A
dverse ischemic events following coronary stenting may be related to either stented or nonstented vascular segments. Although dual antiplatelet therapy (DAPT) improves clinical outcomes following coronary stent deployment through reductions in both stent thrombosis (ST) as well as myocardial infarction (MI) not related to ST, the optimal duration of DAPT following either drug-eluting stent (DES) or bare-metal stent (BMS) deployment has been the subject of debate. Current U.S. clinical practice guidelines recommend at least 1 year of therapy, if tolerated, following DES in stable ischemic heart disease and at least 1 year of therapy following stenting in acute coronary syndromes regardless of stent type (DES or BMS) (1). The benefit of DAPT must be weighed against the risk of bleeding, which is increased in proportion to the intensity and duration of treatment. Multiple randomized trials have compared different durations of DAPT following coronary stenting (2–7). Although these trials differ in their design, the populations enrolled, and durations of therapy, they share the common feature of having been underpowered to detect clinically-meaningful differences in ST and MI, as evidenced by the wide confidence intervals for these endpoints (Table 1). As a result, most studies have combined safety (bleeding) and efficacy (ischemia) measures into a single composite primary endpoint in an attempt to accrue power for the assessment of noninferiority between DAPT treatment durations (4–7). This tactic, which obscures directionally divergent changes in measures of different relative value, may confound the ability to draw accurate conclusions.

The ITALIC (Is There A Life for DES After Discontinuation of Clopidogrel) study, which appears in this issue of the Journal (8), randomly assigned 1,850 aspirin-responsive subjects who were free from death, MI, or target vessel revascularization at 6 months following everolimus-eluting stent (EES) (Xience, Abbott Vascular, Santa Rosa, California; or Promus, Boston Scientific, Marlborough, Massachusetts) deployment to receive either continued dual therapy (aspirin plus a P2Y12 receptor inhibitor) or aspirin only for an additional 18 months (a total of 24 months) on an unblinded basis. Although the stated DAPT duration comparison was 6 months versus 24 months, the trial primary endpoint of death, MI, urgent target vessel revascularization, stroke, or major bleeding event was assessed at 12 months and was observed in 1.6% versus 1.5% of the 6-month versus 12-month treatment groups, respectively (p = 0.85, p < 0.001 for noninferiority). The authors conclude that 6-month DAPT is noninferior to longer duration treatment. However, multiple concerns cloud the interpretation of this conclusion.

First, a lack of power (study was terminated early due to poor enrollment), lower-than-expected event rates (the primary endpoint event rate was anticipated to be 3%), and imbalanced study medication...
TABLE 1 Randomized Trials of Dual Antiplatelet Treatment Duration After DES

<table>
<thead>
<tr>
<th>Trial Name (Ref. #)</th>
<th>Total Randomized</th>
<th>Treatment Duration</th>
<th>DES Type</th>
<th>Stent Thrombosis</th>
<th>Myocardial Infarction</th>
<th>bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>REAL + ZEST LATE (2)</td>
<td>2,701</td>
<td>24 vs. ~12</td>
<td>SES, ZES, or PES</td>
<td>1.23 (0.33–4.58)</td>
<td>1.41 (0.54–3.71)</td>
<td>2.96 (0.31–28.46)</td>
</tr>
<tr>
<td>PRODIGY (4)</td>
<td>1,357</td>
<td>24 vs. 6</td>
<td>PES, ZES, or EES</td>
<td>0.87 (0.41–1.81)</td>
<td>0.94 (0.61–1.45)</td>
<td>2.17 (1.44–3.22)</td>
</tr>
<tr>
<td>EXCELLENT (3)</td>
<td>1,443</td>
<td>12 vs. 6</td>
<td>SES or EES</td>
<td>0.17 (0.02–1.39)</td>
<td>0.54 (0.21–1.35)</td>
<td>2.0 (0.37–11.11)</td>
</tr>
<tr>
<td>OPTIMIZE (5)</td>
<td>3,120</td>
<td>12 vs. 3</td>
<td>ZES</td>
<td>0.95 (0.42–2.04)</td>
<td>0.85 (0.57–1.29)</td>
<td>1.41 (0.63–313)</td>
</tr>
<tr>
<td>ITALIC (8)</td>
<td>1,850</td>
<td>12 vs. 6</td>
<td>EES</td>
<td>0 vs. 3 events*</td>
<td>0.67 (0.19–2.38)</td>
<td>3 vs. 0 events*</td>
</tr>
<tr>
<td>ISAR-SAFE (7)</td>
<td>4,005</td>
<td>12 vs. 6</td>
<td>EES, SES, ZES, or BES</td>
<td>0.80 (0.21–3.03)</td>
<td>1.08 (0.51–2.27)</td>
<td>1.25 (0.34–4.76)</td>
</tr>
<tr>
<td>DAPT (10)</td>
<td>9,961</td>
<td>30 vs. 12</td>
<td>EES, SES, ZES, or PES</td>
<td>0.29 (0.17–0.48)</td>
<td>0.47 (0.37–0.61)</td>
<td>1.61 (1.21–2.16)</td>
</tr>
</tbody>
</table>

Values are n or hazard ratio (95% confidence interval). *Due to 0 events in 1 arm, hazard ratio could not be estimated.

BES = biolimus-eluting stent(s); DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); EXCELLENT = Efficacy of XIENCE/ PROMUS versus CYPHER to reduce late loss after stenting; ISAR-SAFE = The intracoronary stenting and antithrombotic regiment: Safety and efficacy of 6 months dual antiplatelet therapy after drug-eluting stenting; ITALIC = Is There A Life for DES After Discontinuation of Clopidogrel; OPTIMIZE = Optimized duration of clopidogrel therapy following treatment with the zotarolimus-eluting stent in real-world clinical practice; PES = paclitaxel-eluting stent; PRODIGY = Prolonging dual antiplatelet treatment after grading stent-induced intimal hyperplasia; REAL + ZEST LATE = Correlation of clopidogrel therapy discontinuation in real-world patients treated with drug-eluting stent implantation and late coronary arterial thrombotic events – evaluation of the long-term safety after zotarolimus-eluting stent, sirolimus-eluting stent or paclitaxel-eluting stent implantation for coronary lesions - late coronary arterial thrombotic events; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

compliance (24% of short-duration subjects were nonadherent vs. 5.4% of long-duration subjects) all bias toward the null for noninferiority. Second, the 95% confidence interval surrounding the primary endpoint is wide, allowing for a >2-fold increase in events in the short-duration treatment group without negating the noninferiority claim. Third, few events were observed (only 3 [0.16%] STs and 10 [0.45%] MIs), which suggests that the study population was very low risk and perhaps not representative of routine clinical practice. The prerequisite requirement for documented ex vivo platelet responsiveness to aspirin prior to randomization may have contributed to the lower-than-expected event rates. The ITALIC study is novel with respect to this exclusionary (aspirin nonresponsiveness) criterion. Finally, given the low event rates and sample size in the primary analysis, the subgroup analysis of acute coronary syndrome patients is grossly underpowered to examine potential treatment interactions. Although it may be tempting to combine the ITALIC study with prior trials using meta-analysis, the post hoc aggregation of underpowered trials with variable study populations, protocols, methodologies and endpoints not infrequently provides results that are proven incorrect by a subsequent, adequately-powered, randomized, controlled clinical trial (9).

In this context, the DAPT (Dual Antiplatelet Therapy) study, designed in response to a request from the U.S. Food and Drug Administration, is adequately powered for the efficacy coprimary endpoints of ST (Academic Research Consortium definite/probable definition) and major adverse cardiovascular and cerebrovascular events (composite occurrence of death, MI or stroke), as well as a primary safety endpoint of severe/moderate (GUSTO definition) bleeding (10). Following 1 year of DAPT, subjects who had received treatment with a U.S. Food and Drug Administration-approved DES (Xience/Promus EES; Taxus paclitaxel-eluting stent from Boston Scientific; Cypher sirolimus-eluting stent [SES] from Cordis, Fremont, California; or Endeavor zotarolimus-eluting stent from Medtronic, Santa Rosa, California) or BMS, who were free from ischemic cardiovascular events and severe/moderate bleeding, and who were adherent to antiplatelet therapy were randomly assigned to receive either thienopyridine (clopidogrel or prasugrel) in combination with aspirin or aspirin plus matching placebo on a blinded basis for an additional 18 months. This 18-month period on a randomized, blinded study drug was followed by a mandatory 3-month observation period without thienopyridine therapy for all subjects. Among DES-treated subjects (n = 9,961) prolonged thienopyridine therapy for 30 months was associated with a 71% relative reduction in ST and a 29% relative reduction in major adverse cardiovascular and cerebrovascular events (p < 0.001), which was driven by a 53% relative reduction in MI (p < 0.001), 55% of which was not attributable to ST. Bleeding events were increased by 61% (p = 0.001) and were largely due to moderate bleeding. Severe bleeding events, including fatal events, were rare and were not different between groups.

Importantly: 1) adverse ischemic events were observed with increased frequency in the 3 months following thienopyridine discontinuation in both treatment arms: (i.e., 12 to 15 months for the placebo group and 30 to 33 months in the continued
thienopyridine group); and 2) the time to event curves for ST and MI continued to diverge throughout the randomized treatment period (12 to 30 months) (Figure 1). These observations suggest: 1) the preventive benefit of thienopyridine therapy is realized early; 2) treatment duration beyond 30 months may provide additional ischemic benefit; and 3) treatment discontinuation may be associated with ischemic hazard even months to years after coronary stenting. This ongoing risk of cardiovascular events beyond the stented segment should not be surprising in subjects with symptomatic coronary artery disease. Finally, adjusted analyses demonstrated that the magnitude of benefit associated with longer (30 months) duration of thienopyridine for reduction in ST or MI was consistent across all 4 DES types studied, including the 4,703 (47.2%) subjects who received EES similar to what was exclusively utilized in the ITALIC study (10). Specifically, adjusted hazard ratios favoring longer duration therapy in EES-treated patients were 0.38 (95% confidence interval: 0.15 to 0.97) for ST and 0.63 (95% confidence interval: 0.44 to 0.91) for MI.

Thus, although the absolute risk of ST may be less with new-generation DES (11), treatment benefit persists well after the initial procedure, and the hazard of MI not related to ST remains ongoing and is modified by extended DAPT duration. Although the relative risk reductions for ST and MI observed in the DAPT study are dramatic, particularly in the context that subjects were not randomized until 1 year following their index procedure, one might expect these differences to be magnified if the 12-month treatment group had been of even shorter duration, as was examined in the ITALIC study. Such differences would only be detectable in an appropriately-powered trial that enrolled subjects representative of current percutaneous coronary intervention practice (not smaller trials of low-risk subjects).

The decision to continue DAPT beyond any time point must involve a balance of risks (12). The risk of bleeding must not be discounted, despite the magnitude of antithrombotic benefits (often nonstent related) observed in the DAPT study. However, recent calls to “individualize” therapy provide insufficient guidance for practicing clinicians (13). Among patients without prior episodes of severe/moderate bleeding who tolerated DAPT to 1 year, significant ischemic event benefit is accrued by extending DAPT through 30 months if not longer. In this context, the bleeding risk appears to be acceptable. Finally, further analyses are required to provide risk stratification for the purpose of safe discontinuation of DAPT beyond 30 months of treatment.

**REFERENCES**


**KEY WORDS** drug-eluting stent(s), percutaneous coronary angioplasty