Duration of Dual Antiplatelet Therapy After Coronary Stenting
A Review of the Evidence

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ABSTRACT

The duration of dual antiplatelet therapy (DAPT) after coronary stenting has been evaluated in randomized studies with apparently conflicting results. Although longer exposure associates with more bleeding complications, late stent thrombosis (ST) and myocardial infarction are reduced. In addition, as new drug-eluting stents carry a lower risk of ST compared with the first-generation drug-eluting stents and possibly even bare-metal stents, a shift toward better protection from ST may have an effect on the duration and intensity of DAPT. Whether the duration of DAPT should be shorter or longer than the currently recommended 6 to 12 months is analyzed in this review, drawing on lessons from the most recent studies. (J Am Coll Cardiol 2015;66:832-47) © 2015 by the American College of Cardiology Foundation.

Currently, dual antiplatelet therapy (DAPT) refers to the addition of a P2Y12 platelet receptor inhibitor (either a thienopyridine [clopidogrel or prasugrel] or the cyclopentyltriazolopyrimidine, ticagrelor) to aspirin, aiming to reduce stent thrombosis (ST) after coronary stent implantation and prevent coronary atherothrombotic events at sites outside of the stented segment. Although these treatment strategies have been successful, prolonged DAPT is accompanied by an increase in bleeding (1). This complex interaction between the efficacy and safety of DAPT has prompted a series of investigations to determine which duration of DAPT optimizes the risk-benefit equation. All studies thus far have used DAPT initially, although for variable periods, followed by randomly assigned treatment with DAPT versus single-antiplatelet therapy (SAPT). All trials to date have used aspirin...
as SAPT; continuation of P2Y₁₂ inhibition as monotherapy is yet to be studied.

**ISSUES WITH DAPT FOR CORONARY STENTING**

**HISTORICAL CONSIDERATIONS ON DAPT.** Clopidogrel was first shown to be more effective than aspirin in reducing ischemic stroke, myocardial infarction (MI), or vascular death in patients with a prior atherothrombotic event (2). Then, in 2001, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study investigators reported that the combination of clopidogrel and aspirin resulted in a 2% absolute reduction in the risk of cardiovascular death, MI, and stroke in patients with an acute coronary syndrome (ACS) at the expense of an absolute 1% increase in the risk of major bleeding versus aspirin alone (3,4). The percutaneous coronary intervention (PCI)-CURE substudy, in which 82% of patients received a bare-metal stent (BMS), found that adding clopidogrel to aspirin reduced the composite of cardiovascular death, MI, and revascularization within the first 30 days after patients underwent PCI (5). After the CREDO (Clopidogrel for the Reduction of Events During Observation) study demonstrated that 12 months of DAPT after elective PCI reduced the incidence of death, MI, and stroke by 27% when compared with DAPT administered for 30 days followed by aspirin alone (6), DAPT became the standard of care for the first year after an ACS (7) on the grounds that DAPT attenuated recurrent ischemic events. At that time, the mandatory duration of DAPT for ST prevention was only 1 month.

**FIRST CONCERNS ABOUT THE EFFICACY OF SHORT-DURATION DAPT.** Drug-eluting stents (DES) were approved after the demonstration that the frequency of in-stent restenosis was reduced compared with BMS. Some 3 years later, it was recognized that although the restenosis benefit extended beyond 12 months, patients with DES were at continuously higher risk of MI and death after the conversion from DAPT to SAPT, presumably due to late ST (8). Late ST was attributed to delayed stent endothelialization, and was encountered 2.75 × more often with DES than with BMS. The U.S. Food and Drug Administration’s (FDA) 2006 advisory on DES recommended DAPT for 12 months after implantation on the basis of broad expert consensus (9).

Although reports vary, the frequency of ST after DES implantation is probably around 0.5% to 2% per annum and is more prevalent after an ACS (8,10,11). Although a number of risk factors for ST have been identified (12,13), it is neither possible to predict its occurrence accurately nor possible to prevent it entirely with DAPT (14). Despite the low frequency of late ST, it is associated with high rates of acute MI and death. This concern led the FDA to initiate a trial on duration of DAPT after stenting.

**FIRST CONCERNS ABOUT THE SAFETY OF PROLONGED DAPT.** Safety concerns with prolonged DAPT were raised in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study (1). Although DAPT did not provide significant protection against ischemic events in patients with stable vascular disease or at risk of atherothrombotic events, it was associated with a significant 60% excess of moderate bleeding and a non-significant excess of severe or fatal bleeding complications (15). A meta-analysis also suggested harm with prolonged DAPT (16).

Combined antiplatelet therapy was also tested with vorapaxar, an antagonist of protease-activated receptor type 1 receptors. The primary efficacy endpoint—a composite of cardiovascular death, MI, or stroke—was significantly reduced with vorapaxar in addition to aspirin, dipyridamole, thienopyridine, or a combination of these antiplatelet agents in patients with stable atherosclerosis, but it also increased the risk of moderate or severe bleeding, including intracranial hemorrhage (17). In both trials, the issue of safety was less pronounced in patients with symptomatic atherosclerosis or MI.

The recent demonstration that the new second-generation DES reduces ST compared with first-generation paclitaxel-eluting stents (PES) suggests better protection against ST in the future, in particular with the newer cobalt-chromium everolimus-eluting stents (EES) (18,19). A series of randomized studies were then launched to test whether DAPT for <12 months might improve the net clinical benefit after DES implantation.

**CURRENT INTERNATIONAL SOCIETY GUIDELINES ON DAPT DURATION**

**U.S. GUIDELINES. On revascularization.** In relation to the duration of antiplatelet therapy, the 2011 U.S. guidelines on PCI (Table 1) (20) assigned a Class I recommendation to the following strategies:

- Aspirin should be continued indefinitely after PCI.
- P2Y₁₂ inhibition should be continued for at least 12 months after PCI for ACS.
TABLE 1  Guideline Recommendations on Duration of Dual Antiplatelet Therapy Post-Stenting

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Stent (BMS or DES) in patients with ACS</td>
<td>At least 12 months (COR I, LOE: B). Longer durations may be considered in patients with DES (COR IIb, LOE: C)</td>
<td>Up to 12 months (COR I, LOE: A)</td>
<td>Up to 12 months*</td>
<td>12 months (COR I, LOE: B)*</td>
</tr>
<tr>
<td>BMS in non-ACS</td>
<td>At least 1 month (minimum 2 weeks if increased bleeding risk, ideally up to 12 months) (COR I, LOE: B)</td>
<td>At least 1 month (COR I, LOE: A)</td>
<td>According to device-specific instructions*</td>
<td>Endorses U.S. guideline*</td>
</tr>
<tr>
<td>DES in non-ACS</td>
<td>At least 12 months (COR I, LOE: B)</td>
<td>6 months (COR I, LOE: B)</td>
<td>At least 12 months*</td>
<td>Endorses U.S. guideline*</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>May be considered (COR IIb, LOE: B)</td>
<td>Selected patients at high risk of ischemic events*</td>
<td>Not recommended beyond 12 months*</td>
<td>Consider in patients with recurrent ischemic events*</td>
</tr>
</tbody>
</table>

*No COR or LOE provided. †COR and LOE adapted from Australian National Health and Medical Research Council guidelines (87).

ACS = acute coronary syndrome(s); BMS = bare-metal stent(s); COR = class of recommendation; DES = drug-eluting stent(s); LOE = Level of Evidence.

- If a DES is placed for a non-ACS indication, clopidogrel should be administered for at least 12 months if patients are not at high risk of bleeding.
- In patients receiving a BMS for a non-ACS indication, clopidogrel should be administered for at least 1 month (a minimum of 2 weeks in patients at increased bleeding risk) and ideally up to 12 months.

These guidelines suggest that it is reasonable to stop P2Y12 inhibition earlier than 12 months if the risk of bleeding outweighs the anticipated benefit of continuing the second antiplatelet agent. However, extending DAPT beyond 12 months may be considered in patients at high risk of ST and/or low risk of bleeding after DES implantation. This latter recommendation is endorsed in the more recent 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes (21-23).

**On secondary prevention.** The 2011 U.S. secondary prevention guidelines address the duration of antiplatelet therapy in patients with stable CAD (24). Using evidence from the CHARISMA trial, it lends support to combining aspirin and clopidogrel in this population.

**EUROPEAN GUIDELINES.** On revascularization. The 2014 European guidelines on myocardial revascularization, incorporating evidence from studies published between 2011 and 2013 that highlight bleeding hazards associated with DAPT (Table 1) (25), differ from the U.S. guidelines in recommending DAPT for a maximum of 12 months after ACS, for only 1 month after BMS implantation for non-ACS indications, and for only 6 months after DES for non-ACS indications.

**On secondary prevention.** The 2013 recommendations concerning DAPT in the management of stable CAD (26) cite post-hoc analyses from CHARISMA and TRA-2P TIMI-50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) (17), concluding that although DAPT may be beneficial in selected patients at high risk of ischemic events, it cannot be recommended systematically in patients with stable CAD.

**OTHER GUIDELINES.** In the United Kingdom, guidance regarding stenting has not been updated since 2008, and the recommendations broadly align with those of the United States (27-29). DAPT is not recommended for patients more than 12 months post-MI. Australian guidelines broadly reflect those of the United States (30,31), although they uniquely recommend long-term DAPT for secondary prevention in patients with recurrent ischemic events (32).

**STUDIES EVALUATING A 3- TO 6-MONTH DURATION OF DAPT**

**STUDIES.** On the basis of the lower risk of ST with second-generation DES and the reduction of bleeding events with a short duration (S)-DAPT strategy, these studies tested the hypothesis that combining frequent (if not exclusive) use of latest-generation DES with DAPT for <12 months (S-DAPT) would result in an improved net clinical benefit for patients. Net clinical benefit, combining both ischemic and bleeding complications, was chosen as the primary endpoint in 5 of the 7 studies.

The first study assessing S-DAPT was the EXCELLENT (Comparison of the Efficacy of Everolimus-Eluting Versus Sirolimus-Eluting Stent for Coronary Lesions) trial (Table 2) (33). A total of 50% of patients presented with ACS. An EES was implanted in 75% of patients and a sirolimus-eluting stent (SES) in the remainder.

Subsequently, the PRODIGY (PROlonging Dual Antiplatelet Treatment In Patients With Coronary Artery Disease After Graded Stent-induced Intimal Hyperplasia) and RESET (A New Strategy Regarding Discontinuation of Dual Antiplatelet; Real Safety and Efficacy of a 3-month Dual Antiplatelet Therapy Following Zotarolimus-eluting Stents Implantation) studies were published (34,35). The PRODIGY trial
was a 4-by-2 randomized, open-label, multicenter trial that evaluated the efficacy and safety of 6 versus 24 months of DAPT in an all-comer population receiving a balanced mixture of stents. Patients undergoing PCI were 1:1:1:1 randomized to receive 1 of 4 stent types, including BMS, EES, PES and the Endeavor zotarolimus-eluting stent (ZES) (Medtronic, Inc., Santa Rosa, California). More than 70% of patients presented with ACS. The RESET trial was the first study evaluating a mandatory DAPT duration of 3 months with a second-generation DES (35). Patients, 55% of whom had ACS, were randomized in a 1:1 fashion to either an Endeavor ZES with DAPT for 3 months or an EES, Resolute ZES (Medtronic), or SES with DAPT for 12 months.

OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice) was another study to evaluate 3 months of mandatory DAPT (36). It was a multicenter, open-label, randomized trial evaluating 3 versus 12 months of DAPT in patients, of whom 32% had ACS, although none had MI.

In 2014, the SECURITY (Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy), ITALIC (Is There A Life for DES After Discontinuation of Clopidogrel), and ISAR-SAFE (Randomized, Double-Blind, Placebo-controlled Trial of 6 vs. 12 Months Clopidogrel Therapy After Implantation of a Drug-Eluting Stent) trials (37–39) reported on evaluating S-DAPT for 6 months versus 12 months. SECURITY was a randomized, open-label multicenter study evaluating the safety and efficacy of 6 months versus 12 months of DAPT in patients undergoing PCI with a second-generation DES. This study included the largest proportion of bioresorbable polymer DES. The ITALIC study evaluated 6 months versus 24 months of DAPT after Xience EES (Abbott Vascular, Santa Clara, California) implantation. Randomization occurred at the time of the index procedure, and results have so far been reported only up to 1-year follow-up. Interestingly, ITALIC excluded patients resistant to aspirin. The prevalence of ACS at baseline was low (24%). Finally, ISAR-SAFE was a multicenter, double-blind, placebo-controlled, randomized trial testing the efficacy and safety of 6 months versus 12 months of DAPT. Only patients on DAPT who were event-free in the first 6 months after DES implantation were randomized to either continue with DAPT or be treated with aspirin and placebo. A total of 72% had received second-generation DES. The prevalence of ACS at presentation before the index procedure was 40% (8% ST-segment elevation acute coronary syndrome [STEMI] and 32% non-STEMI).
Noninferiority of the primary endpoint for S-DAPT versus long duration (L)-DAPT was demonstrated in each of these studies irrespective of stent type, clinical indication, or DAPT duration. Moreover, no differences were observed in the components of the primary endpoint, ST or bleeding, in most of the studies. The PRODIGY trial was the only exception, in which 24 months of DAPT was associated with higher rates of major bleeding than 6-month DAPT. Most probably, the statistical significance for higher risk of bleeding with L-DAPT in this study was related to the longer exposure in the L-DAPT group compared with the S-DAPT group, as neither group reflected standard practice (i.e., 1-year DAPT) as defined by contemporary guidelines. Of note, prolonged DAPT provided ischemic benefit in certain subgroups—for example, diabetic patients in the EXCELLENT trial and patients with in-stent restenosis target lesions in the PRODIGY trial (33,40).

Accepting differences in study design and baseline clinical risk profile, when pooling the events from all 7 studies (Table 3), S-DAPT (3 or 6 months) was associated with an overall rate of ST of 0.5% compared with 0.4% with L-DAPT (absolute risk reduction with L-DAPT: 0.1%). The pooled rate of MI was 1.7% with S-DAPT and 1.5% with L-DAPT (absolute risk reduction: 0.2%). The rate of major bleeding was 0.4% with S-DAPT and 0.8% with L-DAPT (absolute risk increase with L-DAPT: 0.4%), whereas the death rate was 1.7% with S-DAPT and 1.9% with L-DAPT (absolute risk increase: 0.2%). These results suggest a risk/benefit ratio favoring an S-DAPT regimen (Figure 1). Recently published meta-analyses report similar findings (41,42).

**CLINICAL INTERPRETATION.** Several issues must be considered when interpreting results from these trials evaluating the safety and efficacy of S-DAPT (3 to 6 months). First, all were underpowered to detect differences in hard endpoints, including the composite primary endpoints. The low statistical power among studies was related to study design issues, slow enrollment, premature interruption of several studies, lower than expected event rates, and possibly, under-reporting. Second, with 1 exception, all studies were open-label trials, introducing the potential for observer bias. Third, treatment crossover, selection bias, and regression to the mean pose problems, as a not insignificant proportion of patients who were randomized to the S-DAPT arm were still on DAPT at the end of the follow-up period (and vice-versa). Fourth, most of these trials had only 1 year of follow-up, which is insufficient to evaluate very late clinical outcomes. Fifth, the number of patients lost to follow-up was not always reported and, when reported, was as high as 7%. Sixth, all of the previous issues have a particularly deleterious effect on studies with a noninferiority design; the 7 studies considered here had a noninferiority design with wide noninferiority margins. Seventh, except for the PRODIGY trial, results from these studies lack external validity (generalizability), as high-risk patients were excluded from the majority. Finally, primary endpoint definitions were heterogeneous; some studies included target vessel revascularization, and others did not include ST in the composite endpoint.

Considering these potential limitations, results from S-DAPT trials must be evaluated carefully. As each individual study is inconclusive for events like MI or major bleeding, meta-analytic methods may more reliably approximate the true risk/benefit balance of S-DAPT (Figures 2 and 3). There was no excess risk of MI with S-DAPT, but there was a significant reduction in major bleeding, confirmed recently in several pooled analyses of these studies (41,42). All of these meta-analyses have serious limitations related to heterogeneity in study designs, populations, definitions of events, and lengths of follow-up, in addition to the limitations of the individual studies

**Table 3** Endpoints in Studies Evaluating Abbreviated Duration of DAPT (≤6 Months) After DES

<table>
<thead>
<tr>
<th>Trial (Ref. #)</th>
<th>S-DAPT (Stent Thrombosis)</th>
<th>L-DAPT</th>
<th>ARR</th>
<th>MI (S-DAPT)</th>
<th>L-DAPT</th>
<th>ARR</th>
<th>Major Bleeding (S-DAPT)</th>
<th>L-DAPT</th>
<th>ARR</th>
<th>Death (S-DAPT)</th>
<th>L-DAPT</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-SAFE (39)</td>
<td>5 (0.3)</td>
<td>4 (0.2)</td>
<td>0.1</td>
<td>13 (0.7)</td>
<td>14 (0.7)</td>
<td>0.1</td>
<td>4 (0.2)</td>
<td>5 (0.3)</td>
<td>0.1</td>
<td>8 (0.4)</td>
<td>12 (0.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>ITALIC (38)</td>
<td>3 (0.3)</td>
<td>0</td>
<td>1</td>
<td>6 (0.7)</td>
<td>4 (0.4)</td>
<td>0.3</td>
<td>5 (0.5)</td>
<td>7 (0.7)</td>
<td>0.2</td>
<td>8 (0.9)</td>
<td>7 (0.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>SECURITY (37)</td>
<td>2 (0.3)</td>
<td>3 (0.4)</td>
<td>0.1</td>
<td>16 (2.3)</td>
<td>15 (2.1)</td>
<td>0.2</td>
<td>4 (0.6)</td>
<td>8 (1.1)</td>
<td>0.5</td>
<td>8 (1.2)</td>
<td>8 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>OPTIMIZE (36)</td>
<td>13 (0.8)</td>
<td>12 (0.8)</td>
<td>0</td>
<td>49 (3.2)</td>
<td>42 (2.7)</td>
<td>0.5</td>
<td>10 (0.6)</td>
<td>14 (0.9)</td>
<td>0.3</td>
<td>43 (2.8)</td>
<td>45 (2.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>PRODIGY (34)</td>
<td>15 (1.5)</td>
<td>13 (1.3)</td>
<td>0.2</td>
<td>41 (4.2)</td>
<td>39 (4.0)</td>
<td>0.2</td>
<td>6 (0.6)</td>
<td>16 (1.6)</td>
<td>1</td>
<td>65 (6.6)</td>
<td>65 (6.6)</td>
<td>0</td>
</tr>
<tr>
<td>RESET (35)</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td>0.1</td>
<td>2 (0.2)</td>
<td>4 (0.4)</td>
<td>0.2</td>
<td>5 (0.5)</td>
<td>10 (1.0)</td>
<td>0.5</td>
<td>5 (0.5)</td>
<td>8 (1)</td>
<td>0.5</td>
</tr>
<tr>
<td>EXCELLENT (33)</td>
<td>6 (0.9)</td>
<td>1 (0.1)</td>
<td>0.8</td>
<td>13 (1.8)</td>
<td>7 (1.0)</td>
<td>0.8</td>
<td>4 (0.6)</td>
<td>10 (1.4)</td>
<td>0.4</td>
<td>4 (0.6)</td>
<td>7 (1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>46 (0.5)</td>
<td>36 (0.4)</td>
<td>0.1</td>
<td>140 (1.7)</td>
<td>125 (1.5)</td>
<td>0.2</td>
<td>38 (0.4)</td>
<td>70 (0.8)</td>
<td>0.4</td>
<td>141 (1.7)</td>
<td>152 (1.9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Values are n (%). ARI = absolute risk increase; ARR = absolute risk reduction; L-DAPT = long dual antiplatelet therapy; S-DAPT = short dual antiplatelet therapy; other abbreviations as in Tables 1 and 2.*
outlined earlier. However, they provide additional information that no individual study on its own can provide.

The benefits of prolonged DAPT may be more evident in studies of first-generation DES, in which incomplete strut coverage and delayed vascular healing increase the risk of late ST (43), whereas significant improvement in safety with second-generation DES has been demonstrated (18,44). Moreover, DAPT duration and DES generation interact to attenuate late ST (45). Accordingly, a short mandatory period of DAPT of 3 or 6 months may be considered safe and effective in non-ACS patients undergoing PCI with latest-generation DES, in particular in patients at risk of bleeding and/or at low risk of recurrent ischemia. This may find much wider application henceforth because first-generation DES are no longer routinely implanted.

**STUDIES EVALUATING A DURATION LONGER THAN 12 MONTHS**

**STUDIES.** Characteristics and major findings of the trials evaluating DAPT durations longer than 12 months (very long [VL]-DAPT) are summarized in Table 4. These studies evaluated patients who had completed 1 year of DAPT without ischemic or bleeding complications, perhaps implying selection of a lower-risk population.

The DES-LATE (Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event) trial was a prospective, multicenter, open-label, randomized trial to determine the benefits and risks of continuing DAPT beyond 1 year after DES insertion (n = 5,045) (46). This trial was a seamless extension of the previously conducted REAL-LATE (Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events) and ZEST-LATE (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) studies. It concluded that, compared with aspirin alone, continuing DAPT beyond 1 year after DES implantation was not beneficial (47). Both first- and second-generation DES were used. At 2 years after randomization, the rate of the primary endpoint (death, MI, ST, or stroke) was similar between the aspirin-alone and DAPT groups (2.4% vs. 2.6%, respectively; p = 0.75). The rate of Thrombolysis In Myocardial Infarction (TIMI) major bleeding was also similar between the aspirin-alone and DAPT groups (1.1% vs. 1.4%; p = 0.20). These findings suggest that the 2 antiplatelet strategies provide similar protection against ischemic events with similar risk of bleeding events.

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)-Interruption was a prospective, multicenter, open-label randomized study (48) that was a planned extension of the ARCTIC-Monitoring trial, which had randomly allocated 2,440 patients to a strategy of platelet function testing with antiplatelet treatment adjustment or a conventional antiplatelet strategy without monitoring after coronary stenting with DES (49). After 1 year, 1,259 eligible patients were randomized in the ARCTIC-Interruption trial. After a median follow-up of another 17 months, 78% of patients in the continuation group were still on thienopyridine, and the rate of the primary endpoint (death, MI, ST, stroke, or urgent revascularization) was similar between the interruption L-DAPT group and the continuation VL-DAPT group (4% vs. 4%; p = 0.58). Major bleeding events tended to occur more frequently with VL-DAPT than with L-DAPT (1% vs. <0.5%; p = 0.073); major or minor bleeding events were significantly increased with VL-DAPT, suggesting possible harm with no tangible benefit from a VL-DAPT strategy.

The DAPT trial, a large, international, multicenter, randomized, placebo-controlled trial, was designed to determine the benefits and risks of continuing DAPT beyond 1 year after the placement of a coronary
DES (50). At 12 months after DES implantation, 9,961 patients who had not had a major ischemic or bleeding event and had been adherent to DAPT were assigned to continue thienopyridine and aspirin treatment (VL-DAPT arm) or to receive placebo plus aspirin for the next 18 months (L-DAPT arm). The coprimary efficacy endpoints were ST and the composite of death, MI, or stroke during the period from 12 to 30 months after DES implantation. The primary safety endpoint was moderate or severe bleeding. As secondary analyses, examination of the same endpoints in all patients over the course of the 21-month post-randomization period was undertaken, during the last 3 months of which the patients were not receiving randomized treatment (to assess potential hazards before and after discontinuation of the study drug for qualitative differences). As a primary result, continuing thienopyridine, as compared with placebo, reduced the rates of both coprimary endpoints, ST (0.4% vs. 1.4%; \( p < 0.001 \)) and death, MI, or stroke (4.3% vs. 5.9%; \( p < 0.001 \)). Continued thienopyridine increased the rate of moderate or severe bleeding (2.5% vs. 1.6%; \( p = 0.001 \)). An increased risk of ST and MI was observed in both groups during the 3 months after stopping thienopyridine. A borderline increase in all-cause mortality was observed with continued thienopyridine (2.0%) versus placebo (1.5%; \( p = 0.052 \)).

All 3 trials evidently studied patients who were at lower risk for later adverse events. The screening period of the ARTIC-Interruption trial corresponded with the first phase of the trial. One year after stenting, 47% of the patients were excluded from the second randomization evaluating VL-DAPT. In the DAPT study, 22,866 patients were deemed eligible for the study, but a year later, 56% were excluded at the time of randomization for the evaluation of VL-DAPT. Although the 2 study designs differ, these 2 enrollment processes clearly indicate the difficulties in conducting such trials and the super-selection of patients who finally participated in the evaluation of VL-DAPT.

When considering the 3 trials together, there was a reduction of MI or ST with VL-DAPT, but an increase of major bleeding and, possibly, of all-cause death when compared with L-DAPT. Meta-analysis (Figure 4) indicates a trend toward higher risk of all-cause mortality associated with the use of VL-DAPT. This finding on mortality remains controversial because of the criteria used to select the studies incorporated in different meta-analyses, some suggesting harm with prolonged DAPT after stenting, others not confirming the harm associated with prolonged DAPT (41,52). The recent PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) study is reassuring, with favorable trends on mortality with prolonged DAPT in post-MI patients (51).

CLINICAL INTERPRETATION. The DES-LATE trial included mostly first-generation DES, patients presenting with ACS, and a DAPT regimen using clopidogrel exclusively, which may have reduced the effect of prolonged DAPT in preventing ischemic events when compared with the more potent P2Y\(_{12}\) inhibitors now available (i.e., prasugrel or ticagrelor). When compared with other studies performed in Western populations, the event rates in the DES-LATE study were lower and could be explained by the East Asian paradox (53): the fact that East Asian patients have a similar or even lower rate of ischemic events after stenting compared with Caucasians, despite greater platelet reactivity on DAPT treatment. VL-DAPT did not provide incremental benefit to the subgroup.
of patients with clinical or angiographic high-risk features. High on-treatment platelet reactivity did not help identify optimal candidates for VL-DAPT.

The ARCTIC-Interruption trial was underpowered and published simultaneously with a meta-analysis confirming the main findings of the trial, in particular the safety concern regarding VL-DAPT. Measurement of platelet reactivity was another unique aspect of the ARCTIC-Interruption trial. Although high platelet reactivity was shown to be a marker for ischemic events and was strongly associated with mortality, platelet reactivity did not differ between the continuation and interruption groups, and there was no interaction between interruption and platelet reactivity on clinical outcomes. Once again, platelet reactivity did not assist in selecting patients for VL-DAPT.

The DAPT study is the largest and only double-blinded trial. DAPT is the only study adequately powered for its primary endpoints (ST and major adverse cardiac and cerebrovascular events [MACCE]) and also for major bleeding. Both first- and second-generation DES types were used, and clopidogrel and prasugrel were both utilized. Continued thienopyridine attenuated ischemic events, including late ST; the demonstration of a “rebound” in ischemic events after interruption more than 2 years after stenting adds to the concept of ongoing protection with VL-DAPT. Moreover, the reduction of MI originated within the stented artery as frequently as within the nonstented arteries, suggesting that there is a secondary prevention effect of a VL-DAPT strategy. The PEGASUS-TIMI 54 study, using ticagrelor in addition to aspirin in secondary prevention on average 4 years after an MI, lends additional support to the hypothesis that VL-DAPT provides better global protection (51). Whether these findings substantiate “indefinite” DAPT treatment after DES in selected patients remains uncertain. The effects on ST and MACCE were very consistent across the DAPT trial subgroups, suggesting that the results may not be confined to any specific patient profile. Unexpectedly, VL-DAPT was not better in patients with risk factors for ST and tended to be even less effective in diabetic patients (p value for interaction = 0.01). Similarly, the excess of GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate/severe bleeding complications with VL-DAPT was consistent across subgroups, not identifying profiles of patients at particular excess bleeding risk with VL-DAPT.

In this regard, the remaining question is how robust the finding of excess mortality with VL-DAPT is in this large trial. It should be recognized that this is a weak signal derived from a small number of events appearing late in follow-up. Fatal bleeding (Bleeding Academic Research Consortium 5) occurred in 0.15% versus 0.09% (p = 0.38) for the 30-month versus the 12-month period of DAPT. The excess of deaths from any cause with VL-DAPT was driven by an increase in noncardiovascular deaths. The reasons identified could be related to bleeding, trauma, or cancer, while accepting that some of the trauma- or cancer-related deaths were also related to, revealed, or accentuated by bleeding. There was an asymmetrical split in fatal bleeding (21 with VL-DAPT vs. 5 with L-DAPT) when all noncardiovascular deaths were considered. There were also more cancer-related deaths among patients on VL- than L-DAPT (31 vs. 14; p = 0.02, including 3 vs. 0 bleeding-related deaths) although the incidence of cancer did not differ significantly at the time of randomization. The relationship between major bleeding and death, which is widely documented in the published data, appears to be present here again, although causality cannot be ascertained. The same trend is present in the meta-analysis of the 3 studies, which examined VL-DAPT after DES (Figure 4). However, a large and more global meta-analysis of 14 trials that randomly assigned 69,644 participants to extended-duration DAPT for various medical conditions showed that it was not associated with a difference in the risk of all-cause, cardiovascular, or noncardiovascular death compared with aspirin alone or short-duration DAPT (52). Although the
question remains open, it is fair to state that no survival benefit may be expected from administering VL-DAPT after DES.

Registry data also have shown conflicting results on the optimal duration of DAPT (54,55). The large PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens In Stented Patients) registry also assessed associations between the different modes of DAPT cessation and cardiovascular risk over 2 years after PCI. The overall incidence of any DAPT cessation was 57.3%, and cardiac events differed according to the mode of dual antiplatelet cessation and diminished over time (56).

EVIDENCE AND EXTRAPOLATIONS

TYPE OF STENT. In the DAPT study, VL-DAPT reduced the risks of MACCE and ST across all DES types, with adjusted hazard ratios (HRs) for MACCE ranging from 0.52 to 0.89 (50). The TAXUS Libérite Post Approval Study was embedded in the DAPT study as a surveillance of DES performance after commercial release to fulfill an FDA requirement (57). This exploratory analysis reported overall similar results to the main findings of the DAPT trial, with off-label use of prasugrel in patients who did not all have ACS. It demonstrated that besides patient characteristics and clinical setting (stable vs. unstable presentation), the type of stent also affected clinical outcome. Consistent with meta-analyses of first-generation versus second-generation stents (18,44,45), the safety of PES may be somewhat improved by long-term use of prasugrel (58). Rather than promoting VL-DAPT, this study supports no longer using first-generation DES, particularly paclitaxel stents.

A cohort of patients with BMS were included in the DAPT trial. Among 10,026 propensity-matched subjects, DES-treated subjects had a lower rate of ST through 33 months compared with BMS-treated subjects (1.70% vs. 2.61%; p = 0.008) and a non-inferior rate of MACCE (11.37% vs. 13.24%; non-inferiority p < 0.001) (59). Results in BMS-treated subjects randomized to VL-DAPT are consistent with DES results in relation to ST and bleeding. Interestingly, and in contrast to the DES-treated patients, the BMS-treated cohort did not demonstrate a difference in mortality between VL- and L-DAPT. This information, in addition to the recently published PEGASUS-TIMI 54 trial and Elmariah meta-analysis, is reassuring (51,52).

TYPE OF P2Y12 ANTAGONIST. In the DAPT trial, comparisons between specific thienopyridines may be confounded, as the patients’ therapy was not
randomly assigned. Although protection against MACCE was significant with clopidogrel (HR: 0.80), it was more pronounced with prasugrel (HR: 0.52; p for interaction = 0.03). This data was confirmed in the TAXUS Liberte Post Approval Study, in which off-label use of prasugrel was particularly effective in reducing MI resulting from ST (0% vs. 2.6%; p < 0.001) and from sites remote from the stent (1.9% vs. 4.5%; p = 0.007). Bleeding complications were modestly and nonsignificantly increased with prasugrel, with no effect on mortality. The extended follow-up 3 months after interruption of prasugrel showed a particularly marked rebound of ischemic events beyond 30 months, suggesting that prasugrel was particularly effective in suppressing stent- and nonstent-related thrombotic complications.

In the CHARISMA trial, among patients with prior MI, ischemic stroke, or symptomatic peripheral arterial disease (n = 9,478), there was a significant reduction of the risk of MI, stroke, or death associated with a combination of low-dose aspirin plus clopidogrel compared with aspirin alone at 30 months (60). The TRILOGY-ACS (The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study also showed that, among the patients with angiographic confirmation of CAD after an ACS (n = 3,085), treatment with prasugrel and aspirin significantly reduced death, MI, or stroke compared with clopidogrel and aspirin at 30 months (61). Similarly, in the TRA 2P-TIMI 50 trial, vorapaxar, a protease-activated receptor 1 inhibitor, reduced the composite risk of death, MI, or stroke in patients with prior MI (n = 17,779) compared with the placebo group at 36 months (17). The largest study examining the role of VL-DAPT in secondary prevention is the PEGASUS-TIMI 54 trial (51). This randomized, double-blind trial evaluated the efficacy and safety of ticagrelor in addition to low-dose aspirin for long-term treatment of 21,162 patients in stable condition with a history of spontaneous MI 1 to 3 years before randomization. The PEGASUS-TIMI 54 trial evaluated 2 intensities of antiplatelet therapy using the 90-mg twice-daily dose of ticagrelor studied in PLATO (The Study of Platelet Inhibition and Patient Outcomes) as well as a lower dose: 60 mg twice daily. Both doses of ticagrelor reduced the risk of cardiovascular death, MI, or stroke by 15% and doubled the risk of TIMI major bleeding. The rates of fatal bleeding or nonfatal intracranial hemorrhage did not differ significantly between the ticagrelor dose group and the placebo group. The rates of bleeding and other side effects such as dyspnea were numerically lower with the 60-mg dose of ticagrelor than with the 90-mg dose, resulting in a lower rate of discontinuation of the study drug and a better safety profile with the 60-mg dose. There was a trend with ticagrelor 60 mg twice daily toward a reduction in the rate of cardiovascular death and death from any cause, but this effect was not significant. For every 10,000 patients treated with ticagrelor 60 mg twice daily, 42 ischemic events (death, MI or stroke) per year would be prevented at the cost of 31 TIMI major bleeding. All of these studies support a role for extended and more potent antiplatelet treatment for secondary prevention in patients with proven CAD and, in particular, with a prior history of MI. Interestingly, the subgroup of patients presenting with acute MI in the DAPT trial had a reduction in MACCE with continued thienopyridine that was greater (HR: 0.56) than in patients without MI (HR: 0.83; interaction p = 0.03). Bleeding, however, was similarly increased in both subgroups (62). The consistent excess of bleeding across studies with prolonged DAPT suggests that patients should be selected on the basis of the ischemic versus bleeding risk.

**ONGOING STUDIES.** Alternative strategies with novel therapies, as well as withdrawing some agents, represent an area of investigation that will add to our understanding of optimal antiplatelet management (63). A number of studies are examining the effectiveness of shorter-duration DAPT in patients after coronary stenting. The largest of these, GLOBAL LEADERS (Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy
in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; NCT01813435) will randomize 16,000 patients receiving the Biomatrix DES (Biosensors Interventional Technologies, Singapore) to either 1 month of DAPT with aspirin and ticagrelor followed by 23 months of ticagrelor alone, or 12 months of standard DAPT followed by aspirin monotherapy. Other randomized studies are also exploring the safety of shorter durations of DAPT with novel stent platforms, and some will focus on the ACS population receiving newer-generation DES. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) study [NCT02270242] takes a new approach to SAPT. The active arm will have interruption of aspirin at 3 months post-PCI continuing on ticagrelor alone. The comparator arm will have DAPT with aspirin and ticagrelor for 1 year (Table 5). Other smaller studies evaluating long-term DAPT in stented populations (NCT02079194) are still ongoing.

### THE CLINICIAN’S CHOICE

Medicine is both art and science. The science relies on data provided by randomized clinical trials and observational studies elucidating incidence, risk factors, effect on outcomes, and optimal treatment for a medical condition. The art relies on the ability of the physician to synthesize medical knowledge and translate it into the optimal patient-specific management strategy. The decision to either continue or stop DAPT after a mandatory period after the implantation of a DES perfectly reflects this concept (64). An initial mandatory period of DAPT after DES implantation is needed to prevent stent- and nonstent-related thrombotic complications. During this period, cessation of DAPT is associated with an unacceptably high rate of thrombotic events (65–67). The duration of mandatory DAPT, which can range from 3 to 12 months, depends on the patient’s clinical presentation, overall risk profile, lesion complexity, and the type of stent implanted. Beyond the mandatory period, DAPT prolongation has to be carefully considered (68). Extension of DAPT confers protection against stent- and nonstent-related atherothrombotic events (50). However, the antithrombotic benefit may be counterbalanced by an increased bleeding risk, which affects morbidity and mortality and cannot be disregarded. Therefore, a realistic estimation of the long-term ischemic and bleeding risk in every patient undergoing PCI is of paramount importance to tailor the optimal DAPT duration.

### ISCHEMIC RISK EVALUATION

Coronary thrombotic events after PCI can be classified as stent- and nonstent-related (69). DAPT confers protection on both types of thrombotic events through suppression of platelet reactivity and aggregability (70).

The pathophysiology of ST includes patient-, stent-, and procedure-related factors (71). Patient-related factors include presentation with ACS (in which STEMI carries the highest thrombotic risk), diabetes mellitus, chronic kidney disease, and clinical surrogates such as multivessel CAD, previous MI, left ventricular dysfunction, and high-on-treatment platelet reactivity (65–67,72,73). Procedural factors include

### TABLE 5 Ongoing Studies Examining Abbreviated Duration of DAPT

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Design</th>
<th>Size</th>
<th>Active (Months)</th>
<th>Control (Months)</th>
<th>Population</th>
<th>Primary EP</th>
<th>Expected Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL LEADERS (NCT01813435)</td>
<td>RCT (Biomatrix stent)</td>
<td>16,000</td>
<td>1</td>
<td>12</td>
<td>DES</td>
<td>Composite of all-cause mortality or nonfatal new Q-wave MI up to 2 yrs post-randomization</td>
<td>June 2016</td>
</tr>
<tr>
<td>REDUCE (NCT02118870)</td>
<td>RCT (COMBO dual therapy stent)</td>
<td>1,500</td>
<td>3</td>
<td>12</td>
<td>ACS</td>
<td>Composite of all-cause mortality, MI, ST, stroke, or bleeding at 12 months</td>
<td>March 2017</td>
</tr>
<tr>
<td>SMART-CHOICE (NCT02079194)</td>
<td>RCT</td>
<td>5,100</td>
<td>3</td>
<td>12</td>
<td>DES</td>
<td>Composite of death, MI, cerebrovascular events, or bleeding over 3–12 months after the index procedure</td>
<td>February 2020</td>
</tr>
<tr>
<td>SMART-DATE (NCT01701453)</td>
<td>RCT</td>
<td>3,000</td>
<td>6</td>
<td>12</td>
<td>ACS</td>
<td>Composite of death, MI, CVA, ST, or major bleeding over 6–18 months post-hospitalization</td>
<td>August 2016</td>
</tr>
<tr>
<td>DAPT-STEMI (NCT01459627)</td>
<td>RCT</td>
<td>1,100</td>
<td>6</td>
<td>12</td>
<td>STEMI</td>
<td>Composite of death, MI, revascularization, CVA, or bleeding at 18 months post-randomization</td>
<td>December 2017</td>
</tr>
<tr>
<td>TWILIGHT (NCT02270242)</td>
<td>RCT</td>
<td>8,000</td>
<td>3</td>
<td>12</td>
<td>complex PCI with DES</td>
<td>Major bleeding at 15 months post-PCI</td>
<td>March 2017</td>
</tr>
</tbody>
</table>

CVA = cerebrovascular accident; DAPT-STEMI = Prospective, Randomized, Open Label Trial of 6 Months vs. 12 Months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction; GLOBAL LEADERS = Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy In All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; REDUCE = Randomized Evaluation of Short-term DUAL Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt; SMART-CHOICE = Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; SMART-DATE = Smart Angioplasty Research Team: Safety of 6-month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes; TWILIGHT = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; other abbreviations as in Tables 1 to 3.
stent underexpansion or undersizing, incomplete stent apposition, residual edge dissection, number of stents implanted, final stent length, and lesion complexity. Finally, stent-related factors include polymer hypersensitivity with incomplete endothelialization, stent design, and strut thrombogenicity. A substantial improvement in stent endothelialization and strut thrombogenicity has been achieved with second-generation DES, as compared with their predecessors (18). Moreover, bioresorbable polymer DES have the potential advantage of eliminating polymer-related triggers for late and very late ST after the elution of the antirenostenotic drugs (44).

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study demonstrated that adverse ischemic events occurring at follow-up after PCI for ACS are almost equally distributed between thrombosis in culprit and nonculprit lesions (69). Neoatherosclerosis can occur either inside or outside of the stented vascular segment (74). Evidence from intravascular imaging and histologic studies in DES demonstrate the occurrence of continuous neointimal growth (75). In-stent neoatherosclerosis may be an important mechanism of stent failure, accounting for both ST and restenosis after either BMS or DES implantation (74).

Having considered these factors, the prolongation of DAPT after the mandatory period to prevent the occurrence of future thrombotic events, both within and beyond the target coronary lesion, may be an attractive and “desirable” strategy after meticulous individualized evaluation of the hemorrhagic risk.

BLEEDING RISK EVALUATION. As opposed to ST or recurrent MI, bleeding severity ranges from events that are clinically insignificant to those that are life-threatening or fatal (76). Among existing, commonly-used definitions, Bleeding Academic Research Consortium type 3 or 5, TIMI major or minor, and GUSTO moderate or severe bleeding may seriously affect morbidity and mortality and, therefore, should be considered clinically relevant (77,78).

Several risk scores have been developed to predict late and very late bleeding, most of which do not apply specifically to a PCI population (79). For example, the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) risk score was developed to predict bleeding in patients on chronic anticoagulation for atrial fibrillation and is not relevant to PCI patients (79). Other risk factors, such as malignancy, thrombocytopenia, anemia, white blood cell count, low platelet reactivity, excessive fall risk, and genetic factors have been described (80-83). Considering the heterogeneity of risk factors and potential sites for bleeding, the individual bleeding risk should be carefully evaluated.

IMPORTANT OF THE CLINICAL CHOICE. Clinically significant bleeding events are numerically more frequent than ST or MI, and their effect on late mortality has been extensively described (50,82). In addition, for some patients or clinicians, a moderate bleed may not carry the same weight as an ST or spontaneous MI. On the basis of data derived from early events after PCI, ST is associated with a higher fatality rate than major bleeding (84,85).

Pooling the available evidence, prolonging DAPT after the mandatory period seems to be more appropriate in patients at high risk for ischemic events and relatively low bleeding risk. Conversely, considering the greater safety of newer-generation DES, the relatively high incidence of late bleeding events on DAPT, and their deleterious effect on survival, limiting DAPT to the 3- to 6-month mandatory period may be the optimal strategy in patients at moderate or high risk for bleeding. Similarly, the strategy of S-DAPT would apply to patients who would require oral anticoagulation (e.g., for atrial fibrillation) or semi-urgent noncardiac surgery (e.g., for cancer) or investigation (e.g., gastrointestinal endoscopy). Ideally, prescription of DAPT after PCI with DES has to be a dynamic (i.e., potentially modifiable over time) recommendation. After the procedure, patients should be prescribed DAPT for the initial mandatory period of 3 to 6 or 12 months according to clinical presentation, ischemic risk, bleeding risk, and the type of stent implanted. After this initial mandatory period, the physician may face 3 main scenarios regarding the risk/benefit ratio of a potentially “desirable” longer DAPT recommendation:

1. Patient had a recurrent ischemic event on DAPT; these patients will probably benefit from prolonging DAPT.
2. Patient had clinically significant bleeding; these patients should stop DAPT or at least complete the minimal mandatory period.
3. Patient is event-free; patients at low risk for bleeding and at high risk for ischemia may benefit from DAPT prolongation, considering the beneficial effect of DAPT in preventing stent- and nonstent-related thrombotic events. Conversely, patients at moderate or high risk for bleeding may benefit from DAPT cessation. Finally, patients may present with both high bleeding risk and high ischemic risk, and this is when the science of medicine becomes art (64).
Any change in the patient’s clinical profile that may influence the benefit/risk ratio or tolerance of or compliance with DAPT should be evaluated before deciding whether to prolong DAPT or not. A summary of the factors to consider in deciding whether to continue or discontinue DAPT after a mandatory period is depicted in the Central Illustration.

Finally, a very important and often underestimated aspect of post-procedural PCI management is optimal medical therapy (OMT). The control of multiple cardiovascular risk factors reduces the incidence of cardiovascular events (86). OMT is a broad term that incorporates the control of lifestyle risk factors (weight loss, smoking cessation, dietary regimen, exercise, and life rhythms) and specific pharmacotherapy to control arterial hypertension, hyperlipidemia, and chronic hyperglycemia. As stated by the European Society of Cardiology guidelines “OMT should not be considered an alternative but a synergistic approach to revascularization” (26).

CONCLUSIONS

Considering the consistent results from the reported studies, safe interruption of DAPT 6 months after DES implantation may be possible in selected patients. Two randomized studies and a few registries have suggested that 3 months of DAPT was possible with the latest DES generation. Prolongation of DAPT beyond 1 year after DES implantation is possible. This has been tested now in patients selected after a year of follow-up. The strategy of using DAPT to reinforce secondary prevention is more sensible in patients at high ischemic risk, although the benefit was observed across almost all subgroups. Long-term DAPT reduces stent- and nonstent-related thrombotic events at the cost of more bleeding complications, translating into no survival advantage. Long-term DAPT may use clopidogrel or a new oral P2Y12 antagonist. In either case, removing the P2Y12 antagonist exposes patients...
to a reactivation of the ischemic disease, even 2 years after stenting. Removing the last antiplatelet agent is not recommended in any coronary patient.

Finally, after a short mandatory period of 3 to 6 months, DAPT should be tailored over time on the basis of the clinical profile, the type of stent, and the patient’s tolerance, comorbidities, and preference. At this stage, clinicians are advised to individualize decisions regarding the type and duration of DAPT in stented patients.

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