging from 18 to 48 months) as compared with 6- or 12-month therapy (4).

The ITALIC trial adds fuel to this complex panorama, suggesting that 6-month DAPT is noninferior to longer DAPT. The trial was designed and powered to demonstrate the noninferiority of 6- versus 12-month DAPT at 1 year for the primary net composite endpoint of all-cause mortality, myocardial infarction (MI), target vessel revascularization, stroke, or major bleeding, and indeed supported that rates of bleeding and thrombotic events at 1 year were much the same in both treatment groups (7).

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In this issue of *JACC: Cardiovascular Interventions*, Didier et al. (3) present the 2-year clinical outcomes in aspirin-responsive patients treated with 6- or 24-month DAPT after second-generation DES in the ITALIC trial. Therefore, this study adds new, clinically relevant findings. The investigators report that the composite endpoint, as well as individual rates of MI and stroke, were similar between the groups, though there were nonsignificant trends toward lower ST (0.3% vs. 0.6%; $p = 0.33$) and target vessel revascularization (0.3% vs. 1.0%; $p = 0.10$) at costs of higher mortality (2.2% vs. 1.2%; $p = 0.11$) and major bleeding (0.4% vs. 0%) in the 24-month group.

Importantly, whereas patients were randomly allocated to the 2 DAPT durations at the time of PCI,

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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TABLE 1 Trials Testing DAPT Regimens Longer Than 12 Months

Trial Name	N	Treatment Duration, Months	Stent Type	Primary Endpoint
ARCTIC INTERRUPTION	1,259	17 vs. 12	EES, PES, SES, ZES, other DES	Superiority of prolonged DAPT not demonstrated
DAPT	9,961	30 vs. 12	EES, PES, SES, ZES	Superiority of prolonged DAPT demonstrated
DES-LATE	5,045	12 vs. 36	EES, PES, SES, ZES, other DES	Superiority of shorter DAPT not demonstrated
ITALIC	1,850*	6 vs. 24	EES	Noninferiority of shorter DAPT demonstrated, but prematurely stopped
NIPPON	3,307†	6 vs. 18	BES	Noninferiority of shorter DAPT demonstrated (preliminary data), but prematurely stopped
OPTIDUAL	1,385‡	48 vs. 12	EES, PES, SES, ZES, other DES	Superiority of prolonged DAPT not demonstrated, but prematurely stopped
PRODIGY	1,970	24 vs. 6	BMS, EES, PES, ZES	Superiority of prolonged DAPT not demonstrated

*Of the 2,475 patients initially planned. †Of the 4,598 patients initially planned. ‡Of the 1,966 patients initially planned.

ARCTIC INTERRUPTION = Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting-Interruption; BES = biolimus A9-eluting stent(s); BMS = bare-metal stent(s); DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); DES-LATE = Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events; EES = everolimus-eluting stent(s); ITALIC = Is There a Life for Drug Eluting Stent (DES) After Discontinuation of Clopidogrel; NIPPON = Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL = Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation; PES = paclitaxel-eluting stent(s); PRODIGY = Prolonging Dual Antiplatelet Treatment in Patients With Coronary Artery Disease After Graded Stent-Induced Intimal Hyperplasia Study; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

only those event-free at 6 months from PCI entered the study. Although direct randomization at 6 months would have been preferable from a methodological standpoint, this study design excludes the confounding or chance effect eventually observed in the first 6 months, when all patients receive the same antiplatelet regimen.

Overall, the noninferiority of shorter DAPT and absence of benefits with longer DAPT should be interpreted in the context of the study itself.

First, 2-year follow-up was performed in 94% of patients, and there was suboptimal adherence to treatment assignment: in the 6-month DAPT group, 212 patients (23.2%) failed to respect treatment duration (9 stopped before 6 months; 123 were on DAPT after 6 months, but not at 24 months; and 80 remained on DAPT after 24 months), whereas in the 24-month DAPT group, 170 patients (18.7%) discontinued treatment before 24 months.

Second, the findings reported apply to clopidogrel-treated patients, not to patients receiving ticagrelor or prasugrel.

Third, included patients were at low ischemic and bleeding risk, which could have mitigated benefits and risks of longer DAPT. Overall, event rates were low, even more than expected (primary endpoint at 1 year was postulated to occur in 3%, but was 1.6%). The unique study design (selecting aspirin-responders) may have contributed to the low event rates. Although the high-risk acute coronary syndrome (ACS) subgroup did not show particular benefit from prolonged DAPT, there was a significant interaction for the composite endpoint between patients with or without prior MI (patients with prior MI showed a borderline significant benefit from 24-month DAPT) that is in agreement with previous data (8). It should be appreciated that the ACS subgroup analysis is underpowered, especially considering the premature treatment interruption and low event rates. There was a significant interaction in age-based subgroups, showing that elderly patients did benefit from shorter DAPT. On the other hand, patients with diabetes did not benefit from longer DAPT, as previously shown (9).

The present findings support those previously observed in PRODIGY (Prolonging Dual Antiplatelet Treatment in Patients With Coronary Artery Disease After Graded Stent-Induced Intimal Hyperplasia Study), which also compared 6- versus 24-month DAPT but included a population at higher ischemic/bleeding risk (older age, higher rates of patients with prior MI, with ACS, with ST-segment elevation MI, with chronic renal disease) and with higher overall event rates (net composite 11.3% compared with 3.6% in the ITALIC trial) (10).

Notably, the authors report a 45% increase of all-cause death with 24-month DAPT, whereas cardiac death was similar between groups. This finding is obviously underpowered and inconclusive. However, it contributes to the concerning signal previously

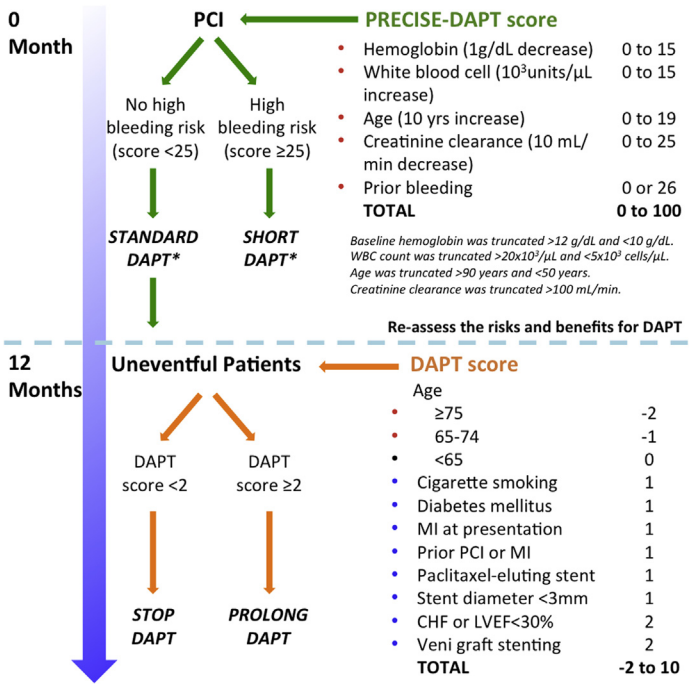
reported for long-term DAPT, which seems to mainly affect noncardiac mortality (11,12).

Altogether, the results of the ITALIC trial fit well with previous evidence and contribute to the current understand of the benefits and risks of prolonged DAPT. New-generation DES are associated with a very low risk of late and very late ST. Therefore, prolonging DAPT because of DES implantation per se does not seem to be justified in an unselected patient population undergoing PCI for stable or unstable coronary artery disease. In this setting, the risk of major bleeding associated with prolonged DAPT roughly equals the benefits in terms of MI prevention, but it largely exceeds the tiny absolute risk reduction in ST.

Consequently, the real question becomes: in which patients to prolong DAPT? For this purpose, 2 scores, the DAPT (13) and PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) (14), have been recently generated and have demonstrated the potential to support clinicians in this delicate decision making. The DAPT score aims at maximizing the benefits over the risks of a prolonged DAPT regimen by integrating predictors of ischemic events (which favor a prolonged DAPT duration) and bleeding (which play against the decision of prolonging DAPT), and should be calculated after 1 year of uneventful DAPT therapy, to decide whether to stop or prolong the treatment. PRECISE-DAPT focuses on bleeding risk only, should be computed soon after PCI, and identifies patients who had, not only bleeding events, but also ischemic recurrences, are lower if treated with a relatively shorter (i.e., 3 to 6 months) DAPT regimen (14). Although both are awaiting large-scale prospective validation, these 2 new decision-making tools should raise awareness in the community on which criteria should influence treatment duration and which characteristics should not (**Figure 1**).

In summary, the 2-year results of the ITALIC study do not generate news on the delicate tradeoff between benefits and risks of prolonging DAPT among DES-treated patients. Because confirmation and replication of study results are a mainstay of science, the absence of news is definitively good news for the interventional community, which is now confronted with the new challenge to tailor DAPT duration to patients' characteristics more than to the implanted coronary devices' characteristics.

FIGURE 1 Use of PRECISE-DAPT and DAPT Scores for Decision-Making of DAPT Duration



Variables included in the scores are associated with increased bleeding risk **(red dots)**, increased ischemic risk **(blue dots)**, or neutral effect **(black dots)**. *In the validation study, short-term DAPT consisted of 3 to 6 months of therapy, and standard DAPT consisted of at least 12-month DAPT duration. CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

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KEY WORDS bleeding event(s), drug-eluting stent(s), dual antiplatelet therapy, ischemic event(s), percutaneous coronary intervention