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Continuation of Dual-Antiplatelet Therapy Following Percutaneous Revascularization with a Drug-Eluting Stent: What Duration Is Optimal?

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Abstract Dual-antiplatelet therapy (DAPT) is required after percutaneous coronary intervention with drug-eluting stents (DESs) to prevent thrombotic complications, particularly stent thrombosis (ST). However, there is still disagreement regarding the optimal duration of DAPT post-DES placement. Compared to bare metal stents, DESs are known to reduce restenosis and target vessel revascularization but may be more prone to late and very late ST due to delayed endothelialization. Several trials have suggested that longer (>12 months) DAPT reduces ischemic events but does so at the cost of increased bleeding. Other trials have demonstrated non-inferiority of shorter (3 to 6 months) DAPT compared to long-term DAPT, with fewer bleeding events. The clinical challenge is how to balance the reduced ischemic risk with increased bleeding associated with longer DAPT. Furthermore, ST is associated with multiple patient- and procedure-specific factors, thereby limiting a "one-size-fits-all" approach to determining optimal duration of DAPT. The evaluation of DAPT duration should therefore be tailored individually. We will review the data supporting current recommendations for DAPT and recent clinical trials comparing varying DAPT durations and discuss patient- and procedure-specific factors affecting the "optimal" DAPT duration.

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Introduction

Dual-antiplatelet therapy (DAPT), defined as the combination of aspirin and a platelet $P2Y_{12}$ receptor inhibitor, is required after percutaneous coronary intervention (PCI) with bare metal stent (BMS) or drug-eluting stent (DES) placement in order to prevent thrombotic complications. The optimal duration of DAPT remains controversial and is individualized, based on patient's risk factors, coronary anatomy, generation of DES, and the careful balance of increased bleeding risk and benefit of preventing stent thrombosis and/or myocardial infarction (MI). Patients are subject to a greater risk of ischemic events, such as stent thrombosis (ST) if DAPT is interrupted, especially in the first weeks to months after PCI with any stent implantation, when this risk is particularly high [1••, 2].

The efficacy of DAPT in reducing ST and subsequent cardiovascular events in patients with acute coronary syndrome (ACS) and after elective PCI has been demonstrated in multiple trials [3••]. ST is a feared consequence of premature DAPT termination, as it has been observed to carry a high mortality rate of ~20–45 % [4, 5]. A prospective analysis of over 3000 patients post-DES implantation showed that discontinuation of thienopyridine therapy was the most powerful predictor of ST during the first 6 months after receiving a drug-coated stent [6]. One of the mechanisms leading to ST is delayed endothelialization that occurs in the setting of DES placement, particularly after first-generation DES. Compared to BMSs, DESs have clearly reduced the need for repeat target lesion and target vessel revascularization [7•, 8, 9] by utilizing an antiproliferative agent (e.g., sirolimus, paclitaxel, everolimus, zotarolimus) that impairs neointimal hyperplasia. This

mechanism comes at the expense of endothelial dysfunction and potentially exposed stent struts that promote ST, particularly in the setting of inadequate platelet inhibition. The Dutch Stent Thrombosis Registry demonstrated that the lack of clopidogrel therapy at the time of ST in the first 30 days after the index PCI (hazard ratio (HR) 36.5, 95 % confidence interval (CI) 8.0 to 167.8), between 30 days and 6 months after the index PCI (HR 4.6, 95 % CI 1.4 to 15.3), and beyond 6 months after the index PCI (HR 5.9, 95 % CI 1.7 to 19.8) was strongly associated with developing ST [2]. Recent data suggest that everolimus-eluting stents and zotarolimus-eluting stents, which are second-generation DESs, are associated with lower rates of restenosis and repeat revascularization, as well as decreased rates of late and very late ST, when compared with the first-generation DES [10–12].

Several randomized clinical trials have indicated that DAPT duration exceeding 12 months may negatively impact patient outcomes by unnecessarily increasing bleeding events and raising health care costs [1••]. Furthermore, bleeding is an independent predictor for poor outcomes, including long-term mortality, in patients with ACS and in those undergoing PCI [13, 14]. However, short-term (3 to 6 months) DAPT duration may be associated with higher rates of ST, when compared with longer (≥12 months) DAPT [15]. Initially, based on randomized clinical trials leading to approval of first-generation DES, the recommended DAPT durations for sirolimus-eluting and paclitaxel-eluting stents were 3 and 6 months, respectively [3••]. After several concerning reports of an increase in major adverse cardiovascular events (MACE) when discontinuing DAPT within 6 months of first-generation DES implantation [2, 3••, 16–18], the recommended DAPT duration was extended. The latest American Heart Association/American College of Cardiology guidelines recommend a minimum of 12 months of DAPT following PCI with DES, whereas more recent European Society of Cardiology guidelines recommend a minimum of 6 to 12 months of DAPT [4, 19]. We will review the data leading to current recommendations for DAPT following DES placement and discuss individual patient-specific factors (e.g., presentation with ACS, stent length, and diameter) that should be factored into the decision making for "optimal" DAPT duration.

Three- or 6-Month DAPT Discontinuation Trials

The Safety and Efficacy of 6 Months Dual-Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) trial was an international, multicenter, double-blinded, randomized controlled trial that sought to assess the risks and costs associated with varying durations of DAPT and aimed to establish non-inferiority for 6 months of DAPT as compared with 12 months in 4000 patients who were receiving clopidogrel therapy at 6 months after DES implantation [20]. Patients were excluded if they had clinical signs or symptoms of active ischemia, non-ST segment elevation MI or ST segment elevation myocardial infarction (STEMI) within the last 6 months post-DES, DES to the left main coronary artery as index intervention, or active anticoagulation. The primary endpoint was defined as the composite of death, MI, definite or probable ST, stroke, or major bleeding (according to Thrombolysis in Myocardial Infarction (TIMI) criteria) 9 months after randomization. There were eight cases of definite ST, five (0.3 %) in the 6-month group, and three (0.2 %) in the 12-month group (HR 1.66; 95 % CI 0.40 to 6.96). Rates of MI and stroke were low and comparable in both groups (MI 13 patients [0.7 %] vs. 14 patients [0.7 %; HR 0.93; 95 % CI 0.44 to 1.97] and stroke 7 patients [0.4 %] vs. 5 [0.3 %; HR 1.40; 95 % CI 0.44 to 4.41]). There was a trend to having a lower rate of TIMI minor bleeding in the 6-month group with two patients (0.1 %) compared to eight patients (0.4 %) in the 12-month group (HR 0.80; 95 % CI 0.21 to 2.98; p=0.08). There was an increase in Bleeding Academic Research Consortium (BARC) ≥class 2 bleeding 20 patients (1.0 %) in the 6-month group vs. 40 patients (2.0 %) in the longer DAPT group (p=0.01). There was no significant difference with 6 months of clopidogrel compared to 12 months when looking at rates of the primary endpoint (1.5 vs. 1.6 %), which met the criterion for non-inferiority ($p_{\text{non-inferiority}}$<0.001) and no difference in the composite of death, MI, ST, or stroke (1.3 vs. 1.5 %; p=0.59). Caution should be exercised when interpreting these data given that the study was underpowered as a result of early termination due to slow recruitment and lower than anticipated event rates (1.6 % actual vs. 10 % anticipated).

The Is There A Life for DES after Discontinuation of Clopidogrel (ITALIC) trial was a multicenter, prospective, open-label randomized controlled trial designed to demonstrate non-inferiority of 6 to 24 months of DAPT in 1822 aspirin-sensitive patients with at least one everolimus-eluting stent; patients were excluded if undergoing primary PCI for acute MI or left main disease [21]. The investigators demonstrated no significant difference in primary endpoints (composite of death, MI, urgent target vessel revascularization (TVR), stroke, major bleeding) between the two cohorts (1.5 vs. 1.6 %; p=0.85 and $p_{\text{non-inferiority}}$<0.0002). There were no ST events in the 6-month DAPT group and three ST events in the 24-month group. The study was also terminated early due to slow recruitment, and once again had a lower-than-expected event rate. Thus, this trial has also demonstrated non-inferiority of 6 months compared to 24 months of DAPT in good aspirin responders, with no significant difference in bleeding and thrombotic event rates between these two groups.

The Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual-Antiplatelet Therapy (SECURITY) trial was a randomized, multicenter, international, non-inferiority study of 1399 patients with stable or

unstable angina or documented silent ischemia undergoing revascularization with at least one second-generation DES [7•]. The primary endpoint was a composite of cardiac death, MI, stroke, definite or probable ST, and BARC type 3 or 5 bleeding at 12 months. The secondary endpoint was a composite of cardiac death; MI; stroke; definite or probable ST; or BARC type 2, 3, or 5 bleeding at 12 and 24 months. Slow enrollment and minimal differences in the primary endpoint rates resulted in early study termination and suggested non-inferiority of 6-month DAPT compared with 12-month DAPT in this low-risk population. The primary endpoint occurred in 4.5 versus 3.7 % at 12 months, respectively (risk difference 0.8 %; 95 % CI −2.4 to 1.7 %). There were no differences in secondary endpoints at 12 months (5.3 vs. 4.0 %, difference 1.2 %; 95 % CI −1.0 to 3.4) or between 12 and 24 months (1.5 vs. 2.2 %, difference −0.7 %; 95 % CI −2.1 to 0.6). No differences in ST rates at 12 months (0.3 vs. 0.4 %; difference −0.1 %; 95 % CI −0.7 to 0.4) and between 12 and 24 months (0.1 vs. 0 %; difference 0.1 %; 95 % CI −0.1 to 0.4) were observed. Bleeding rates between both groups were similar, though the incidence rates were lower than expected: six cases (0.9 %) of any bleeding in the 6-month group and ten cases (1.4 %) in the 12-month group. There were no significant differences in bleeding BARC type 3 or 5 between both groups, with four events (0.6 %) in the 6-month group and eight events (1.1 %) in the 12-month group (difference −0.5 %; 95 CI −1.4 to 0.4 %). Investigators identified several independent predictors of the primary endpoint: age ≥75 years, stent type used, mean number of stents implanted, mean stent length, and mean stent size. Furthermore, multivariable analysis did not identify DAPT for 6 versus 12 months to be an independent predictor of the primary endpoint (HR 1.27; 95 % CI 0.75 to 2.15). Of note, close to 34 % of patients in the 6-month group had continued DAPT after 6 months, possibly biasing the findings of this study.

The Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice (OPTIMIZE) trial by Feres et al. was a single-blinded, randomized trial of 3119 patients designed to compare 3 versus 12 months of DAPT in patients who had received a single zotarolimus-eluting stent for stable angina, unstable angina, or recent (but not acute) MI (<30 days); patients with elevated biomarkers at the time of the index procedure, ST segment elevation MI, or rescue PCI were excluded [22]. The primary endpoint of the trial was a combined endpoint, net adverse clinical and cerebral events (NACCE), including all-cause death, MI, stroke, or major bleeding. Non-inferiority was demonstrated with 3 versus 12 months of DAPT for the primary endpoint: 6.0 % in the 3-month group vs. 5.8 % in the 12-month group; $p_{\text{non-inferiority}}=0.002$. Also, MACE rates did not differ significantly between the two study groups (8.3 % in the 3-month group vs. 7.4 % in the 12-month group; $p_{\text{non-inferiority}}=0.002$). Comparable rates of NACCE, ST, and TVR were demonstrated at 90 days in the two groups. The authors concluded, based on the low event rates in both groups, that short-term DAPT may be sufficient in a low-risk population after DES placement.

Palmerini et al. performed an individual-patient data pairwise and network meta-analysis of four trials, which included 8180 randomized patients, comparing short-term (≤6 months) and long-term (1 year) DAPT, and demonstrated that short-term DAPT was associated with similar rates of MACE and lower rates of bleeding events when compared with long-term DAPT [23••]. The four trials analyzed included the following: (1) The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial, a randomized, multicenter, non-inferiority study comparing 6 to 12 months of DAPT; (2) the aforementioned OPTIMIZE trial; (3) randomized comparison of 6- versus 24-month clopidogrel therapy after balancing antiintimal hyperplasia stent potency in all-comer patients undergoing PCI design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia (PRODIGY), an unblended, multicenter, randomized, superiority study; (4) a new strategy for discontinuation of dual-antiplatelet therapy: the REal Safety and Efficacy of 3-month dual-antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation (RESET Trial), a randomized, non-inferiority study. Primary endpoints included (cardiac) death, MI, stroke, ST, major bleeding, and ischemia-driven TVR. The most prevalent DES platforms in the pooled cohort were everolimus-eluting and zotarolimus-eluting stents, both second-generation DESs. There were non-significant differences in 1-year rates of MACE among 3-month versus 1-year DAPT, 6-month versus 1-year DAPT, or 3-versus 6-month DAPT. At 1-year follow-up, there was no significant difference in the risk of MACE between treatment groups (HR 1.11; 95 % CI 0.86 to 1.43). Short-term DAPT was associated with significantly lower 1-year rates of any bleeding compared with prolonged DAPT (HR 0.66; 95 % CI 0.46 to 0.94; $p=0.03$), with a trend toward lower rates of major bleeding (HR 0.58; 95 % CI 0.32 to 1.03; $p=0.06$). The study suggested that compared with prolonged DAPT, short-term DAPT was associated with similar rates of MACE and lower rates of bleeding after DES placement. Thus, in selected patients (without high-risk clinical or lesion characteristics) receiving second-generation DES, 3 or 6 months of DAPT may be acceptable. Of note, in a PRODIGY substudy analyzing patients with in-stent restenosis, there was a statistically significant lower occurrence of death and MI in long-term DAPT versus short-term DAPT (6.5 versus 15.5 %; $p=0.03$); thus, a longer duration of DAPT may be of benefit in in-stent restenosis patients [24] (Table 1).

Table 1 Three- or 6-month DAPT discontinuation trials

Trial	Year	Study population (*n*)	Design	DAPT regimen	Primary endpoint	Mean age	ACS (%)	First-generation DES (%)	Second-generation DES (%)	Study outcome
OPTIMIZE	2013	3119	3- vs. 12-month DAPT Single-blinded RCT	Aspirin + clopidogrel	All-cause death, MI, stroke, or major bleeding	61	32	-	100	3 months non-inferior to 12 months
ISAR-SAFE	2014	4000	6- vs. 12-month DAPT Single-blinded RCT	Aspirin + clopidogrel	Composite of death MI, define or probable ST, stroke, or major bleeding	67	40	10	72	6 months non-inferior to 12 months
ITALIC	2014	1822	6- vs. 24-month DAPT Open-label RCT	Aspirin + clopidogrel/ prasugrel/ticagrelor	Composite of cardiac death, MI, stroke, or major bleeding	62	38	-	100	6 months non-inferior to 24 months
SECURITY	2014	1399	6- vs. 12-month DAPT Randomized non-inferiority study	Aspirin + clopidogrel/ prasugrel/ticagrelor	Composite of cardiac death, MI, stroke, define or probable ST, and BARC type 3 or 5 bleeding	65	38	-	100	6 months non-inferior to 12 months

DAPT dual-antiplatelet therapy, *ACS* acute coronary syndrome, *DES* drug-eluting stent, *ISAR-SAFE* Safety and Efficacy of 6 Months Dual-Antiplatelet Therapy After Drug-Eluting Stenting, *RCT* randomized controlled trial, *MI* myocardial infarction, *ST* stent thrombosis, *ITALIC* Is There A Life for DES after Discontinuation of Clopidogrel, *TVR* target vessel revascularization, *SECURITY* Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual-Antiplatelet Therapy, *BARC* Bleeding Academic Research Consortium, *OPTIMIZE* Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice

Twelve-Month DAPT Discontinuation Trials

An analysis by Park et al. in 2010 sought to evaluate if continuing DAPT beyond 1 year would be beneficial by evaluating data from two randomized clinical trials, which compared continuation versus cessation of clopidogrel in patients free of major adverse cardiac or cerebrovascular events and major bleeding after 12 months of DAPT following DES placement [25]. These two trials, Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) and 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 (ZEST-LATE) included 2701 patients who were randomly assigned to DAPT (clopidogrel plus aspirin) or to aspirin alone. The event rate for the primary endpoint (composite of MI or cardiac death) at 2 years was no different between the DAPT and aspirin monotherapy groups (1.8 vs. 1.2 %, respectively; HR 1.65; 95 % CI 0.80 to 3.36). Overall, there was a marginally non-significant increase in the composite endpoint of MI, stroke, or all-cause death in the DAPT continuation group compared to aspirin monotherapy (HR 1.73; 95 % CI 0.99 to 3.00; p=0.051) and in the composite endpoint of MI, stroke, or cardiac death (HR 1.84; 95 % CI 0.99 to 3.34; p=0.06). No difference in definite ST events was seen between the two groups. Thus, continuing clopidogrel beyond 12 months after DES placement was not shown to be more effective than aspirin monotherapy in reducing MI or cardiac death in patients receiving DES.

The Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Event (DES-LATE) trial was a prospective, multicenter, open-label, randomized study of 5045 patients designed to assess if an additional 24 months of DAPT after completing 12 months post (first- or second-generation)-DES placement would reduce the composite endpoint of cardiac death, MI, or stroke when compared to aspirin monotherapy [26]. Patients were enrolled with stable angina, unstable angina, non-ST segment elevation MI, or ST segment elevation MI at the time of the index procedure. The cumulative event rate of the primary endpoint (composite of cardiac death, MI, or stroke 24 months after randomization) was no different between the two groups: 2.4 % in the aspirin monotherapy group and 2.6 % in the DAPT group (HR 0.94; 95 % CI 0.66 to 1.35). The aspirin monotherapy group had a numerical, but non-significant, decrease in TIMI major bleeding with a cumulative incidence of 2.5 versus 3.9 % in the DAPT group (HR 0.71; 95 % CI 0.42 to 1.20; p=0.20). Thus, this trial showed that extending DAPT to 36 months was not effective in reducing death from cardiac causes, MI, or stroke when compared with aspirin monotherapy but might result in a small increase in the risk of bleeding. The limitations of this study included the open-label nature without placebo control, such that physicians and patients were not blinded to the duration of clopidogrel, the ability to easily switch therapies during follow-up, the low event rates, and the fact that only patients who were free of adverse clinical events for at least 12 months post-DES were enrolled, limiting the applicability of these results.

The 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 (ARCTIC)-Interruption trial was designed to establish superiority of continuing DAPT beyond 1 year after DES placement versus discontinuing the thienopyridine at that time point [27]. This trial was an extension of the ARCTIC-Monitoring trial, which was a randomized controlled trial of 2440 patients assigned to a strategy of platelet function testing with antiplatelet treatment adjustment versus a conventional antiplatelet strategy after either first- or second-generation DES placement. After 1 year, 1259 eligible patients without contraindication to interruption of DAPT (clopidogrel or prasugrel) were randomized to the second phase, ARCTIC-Interruption, in which patients were randomly separated into a single aspirin antiplatelet treatment group or a DAPT continuation group for 6 to 18 months. The primary endpoint (the composite of all-cause death, MI, ST, stroke, or urgent coronary revascularization) occurred in 4 % of patients in both groups (27 patients in the interruption group versus 24 patients in continuation group; HR 1.17; 95 % CI 0.68 to 2.03; p=0.58). The main secondary efficacy endpoint (the composite of ST, whether revascularized or not, and urgent revascularization) occurred in ten (2 %) in the interruption group and in eight (1 %) patients in the continuation group (HR 1.30; 95 % CI 0.51 to 3.30; p=0.58). Major bleeding events, classified by Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) criteria, were numerically, though not significantly, higher in the continuation group versus interruption group (1 % [seven patients] vs. 0.5 % [one patient]; HR 0.15 [0.02–1.20]; p=0.073). Based on these data, the authors concluded that there was no benefit in continuing DAPT beyond 1 year after DES placement if no event has occurred within the first year after PCI, given a potentially small increase in bleeding events. Limitations of this study included the smaller-than-anticipated study size, inability to generalize results to higher-risk patient cohorts, and data that combined first- and second-generation DES treatments.

Mauri et al. recently published the Twelve or 30 months of Dual-Antiplatelet Therapy after Drug-Eluting Stents (DAPT) trial, an international, multicenter, randomized, placebo-controlled trial of 9961patients designed to determine the risks and benefits of prolonging DAPT beyond 12 months after PCI [28••]. Patients were randomized to continue treatment with a thienopyridine (clopidogrel or prasugrel) or placebo; all

patients were continued on aspirin. The co-primary efficacy endpoints were the cumulative incidence of (i) definite or probable ST and (ii) MACE and cerebrovascular events between 12 and 30 months. The primary safety endpoint was the incidence of moderate to severe bleeding (as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] criteria and the Bleeding Academic Research Consortium [BARC] criteria). Interestingly, in this large trial, they found that continued treatment with a thienopyridine reduced rates of ST (0.4 vs. 1.4 %; HR 0.29 [95 % CI 0.17 to 0.48]; $p<0.001$) and MACE and cerebrovascular events (4.3 vs. 5.9 %; HR 0.71 [95 % CI 0.59 to 0.85]; $p<0.001$). The rate of MIs in the thienopyridine arm was lower than with placebo (2.1 vs. 4.1 %; HR 0.47; $p<0.001$). All-cause mortality was higher in the thienopyridine group (2.0 %) compared to the placebo group (1.5 %) (HR 1.36 [95 % CI 1.00 to 1.85]; $p=0.05$), but cardiac mortality rates (0.9 vs. 1.0 %) were similar in the two arms. As expected, the rate of GUSTO moderate to severe bleeding during the primary analysis period was higher with continued thienopyridine treatment (2.5 vs. 1.6 %, HR 1.61 [95 % CI 1.21 to 2.16]; $p=0.001$). Of note, there was no significant difference between the randomized treatments with respect to severe bleeding according to GUSTO criteria (0.8 % with continued thienopyridine and 0.6 % with placebo, $p=0.15$) or with respect to fatal bleeding according to BARC criteria (0.15 and 0.09 %, respectively; $p=0.38$); severe or fatal bleeding was uncommon, and the rates did not differ significantly between the two groups. In addition, there was an elevated risk of ST and MI in both groups during the 3 months after discontinuation of thienopyridine treatment. Based on this large trial data with sufficient power to detect differences in MACE, ST, and bleeding, the use of thienopyridine in combination with aspirin beyond 1 year seems to reduce the risk of very late ST and spontaneous MI in this heterogeneous cohort of first- and second-generation DESs (38 % first-generation DES, 60 % second-generation DES), in those presenting with PCI for stable CAD, unstable angina (UA)/NSTEMI, or STEMI (Table 2).

Discussion

The optimal duration of DAPT after DES placement remains controversial despite numerous, randomized clinical trials examining various time points of therapy [29]. A systematic review and meta-analysis of ten randomized controlled trials that evaluated different durations of DAPT (3 to 36 months) after DES placement in >30,000 patients by Giustino et al. [1••], arrived at conclusions similar to the DAPT investigators. First, longer DAPT was associated with a lower risk of definite/probable ST and MI compared with shorter DAPT duration. Second, longer DAPT was associated with a higher

Table 2 Twelve-month DAPT discontinuation trials

Trial	Year	Study population (*n*)	Design	DAPT regimen	Primary endpoint	Mean age	ACS (%)	First-generation DES (%)	Second-generation DES (%)	Study outcome
DES-LATE	2013	5045	12 vs. 36 months DAPT (compared to aspirin monotherapy) Open-label RCT	Aspirin + clopidogrel	Composite endpoint of cardiac death, MI, or stroke	62	61	90	42	36 months of DAPT associated with higher bleeding compared to aspirin monotherapy
ARCTIC-Interruption	2014	1259	12 vs. 24 months DAPT Open-label RCT	Aspirin + clopidogrel/ prasugrel	Composite of all-caused death, MI, ST, stroke, or urgent coronary revascularization	64	26	42	63	No benefit to >12 months DAPT; longer DAPT associated with increase bleeding
DAPT	2014	9961	12- vs. 30-month DAPT Double-blinded RCT	Aspirin + clopidogrel/ prasugrel	Co-primary efficacy endpoints were the cumulative incidence of (i) definite or probable ST and (ii) MACE and cerebrovascular events between 12 and 30 months	61	43	38	60	Prolonged DAPT associated with lower risk of ST, MACE, and cerebrovascular events, but increased bleeding

DAPT dual-antiplatelet therapy, *ACS* acute coronary syndrome, *DES* drug-eluting stent, *DES-LATE* Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Event, *RCT* randomized controlled trial, *MI* myocardial infarction, *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, *ST* stent thrombosis, *DAPT* Twelve or 30 months of Dual-Antiplatelet Therapy after Drug-Eluting Stents, *MACE* major adverse cardiovascular events

risk of clinically significant bleeding, with an excess of ~2.1 clinically significant bleeding events for each episode of ST averted. Importantly, the benefit of longer DAPT on ST was significantly attenuated with use of second-generation DES compared with first-generation DES. Multiple analyses have now demonstrated that everolimus-eluting stents are associated with less early and late ST compared with sirolimus- or paclitaxel-eluting stents [30]. Thus, it should not be surprising that the benefit of longer DAPT on ST is seen primarily with first-generation DES, devices that are obsolete in the current era of PCI. This large meta-analysis demonstrated a numerically lower, but not statistically different, all-cause mortality with shorter DAPT. However, cardiovascular mortality rates were similar between shorter and longer DAPT durations. The all-cause mortality numbers potentially favoring shorter DAPT duration may be partly explained by more clinically significant bleeding events with longer DAPT but may also reflect a chance imbalance of non-cardiac deaths, as was seen in the DAPT trial [28].

Premature discontinuation of DAPT is a major predictor of ST, particularly if DAPT is stopped within the first 3 months. In addition to an abbreviated duration of DAPT, there are other important clinical risk factors (e.g., renal insufficiency, diabetes, presentation with UA/NSTEMI or STEMI) and angiographic risk factors (e.g., bifurcation lesions, longer- and smaller-diameter stents, stent underexpansion) that are associated with a greater propensity for development of ST [31]. ST occurs in 1.8 % of patients presenting with ACS, but given the large number of PCI procedures performed annually in the USA, very late ST events have become quite prevalent [32]. Factors other than premature DAPT discontinuation that have been commonly associated with increased risk of ST include prior brachytherapy, renal failure, low ejection fraction, diabetes, presentation with ACS, and smoking [31, 33]. Furthermore, procedural characteristics that have been linked with ST include bifurcation disease and bifurcation stenting with a two-stent strategy, stent length, overlapping long stents, incomplete lesion coverage, stent underexpansion and malapposition, and edge dissection [3••, 33–35]. Important differences between second- and first-generation DESs with respect to ST may be related to differences in drug elution, but more importantly, late and very late ST events may be related to delayed healing and allergic reactions to stent polymers, a process in which eosinophils play an important role by inducing thrombosis [36].

The totality of the reviewed data suggests a trade-off between ischemic and bleeding events. Longer DAPT is associated with fewer ST and spontaneous MIs but increases the risk of bleeding. The risk of late and very late ST with shorter DAPT is greatest with first-generation DES, with this risk being attenuated with second-generation DES. Therefore, in the current era of contemporary PCI and new generation stent use, one would need to treat a very large number of patients with longer DAPT and expose them to potentially harmful bleeding to prevent one ST. On the other hand, recent data from the PEGASUS trial demonstrated that longer and stronger DAPT is beneficial in terms of MI protection, unrelated to ST. This trial utilized a more potent antiplatelet medication (ticagrelor) in stable CAD patients with prior MI, which reduced future cardiovascular events [37]. Thus, the optimal duration of DAPT with second-generation DES and newer pharmacotherapy remains undefined and should be individualized. The DAPT could be as short as 3 or 6 months in those not presenting with ACS and at low risk for ST and future MIs. On the other hand, DAPT could be extended if the risk of very late ST is high and prevention of MI (and strokes) in the future is important, particularly in those who have low bleeding risk and tolerate DAPT initially without complications.

The efficacy and safety of DAPT up to 36 months has been evaluated, but DAPT for longer than 36 months needs to be further studied. OPTImal DUAL-antiplatelet therapy trial (OPTIDUAL) is a currently ongoing clinical trial designed to evaluate the safety of 12 versus 48 months of DAPT post-DES placement [38]. Future trials will also be needed to examine newer generations of DES and novel, higher potency antiplatelet therapy (e.g., ticagrelor and prasugrel) [39]. In the future, bioabsorbable drug-eluting stents may serve to potentially eliminate the risk of very late ST by leaving no permanent metallic or polymeric foreign body behind. Furthermore, once the struts and polymeric coating are completely absorbed, ongoing intra-arterial inflammation would be resolved and endothelial function would be restored [40–42]. This in turn may allow for a definite period of DAPT, assuming that once the stent struts have been fully absorbed, DAPT will no longer be necessary to prevent ST. However, longer duration of DAPT may still be beneficial in high-risk patients to prevent spontaneous MIs unrelated to stents.

Conclusion

There remains uncertainty regarding the optimal duration of dual antiplatelet therapy after drug-eluting stent implantation due to limitations of currently available randomized controlled trials. Importantly, a “one-size-fits-all” approach to guide DAPT duration is likely to oversimplify what is a rather more complex clinical decision. Ultimately, duration will depend on a combination of individualized patient risk, procedural characteristics, and patient preference. The latter should promote initiatives to implement novel patient engagement tools to support shared decision making and augment patient understanding of the risks and benefits of shorter versus longer DAPT.

Compliance with Ethics Guidelines

Conflict of Interest Rupa K. Patil and Rajesh V. Swaminathan declare that they have no conflict of interest.

Dmitriy N. Feldman has served as a consultant/speakers' bureau member for Eli Lilly, Daiichi-Sankyo, Pfizer, Bristol Myers Squibb, and Abbott Vascular.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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