Long-Term Secondary Prevention After High-Risk Stenting
A Good Drug for a Bad Stent
Jean-Philippe Collet, MD, PhD; Johanne Silvain, MD, PhD; Gilles Montalescot, MD, PhD

Dual antiplatelet therapy (DAPT), the combination of aspirin and an inhibitor of the platelet P2Y$_{12}$ receptor, is the foundation to prevent acute stent thrombosis (ST), the sudden thrombotic coronary occlusion that can lead to myocardial infarction or death in one third of patients. The appropriate duration of DAPT in patients who have received coronary stents is an important dilemma for interventional cardiologists and a daily concern. We have entered the third decade of coronary stent implantation, the dominant strategy for myocardial revascularization, without clear guidance on the duration of DAPT. Professional guidelines are not entirely consistent, recommending extension of DAPT up to 6 months after implantation of a second-generation drug-eluting stent (DES) or at least 12 months after implantation of a DES unless patients are at high risk for bleeding. None of these guidelines recommend long-term or lifelong DAPT. The current discrepancies may reflect either a different interpretation of the data by experts of the guideline committees or, more likely, an active area of clinical investigation in which early certainties about DAPT duration after coronary stenting are being challenged.

Article see p 62

So far, 12 randomized, interruption studies investigating various durations of DAPT, whether short, intermediate, or prolonged (≥2 years), have been conducted (Figure). All published randomized trials to date (n>19,000) indicate no benefit of extended DAPT with clopidogrel beyond 6 or 12 months after DES but harm, suggesting that the pendulum has swung back toward short DAPT duration (Table). The lack of power for important safety end points such as death, major bleeding, or ST is a common limitation of these trials. In addition, 1 randomized trial and 2 registries suggest that DAPT duration should be device specific, further adding complexity to this unresolved issue. Finally, most of the evidence has been obtained with clopidogrel, whereas more potent P2Y$_{12}$ inhibitors such as ticagrelor and prasugrel have demonstrated superiority over clopidogrel in reducing spontaneous myocardial infarction and ST after stenting.

Long-term DAPT of 6 to 12 months has been recommended to overcome the susceptibility of first-generation DES to ST, accounted for mainly by delayed endothelialization and polymer hypersensitivity. There was no randomized evidence to support this endorsement for the approved devices. The 2014 European myocardial revascularization guidelines recommend 6 months of DAPT after implantation of a new-generation DES on the basis of randomized trials demonstrating enhanced safety and effectiveness with these devices compared with their earlier counterparts. An even shorter duration may be used when there is a high risk of bleeding. These guidelines refer only to new-generation DES. The same guidelines also specify that DAPT may be used beyond 6 months in patients at high ischemic risk and low bleeding risk, further recognizing that prolonged DAPT may be useful and that optimal duration for DAPT is difficult to appraise.

Avoidance of spontaneous myocardial infarction is a clear advantage of prolonged DAPT as demonstrated with clopidogrel versus placebo and more recently with prasugrel versus clopidogrel when coronary artery disease is characterized angiographically. In the prespecified angiographic substudy of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) substudy, treatment effect diverged significantly after 12 months in favor of prasugrel without a significant excess of major bleeding in this medically managed non-ST-segment-elevation acute coronary syndrome population. Reaching the optimal net clinical benefit by fine-tuning the potency and duration of DAPT is a key step to further improve outcomes after DES. This was the main goal of the TAXUS Liberté Post-Approval Study (TL-PAS), a surveillance of DES performance after commercial release to fulfill a US Food and Drug Administration requirement. The primary objective of this observational registry was to collect safety

Figure. Randomized studies on dual antiplatelet therapy (DAPT) duration. Completed studies are in bold. Study sample sizes are according to character template (large, ≥20,000; intermediate, 2000–5000; small, ≤2000). DES indicates drug-eluting stents.
Table. Main Features of Published Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n (% ACS)</th>
<th>DAPT Duration, mo</th>
<th>Timing of Randomization</th>
<th>Stent Type</th>
<th>Primary End Point</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESET (2013)</td>
<td>2117 (55)</td>
<td>3 vs 12</td>
<td>Index PCI</td>
<td>ZES in the 3-mo DAPT arm vs SES in the 12-mo DAPT arm</td>
<td>CV death, MI, ST, TVR, bleeding: 4.7% in aspirin vs 4.7% in DAPT; ( P ) for noninferiority=0.01</td>
<td>TMI major bleeding: 0.2% in aspirin vs 0.6% in DAPT; ( P=0.24 )</td>
</tr>
<tr>
<td>OPTIMIZE (2013)</td>
<td>3119 (32)</td>
<td>3 vs 12</td>
<td>Index PCI</td>
<td>E-ZES (100%)</td>
<td>Death, MI, stroke, major bleeding: 6% in aspirin vs 5.8%; HR, 1.03 (95% CI, 0.77–1.38); log-rank ( P=0.84 ); noninferiority ( P=0.002 )</td>
<td>TMI major bleeding: 0.6% in aspirin vs 0.9% in DAPT; ( P=0.41 )</td>
</tr>
<tr>
<td>EXCELLENT (2012)</td>
<td>1372 (52)</td>
<td>6 vs 12</td>
<td>Index PCI</td>
<td>2:1 Randomization EES (75%) vs SES (25%)</td>
<td>Cardiac death, MI, or TVR: 4.7% in the aspirin vs 4.4% in the DAPT group (HR, 1.10; 95% CI, 0.67–1.80); ( P ) for superiority=0.72; ( P ) for noninferiority=0.0031</td>
<td>TMI major: 0.3% in aspirin vs 0.6% in DAPT group (HR, 0.71; 95% CI, 0.42–1.20; ( P=0.20 )</td>
</tr>
<tr>
<td>SECURITY (2014)</td>
<td>1399 (38)</td>
<td>6 vs 12</td>
<td>Index PCI</td>
<td>E-ZES (41%), EES (20%), others (33%)</td>
<td>Cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeding at 12 mo: 4.5% vs 3.7% in aspirin vs DAPT (risk difference, 0.8%; 95% CI, −2.4 to 1.7); ( P=0.469 ); ( P ) for noninferiority=0.05</td>
<td>BARC 3 or 5 bleeding: 0.6% in aspirin vs 1.1% in the DAPT group (risk difference, −0.5%; 95 CI, −1.4 to 0.4); ( P=0.283 )</td>
</tr>
<tr>
<td>PRODIGY( ^6 )</td>
<td>1970 (75)</td>
<td>6 vs 24</td>
<td>1 mo after index PCI</td>
<td>1:1:1:1 randomization, BMS (25%) vs E-ZES (25%) vs PES (25%) vs EES (25%)</td>
<td>Death, MI, CVA: 10% in aspirin vs 10.1% in DAPT group (HR, 0.98; 95% CI, 0.74–1.29); ( P=0.91 )</td>
<td>BARC type 5, 3, or 2: 3.5% in aspirin vs 7.4% in DAPT (HR, 0.46; 95% CI, 0.31–0.69; ( P=0.00018 )</td>
</tr>
<tr>
<td>DES LATE (2014)</td>
<td>5045 (61)</td>
<td>12 vs 24</td>
<td>12 mo after index PCI</td>
<td>SES (44%), PES (19%), ZES (19%), EES (11), others (6%)</td>
<td>CV death, MI, or stroke: 2.4% in the aspirin vs 2.6% in the dual-therapy group (HR, 0.94; 95% CI, 0.66–1.13); ( P=0.75 )</td>
<td>TMI major bleeding: 1.1% in aspirin vs 1.4% in DAPT group (HR, 0.71; 95% CI, 0.42–1.20; ( P=0.20 )</td>
</tr>
<tr>
<td>REAL/ZEST-LATE(2010)</td>
<td>2701 (62)</td>
<td>12 vs 24</td>
<td>12 mo after index PCI</td>
<td>SES (57%), PES (24%), ZES (19), others (5%)</td>
<td>CV death or MI: 1.8% with DAPT vs 1.2% with aspirin monotherapy (HR, 1.65; 95% CI, 0.80–3.36); ( P=0.17 )</td>
<td>TMI major bleeding: 0.2% in DAPT vs 0.1% in aspirin group (HR, 2.96; 95% CI, 0.31–28.46; ( P=0.35 )</td>
</tr>
<tr>
<td>ARTIC-INTERUPT( ^1 ) (2014)</td>
<td>1259 (30)</td>
<td>12 vs 24</td>
<td>12 mo after index PCI</td>
<td>SES (22%), PES (21%), ZES (19%), EES (17), others (30%)</td>
<td>Death, MI, ST, stroke, or UR: 4% with aspirin alone vs 4% in DAPT group (HR, 1.17; 95% CI, 0.68–2.03); ( P=0.58 )</td>
<td>STEEPLE major bleeding: 1% in DAPT vs &lt;0.5% in aspirin group (HR, 0.15; 95% CI, 0.02–1.20); ( P=0.073 )</td>
</tr>
<tr>
<td>TL-PAS (2014)( ^1 )</td>
<td>2191 (55)</td>
<td>12 vs 30</td>
<td>12 mo after index PCI</td>
<td>PES (100%)</td>
<td>Death, MI, or stroke: 3.7% in DAPT vs 8.8% in aspirin (HR, 0.407); ( P=0.001 )</td>
<td>GUSTO moderate or severe bleeding: 2.4% in DAPT vs 1.7% in aspirin (HR, 1.438); ( P=0.234 )</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; BMS, bare metal stent; CI, confidence interval; CV, cardiovascular; CVA, cardiovascular accident; DAPT, dual antiplatelet therapy; EES, everolimus-eluting stent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; STEEPLE, Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation; TIMI, Thrombolysis in Myocardial Infarction; UR, urgent revascularization; and ZES, zotarolimus-eluting stent.

and clinical outcomes data for the first 12 months after implantation of ≥1 TAXUS Liberté stents with prasugrel as the thienopyridine component of DAPT; then patients who had no contraindication to prolonged DAPT could be randomized to receive in a double-blind fashion prolonged DAPT or single aspirin therapy. This second part of the study, published in this issue of Circulation,\(^1\) was also included in the randomized, double-blind DAPT Trial, which has been published in the New England Journal of Medicine.\(^4\) The results of both studies were also recently presented and discussed at the American Heart Association Scientific Sessions.

In the present study by Garratt et al,\(^1\) a newer version of the paclitaxel-eluting stent was evaluated with a thinner-strut stainless steel novel cell design (97-μm struts) with a more conformable platform embedded with a durable polymer (Boston Scientific, Natick, MA). This evaluation of the TAXUS Liberté stent beyond 12 months after implantation included in the randomized, double-blind DAPT Trial represents a subset of this large trial and can be interpreted only according to the main results of the DAPT Trial. Although, the present study is an exploratory analysis without initial power calculation and is not powered for the DAPT study end points, the results are globally similar, with the main findings of the larger overall DAPT Trial of all stent types and P2Y12 inhibitors suggesting that the information is not only plausible but certainly real. The first insight is that DAPT beyond 1 year reduces ischemic events in low-risk patients who received a stent at high risk of ST without significant harm. Second, this is the first long-term assessment of an off-label use of prasugrel in patients who were not all acute coronary syndrome patients and were implanted with a first-generation DES. Third, the extended follow-up 3 months after interruption provides additional information in line with
prior studies showing a rebound of platelet reactivity and clinical events that suggest a causal relationship between the two; this finding appears to justify long-term, if not lifelong, treatment in these patients who received a paclitaxel stent.14 Fourth, the TL-PAS outlines that, besides patient characteristics and clinical setting (stable versus unstable presentation), the type of stent drives also clinical outcome. Finally, randomization at 12 months selected patients free of events and drug compliant. Not all eligible patients were randomized, reflecting the real-life management of antiplatelet therapy.15 The authors should be commended for the low rate of premature study interruption. The unusual high event rates in the study provide additional evidence that paclitaxel-eluting stents, even after refinement of the platform design, are associated with an excess risk of ST and major adverse cardiac events. These stents are a concern in terms of safety, which may be somewhat handled by long-term use of prasugrel. This is a call for no longer using first-generation DES, paclitaxel-eluting stents in particular. This is also use of prasugrel. This is a call for no longer using first-generation DES, paclitaxel-eluting stents in particular. This is also use of prasugrel. This is a call for no longer using first-generation DES, paclitaxel-eluting stents in particular. This is also use of prasugrel. This is a call for no longer using first-generation DES, paclitaxel-eluting stents in particular. This is also use of prasugrel. This is a call for no longer using first-generation DES, paclitaxel-eluting stents in particular. This is also

Disclosures

Dr Collet reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Medtronic, Boston Scientific, Cordis, Stago, Fondation de France, INSERM, Nanospheres, FédérationFrançaise de Cardiologie, and Société Française de Cardiologie; consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca.

Dr Silvain reports receiving research grants to his institution from AstraZeneca, Sanofi Aventis, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consultancy fees from AstraZeneca, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, and The Medicines Company; and lecture fees from AstraZeneca, Boehringer Ingelheim, Cordis, Daiichi Sankyo, Eli Lilly, Iroko Cardio, Stentys, and Servier.


References


**Key Words:** Editorial ▪ myocardial infarction ▪ platelet aggregation inhibitors ▪ secondary prevention ▪ stent ▪ thrombosis
Long-Term Secondary Prevention After High-Risk Stenting: A Good Drug for a Bad Stent
Jean-Philippe Collet, Johanne Silvain and Gilles Montalescot

_Circulation_. 2015;131:13-16; originally published online November 19, 2014;
doi: 10.1161/CIRCULATIONAHA.114.014112

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/131/1/13

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/