The goal of dual-antiplatelet therapy (DAPT) is to prevent local thrombotic complications related to stent implantation and to reduce systemic atherothrombotic events. After implantation of bare-metal stents, DAPT reduces stent thrombosis by 85% (relative risk: 0.15; 95% confidence interval [CI]: 0.05 to 0.43) compared with aspirin alone (1). After implantation of drug-eluting stents (DES), DAPT for 30 months reduces stent thrombosis by 71% (hazard ratio [HR]: 0.29; 95% CI: 0.17 to 0.48) and late ischemic complications by 29% (HR: 0.71; 95% CI: 0.59 to 0.85) compared with DAPT for 12 months (2).

Because increased bleeding has been reported in several randomized clinical trials (RCTs), the net benefit of long-term DAPT after stent implantation remains uncertain and prolonged DAPT seems unlikely to be lifesaving (3).

Benefits of long-term DAPT may outweigh risks in patients with diabetes mellitus, a condition associated with vasculopathy, cardiomyopathy, nephropathy, and suboptimal outcomes after percutaneous coronary intervention (4). To study DAPT in a high-risk population, Thukkani et al. (5), in this issue of the Journal, completed an observational study within the Veterans Administration health care system and compared rates of death and myocardial infarction (MI) in diabetic and nondiabetic cohorts defined by whether clopidogrel was used for >12 or ≤12 months with aspirin after coronary stent implantation. As reported by Thukkani et al. (5), the key findings were lower rates of death (HR: 0.59; 95% CI: 0.48 to 0.92 for insulin-dependent diabetic patients; HR: 0.61; 95% CI: 0.48 to 0.77 for non-insulin-dependent diabetic patients) and death or MI (HR: 0.67; 95% CI: 0.49 to 0.92 for insulin-dependent diabetic patients; HR: 0.61; 95% CI: 0.50 to 0.75 for non-insulin-dependent diabetic patients) when DAPT was used for 18 months than when it was used for only 6 months after the implantation of first-generation DES.

The study (5) was performed rigorously. Because the results are provocative, it is important to determine whether they are supported by other evidence, preferably from RCTs. A pooled analysis of the 7 RCTs presenting a breakdown of diabetes mellitus results (2,6–12) suggests that 12 to 30 months of DAPT is no better than 3 to 12 months of DAPT after the implantation of predominantly newer generation DES (Figure 1). Discrepancies between the pooled analysis (2,6–12) and the present study (5) in identifying the benefits of prolonged DAPT are attributed to differences in baseline risk, the type of stent used, and fundamental differences in study design.

The present report (5) describes an observational study that compared outcomes in patients whose exposure to DAPT differed “naturally,” that is, not as a result of random assignment, as in RCTs (13). In an observational analysis, something other than chance leads to early DAPT discontinuation and potentially puts a subject in double jeopardy from stopping therapy early and having an underlying condition such as major surgery or bleeding, leading to platelet activation and hyperfibrinogenemia.

Observational studies lack randomization, which distributes the determinants of outcomes equally.
between groups and prevents prognostic imbalance from threatening the results (14). An observational analysis should identify the reasons for stopping treatment early (13). The Veterans Health Administration investigators (5) were able to capture intracranial and intraocular bleeding events in their administrative database but were unable to identify all the bleeding events or reasons why DAPT was stopped at ≤12 months after stent implantation at a time when evidence from RCTs supported the use of DAPT for 1 year (15).

In an effort to account for differences between the groups sorted by DAPT duration, the Veterans Administration investigators used several statistical adjustments, but patients who tolerated prolonged DAPT and “passed a bleeding stress test” were arguably different from those who stopped their medication early. The 2 groups had different outcomes, and “adjustment” is unlikely to eliminate selection bias (16).

This is not meant to be a criticism of a fine observational study (5), but follow-up for the landmark analyses seems to have been more complete for patients who received DAPT for ≤12 months than for those who continued for >12 months. Although a common assumption is that patients who return for follow-up have the same probabilities of death and MI as those who are lost to follow-up, in a real-world setting, patients at high risk are followed more intensively than those at low risk (17). Ideally an observational study will record all relevant outcomes for all study participants, and if the degree of ascertainment is identical for both groups, bias will be small to absent. If the degree of ascertainment differs between groups, the risk for bias can threaten the validity of the results (13).

The key finding of the present study (5), which suggests that prolonged DAPT conferred a benefit in diabetic patients after DES implantation, is not supported by the neutral findings for death or MI in diabetic patients after bare-metal stent implantation (HR: 0.88; 95% CI: 0.69 to 1.13 for insulin-dependent diabetic patients; HR: 0.88; 95% CI: 0.75 to 1.03 for non-insulin-dependent diabetic patients), despite absolute event rates that were higher than those after DES implantation. The inability to show a benefit after bare-metal stent implantation or in several RCTs after newer-generation DES implantation (Figure 1) weakens support for prolonged DAPT for diabetic patients undergoing stenting in current practice and emphasizes that observational studies, like philosophy, although indispensable for interpreting contemporary events, cannot change them. Before prolonged DAPT can be routinely recommended for diabetic patients undergoing stent implantation, additional

### Figure 1
Pooled Analysis of Diabetic Subgroups From Randomized Trials Comparing Prolonged With Short-Course DAPT

<table>
<thead>
<tr>
<th>Study (Primary Endpoint)</th>
<th>Prolonged DAPT</th>
<th>Short DAPT</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES–LATE (MACCE–36 vs. 12 mos)</td>
<td>33 709</td>
<td>21 709</td>
<td>1.60 (0.92-2.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXCELLENT (TVF–12 vs. 6 mos)</td>
<td>8 278</td>
<td>24 272</td>
<td>0.31 (0.14-0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESET (NACE–12 vs. 3 mos)</td>
<td>14 305</td>
<td>11 316</td>
<td>1.33 (0.60-2.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIMIZE (NACCE–12 vs. 3 mos)</td>
<td>37 549</td>
<td>34 554</td>
<td>1.11 (0.68-1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARCTIC (MACCE–18 vs. 12 mos)</td>
<td>11 198</td>
<td>10 222</td>
<td>1.25 (0.52-3.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR-SAFE (NACCE–12 vs. 6 mos)</td>
<td>12 484</td>
<td>9 495</td>
<td>1.37 (0.57-2.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPT (MACCE–30 vs. 12 mos)</td>
<td>101 1556</td>
<td>100 1481</td>
<td>0.96 (0.72-1.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fixed effect model

Random effects model

Heterogeneity: I–squared=50.7%, tau–squared=0.0889, p=0.0584

Original plot created with R version 3.0.2 and the library package meta using published study-level results for prospectively defined primary endpoints for each study (2,7,12). ARCTIC = Assessment by a Double Randomization 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; CI = confidence interval; DAPT = dual-antiplatelet therapy; DES-LATE = Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; MACCE = major adverse cardiac and cerebrovascular event(s); NACE = net adverse cardiac event(s); OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice; Pts = patients; RESET = Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; TVF = target-vessel failure.
investigation is needed to define the pathogenetic links between the metabolic changes and clinical manifestations of diabetes mellitus (4), and dedicated clinical trials are needed to identify best practices.

REFERENCES


KEY WORDS drug-eluting stent(s), percutaneous coronary intervention, randomized controlled trials