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REVIEW

Optimal Duration of Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents: Shorter or Longer?

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ABSTRACT

Use of dual antiplatelet therapy (DAPT; the combination of aspirin and an inhibitor of platelet $P2Y_{12}$) is the key pharmacological component in the management of acute coronary syndrome and percutaneous coronary intervention (PCI) with stent implantation, but the optimal treatment duration is still unclear. Although current guidelines recommend prescription of DAPT for at least 12 months after implantation of drug-eluting stents (DES) if patients are not at high risk of bleeding, several studies showed conflicting results. Observational studies have shown inconsistent findings (i.e., some studies suggested longer duration would be better, and others vice versa) and small-to-moderate sized randomized clinical trials suggested that prolonged use of DAPT beyond 12 months would not be more beneficial and could be detrimental in safety outcomes. However, these studies suffer from insufficient statistical power, data from old version of DES, and non-uniform duration of DAPT. Given there might be the relative risk and benefit associated with combination of DES use and DAPT prescription, the optimal decision making with regard to DAPT duration would be essential for patients who underwent PCI with DES. Thus, by understanding and comparing the evidences of recent studies that support for shorter and longer duration of DAPT, we sought to guide the treating physician in deciding optimal duration of DAPT in such patients. Up to now, there is no strong evidence supporting that longer duration of DAPT is better than shorter duration of DAPT in terms of efficacy and safety outcomes after DES placement.

Keywords: Coronary artery disease; Drug-eluting stent; Dual antiplatelet therapy; Percutaneous coronary intervention

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INTRODUCTION

Many randomized clinical trials have demonstrated better efficacy of drug-eluting

stents (DESs) in reducing restenosis and rate of repeat revascularization as compared with bare-metal stents (BMSs) [1, 2]. Although DESs were widespread and worked as a default device strategy in the majority of patients receiving percutaneous coronary intervention (PCI) for more than a decade, there was a considerable concern regarding late stent thrombosis (ST) [3–6]. Pathologic studies suggested that incomplete endothelialization of DESs was frequently observed even after 6 or 12 months after PCI [7–9], and clinically, most of thrombotic events tended to occur in the first 6–12 months after procedure and sometimes happened after the first year after DES implantation [5, 6]. As a result, prolonged use of dual antiplatelet therapy (DAPT) has become prevalent in clinical practice; however, careful balancing between ischemic benefits and bleeding risks according to the duration of DAPT has been an issue for several years [10–12].

On the basis of cumulative evidence, the current guidelines recommend that DAPT should be given either for 6–12 months (European guidelines [13]) or for at least 12 months (U.S. guidelines [14]) after DES implantation unless patients are at high risk for bleeding. However, these recommendations are largely based on registry data and randomized trials with a limited number of patients, and therefore the optimal duration of DAPT remains in question. Up to recently, several clinical studies have been performed to address questions about the optimal duration of DAPT in patients who have received DESs [15–21]. This article systemically reviews the current evidence from available clinical studies with the aim of helping physicians to make decisions on the optimal duration of DAPT for patients who are undergoing DES implantation.

METHODS

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials and prospective or retrospective observational studies published between January 2002 and June 2014. Search terms were: “coronary artery disease”, “clopidogrel”, “drug-eluting stents”, “dual antiplatelet therapy”, and “percutaneous coronary intervention”. Reference lists of review articles, meta-analyses, and original studies identified by the electronic searches were also checked to find other eligible studies for systemic reviews. In addition, conference proceedings/abstracts from the American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, Society of Cardiovascular Angiography and Intervention, European Society of Cardiology, and Euro-PCR were searched. There was no language restriction for the search. We excluded studies with number of enrolled patients less than 500. The search process was fairly extensive, and efforts were made to obtain the longest reported follow-up data from a combination of sources.

DISCUSSION

Longer Is Better

There were several observational studies (not, randomized clinical trials) that supported relatively longer duration, more than 12 months of DAPT after DES implantation. Those were mostly from the early experiences of DESs which implies that these were data from the first-generation DES. Brief summary of each study design and primary results are summarized in Table 1 [22–26].

Table 1 Characteristics of the studies supporting longer duration of dual antiplatelet therapy

Study	Total *N* (DES)	Stent types	Clinical diagnosis		DAPT duration	Endpoint	Follow-up duration (months)	Findings
			SA	ACS				
BASKET-LATE (ISRCTN75663024) [22]	746 (545)	BMS, DES	42.3%	57.7%	7–18 m	Cardiac death or MI	18	Discontinuation of clopidogrel between 7 and 18 months after PCI: DES 4.9% vs. BMS 1.3%
Duke registry [23]	4,666 (1,501)	BMS, DES			12 m	Cardiac death or MI	24	Discontinuation of clopidogrel at 12 months after PCI vs. continuation: 4.5% vs. 0% ($p < 0.001$)
Dutch registry [24]	1,303 (418)	BMS, DES	27.2%	72.8%	6–12 m	ST	31	Discontinuation of clopidogrel between 6 and 12 months after PCI: HR 5.87 ($p = 0.004$)
Melbourne registry [25]	2,980 (1,669)	BMS, DES	38.5%	61.5%	<6 vs. ≥12 m	All-cause death	12	5.3% vs. 2.8%, $p = 0.012$
SWEDEHEART registry (NCT01623700) [26]	42,268 (9,138)	BMS, DES, no stent	0.0%	100.0%	>6 m	All-cause death, MI or CVA	12	Adjusted HR 0.75, $p = 0.0155$

ACS acute coronary syndrome, *BMS* bare-metal stents, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stents, *HR* hazard ratio, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SA* stable angina, *ST* stent thrombosis

A first safety concern with regard to DES implantation without long-term maintenance of clopidogrel was raised by data from the Basel Stent KostenEffektivitäts Trial—Late Thrombotic Events (BASKET-LATE) (ISRCTN75663024) [22]. This study intended to define the incidence of late clinical events [cardiac death or myocardial infarction (MI)] and late ST in patients treated with the first-generation DESs versus BMSs after the discontinuation of clopidogrel and showed that more thrombotic events were found to occur 7–18 months after the procedure during the period with absence of DAPT, which were twice as frequent after DESs than BMSs. A subsequent, observational study from Duke registry highlighted the apparent benefits of extended clopidogrel use after first-generation

DES implantation [23]. In patients who continued clopidogrel for more than 6 or 12 months after DES placement, adjusted rates of death or MI at 24 months were significantly lower as compared with those in patients who did not continue clopidogrel (3.1% vs. 7.2%, $p = 0.02$). Patients in the BMS group had similar long-term mortality and rates of death/MI regardless of duration of clopidogrel at both landmark time points. In the Dutch registry, albeit in small numbers of DES patients, early discontinuation of clopidogrel, less than 12 months after the index PCI, was suggested as a strong predictor of ST [hazard ratio (HR): 5.9, 95% confidence interval (CI) 1.7–19.8] [24]. Similarly, in the Melbourne Interventional Group registry, 12 months of DAPT resulted in reduced mortality than a shorter duration (≤6 months) of DAPT (2.8% vs. 5.3%, $p = 0.012$) [25]. The SWEDEHEART(NCT01623700) registry data showed that >6 months of DAPT compared with 6 months of DAPT among acute coronary syndrome (ACS) patients was associated with a lower risk of death, stroke, or re-infarction (HR 0.75, 95% CI 0.59–0.95) [26]. Even in the subgroup analysis, with less than 6-month duration of DAPT, more than 3 months of DAPT lowered the risk of death, stroke, or re-infarction (HR 0.84, 95% CI 0.75–0.95) compared to less than 3 months of DAPT.

Shorter Is Better

By contrast, some observational studies and randomized trials suggested the safety and efficacy of shorter duration (less than 6–12 months) of DAPT would be comparable or better in safety outcomes compared to longer duration of DAPT among patients receiving DES implantation. Summary of these studies is shown in Table 2 [4, 5, 16–21, 27].

Observational Studies

Airoldi et al. [4] suggested that discontinuation of thienopyridine therapy was the key determinant of ST occurrence within the first 6 months, but not longer than 6-month period. They suggested that a vulnerable period of ST associated with DAPT continuation would be within 6 months. Schulz et al. [5] also demonstrated that the discontinuation of clopidogrel was a strong predictor for ST within the first 6 months but not thereafter after the first-generation DES implantation. The Two-Year Clopidogrel Need (TYCOON) study which is also based on the first-generation DES data, suggested that there was no long-term survival benefit in 24 months of DAPT compared to 12 months of DAPT, although early discontinuation of DAPT was the important predictor of ST (1% vs. 3%, $p = 0.02$) [27].

Randomized Trials

Several randomized clinical trials demonstrated no reduction in death or MI with prolonged DAPT compared to standard or shorter duration of DAPT use. The first randomized trial, 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 (NCT00590174)]/Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events [REAL-LATE (NCT00484926)] randomized patients who were event free within 1 year after DES implantation to receive DAPT or aspirin alone [17]. At 24 months, no difference was observed in the primary endpoint (composite of cardiac death or MI) or the risk for ST. However,

Table 2 Characteristics of the studies supporting shorter duration of dual antiplatelet therapy

Study	Total *N* (DES)	Stent types	Clinical diagnosis		DAPT duration	Endpoint	Follow-up duration (months)	Findings
			SA	ACS				
Registry data								
Airoldi et al. [4]	3,021	SES, PES			6 m	ST	18	Discontinuation of clopidogrel within 6 months vs. after 6 months of PCI: HR 13.74 ($p < 0.001$) vs. HR 0.94 ($p = 0.92$)
Munich registry [5]	6,816	SES, PES	65.0%	35.0%	6 m	ST	48	Discontinuation of clopidogrel within 6 months after PCI: significantly associated with ST ($p < 0.001$)
TYCOON [27]	897 (447)	BMS, DES			12 vs. 24 m	ST, cardiac death, TVR or MI	48	3% vs. 0.4% of ST ($p = 0.02$) 2% vs. 2% of cardiac death ($p = 0.74$) 2% vs. 0.4% of MI ($p = 0.30$)
Randomized trials								
ZEST-LATE (NCT00590174)/ REAL-LATE (NCT00484926) [17]	2,701	SES, PES, ZES	37.6%	62.4%	12 vs. 24 m	Cardiac death or MI	24	1.8% vs. 1.2% ($p = 0.17$)
PRODIGY (NCT00611286) [20]	2,013 (1,497)	BMS, PES, EES, ZES, no stent	25.6%	74.4%	6 vs. 24 m	All-cause death, MI or CVA	24	10.0% vs. 10.1% ($p = 0.91$) Significantly high risk for bleeding in the 24-month group
EXCELLENT (NCT00698607) [16]	1,443	SES, EES	48.4%	51.6%	6 vs. 12 m	TVF (cardiac death, MI or TVR)	12	4.8% vs. 4.3% ($p = 0.001$ for noninferiority) Diabetic patients in 6 month group: TVF was significantly frequent (HR 3.16, 95% CI 1.42–7.03, $p = 0.005$)
RESET (NCT01145079) [19]	2,117	E-ZES	45.4%	54.6%	3 vs. 12 m	Cardiac death, MI, ST, TVR or bleeding	12	4.7% vs. 4.7% ($p < 0.001$ for noninferiority)

Table 2 continued

Study	Total *N* (DES)	Stent types	Clinical diagnosis		DAPT duration	Endpoint	Follow-up duration (months)	Findings
			SA	ACS				
OPTIMIZE (NCT01113372) [21]	3,119	ZES	68.2%	31.9%	3 vs. 12 m	All-cause death, MI, CVA or bleeding	12	6.0% vs. 5.8% ($p = 0.02$ for noninferiority)

ACS acute coronary syndrome, *BMS* bare-metal stents, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stents, *EES* everolimus-eluting stent, *HR* hazard ratio, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PES* paclitaxel-eluting stent, *SA* stable angina, *SES* sirolimus-eluting stent, *ST* stent thrombosis, *TVR* target-vessel revascularization, *TVF* target-vessel failure, *ZES* zotarolimus-eluting stent

majority of patients in these trials were treated with first-generation DES and the observed event rate was lower than expected, favoring a shorter duration of DAPT. Subsequently, in the DES-LATE (NCT01186146) study (extended study of ZEST-LATE/REAL-LATE), a total of 5,045 patients were randomized to either DAPT continuation or aspirin alone after 1 year of DES implantation [18]. After 12 months, DAPT compared to aspirin alone showed no benefit in preventing ST (HR 1.59, 95% CI 0.61–4.09, $p = 0.34$), MI (HR 0.96, 95% CI 0.63–1.48, $p = 0.86$), or death (HR 0.71, 95% CI 0.45–1.10, $p = 0.12$). Incidence of major bleeding events between two groups was similar up to 24 months, but longer follow-up after 24 months revealed higher incidence of bleeding events in the DAPT continuation group (HR 0.67, 95% CI 0.47–0.95, $p = 0.026$).

The Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia [PRODIGY(NCT00611286)] trial provided a major next step to answer this issue by including more diverse stent types (BMSs, first- and second-generation DESs) and by shortening the duration DAPT into 6 months [20]. They randomized more than 2,000 patients to receive either 6 or 24 months of DAPT among patients who received a thin-strut BMS, a paclitaxel-eluting stent (PES), a zotarolimus-eluting stent (ZES), or an everolimus-eluting stent (EES) and therapy. There was no difference in the primary endpoints [the composite of death from any cause, MI, or cerebrovascular accident (CVA)] between the two groups. However, there was an excess of bleeding in patients assigned to 24 months of DAPT.

The Efficacy of Xience/Promus versus Cypher to Reduce Late Loss After Stenting [EXCELLENT (NCT00698607)] trial compared shorter duration of DAPT, 6 versus 12 months,

following DES implantation [16]. This study population predominantly received an EES (Xience or Promus, 74.8%) and rest of the patients received sirolimus-eluting stent (SES) (25.2%). The rate of target-vessel failure (TVF) (composite of cardiac death, MI, or ischemia-driven TVR) at 12 months was 4.8% in the 6-month DAPT group and 4.3% in the 12-month DAPT group ($p = 0.001$). Although ST tended to occur more frequently in the 6-month DAPT than 12-month DAPT (0.9% vs. 0.1%, HR 6.02; 95% CI 0.72–49.96; $p = 0.10$), the risk of death or MI did not differ between the two groups.

The REal Safety and Efficacy of 3-month DAPT following Endeavor zotarolimus-eluting stent implantation [RESET (NCT01145079)] trial compared the safety and efficacy of shorter duration (3 months) of DAPT and standard duration of 12 months of DAPT after Endeavor zotarolimus-eluting stent (E-ZES) implantation [19]. Three-month DAPT was shown to be non-inferior to the standard 12-month therapy with respect to the primary endpoint (cardiac death, MI, ST, TVR, or bleeding).

Recently, the OPTIMIzed duration of clopidogrel therapy following treatment with the zotarolimus-eluting stent in real-world clinical practice [OPTIMIZE (NCT01113372)] trial, which included 3,119 patients with stable coronary artery disease or low-risk ACS treated with ZES to compare 3 versus 12 months of DAPT, suggested that 3 months of DAPT was non-inferior to 12 months of DAPT for reducing net adverse clinical and cerebral events (a composite of all-cause death, MI, stroke, or major bleeding), without significantly increasing the risk of ST [21].

A meta-analysis of four randomized trials (REAL/ZEST-LATE, PRODIGY, EXCELLENT, RESET) was performed and the median DAPT duration was 16.8 months in the extended group versus 6.2 months in the control group [28, 29]. During follow-up, extended DAPT did not provide more clinical benefit [no difference in mortality, odds ratio (OR) 1.15, 95% CI 0.85–1.54; MI, OR 0.95, 95% CI 0.66–1.36; and ST, OR 0.88; 95% CI 0.43–1.81] as compared to shorter duration of DAPT; however, prolonged use of DAPT was associated with an increase of major bleeding (OR 2.64, 95% CI 1.31–5.30). Consistent findings were obtained in another meta-analysis, further including the OPTIMIZE trial [30, 31]. A total of 4,081 patients received DAPT for 3–6 months, and 4,076 patients were treated with DAPT for 12–24 months. There was no significant difference in the rate of the composite of cardiac death or MI between the short and prolonged DAPT groups (3.3% vs. 3.0%; OR 1.11, 95% CI 0.87–1.43, $p = 0.41$). But major bleeding was significantly higher in the group of patients treated with prolonged DAPT (0.29% vs. 0.71%, $p = 0.01$).

Therefore, current available randomized clinical trials and meta-analyses suggest that extension of the duration of DAPT after DES implantation might increase the risk of bleeding without reducing ischemic events. But, considering the limited sample size and the inclusion of mainly low-risk patients with low event rates in these trials, still the safety of short-term DAPT remains uncertain.

Ongoing Randomized Trials

Several unresolved issues and unmet needs with regard to optimal DAPT duration after DES placement in clinical practice should be addressed from large-sized ongoing clinical trials. The previous, five randomized trials comprising nearly 10,000 patients indicated that extended courses of clopidogrel did not contribute favorably to patient outcomes and

might in fact be detrimental in terms of safety outcomes. However, this conclusion would be too early to make a firm statement due to several limitations in terms of relatively small numbers of patients, a low rate of events, and shorter follow-up period. All of these trials adopted open-label designs and none of the trials have been evaluated systematically according to clinical and anatomic risk profiles. Therefore, much larger, blinded, randomized clinical trials would provide more confirmative answer to determine the optimal DAPT duration after DES implantation (Table 3) [32–37].

In the largest scale study to date, the Dual Antiplatelet Therapy [DAPT (NCT00977938)] study enrolled more than 20,000 patients treated with any generation of DES and approximately 3,000 patients with BMSs to either 12 or 30 months of DAPT, with patients stratified according to clinical and angiographic complexity [32]. Unlike the preceding randomized trials (except OPTIMIZE), study therapy was blinded and was masked. The primary results will be presented in the upcoming scientific meeting of the American Heart Association later this year. Another ongoing trial is The Safety And Efficacy of 6-month Dual Antiplatelet Therapy After Drug-Eluting Stenting [ISAR-SAFE (NCT00661206)], which evaluates a 6- or 12-month DAPT among 6,000 patients [33]. And OPTImal DUAL antiplatelet therapy trial [OPTIDUAL (NCT00822536)] is ongoing to assess the efficacy and safety of 12 versus 48 months of DAPT after DES implantation [34]. In the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting [ARCTIC (NCT00827411)] study, diverse durations of DAPT based on the platelet function monitoring is currently under investigation among 2,500 patients [35].

Currently, an increasing number of patients are receiving the second-generation $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) instead of clopidogrel which demonstrate more potent suppression of platelet activity, leading to reduction of recurrent ischemic events [37, 38]. Based on these results, recent guidelines recommended prasugrel and ticagrelor on equal terms with clopidogrel in the patient with ACS or stent implantation [13]. However, studies on optimal duration of DAPT with these newer drugs are still very limited. In the upcoming years, a variety of trials with unique combinations with newer $P2Y_{12}$ inhibitors in a diverse duration could be suggested among patients who are undergoing PCI with DES implantation. The MEDTRONIC Endeavor Drug-Eluting Stenting: Understanding Care, Antiplatelet Agent and Thrombotic Events (EDUCATE, NCT01069003) study is designed to analyze 12 versus 30 months of DAPT; after 12 months of routine DAPT, patients will be randomly allocated to the placebo, clopidogrel or prasugrel group. In the clinical study comparing two forms of antiplatelet therapy after stent implantation trial [GLOBAL LEADERS (NCT01813435)], 1 month of ticagrelor plus aspirin followed by 23 months of ticagrelor monotherapy will be compared to 12 months of DAPT followed by aspirin monotherapy.

There was an also effort to figure out the optimal mode of DAPT discontinuation. The Abrupt Versus Tapered Interruption of Chronic Clopidogrel Therapy After DES Implantation [ISAR-CAUTION (NCT00640679)] study addressed the question of whether clopidogrel should be discontinued abruptly or with a progressive downgraded dosing [36]. Patients with planned discontinuation of chronic

Table 3 Ongoing trials on duration of dual antiplatelet therapy

Study	Total *N* (DES)	Stent types	DAPT duration	Follow-up duration (months)	Primary endpoint
DAPT (NCT00977938) [32]	20,645	BMS, DES	12 vs. 30 m	30	All-cause death, MI or CVA
ISAR-SAFE (NCT00661206) [33]	6,000	DES	6 vs. 12 m	15	All-cause death, MI, ST, CVA or bleeding
OTIDUAL (NCT00822536) [34]	3,120	ZES	3 vs. 12 m	36	Nonfatal MI, CVA or bleeding
ARCTIC (NCT00827411) [35]	2,500	DES	12 vs. >12 m	18–30	All-cause death, MI, ST, CVA or urgent revascularization
EDUCATE (NCT01069003)	2,500	ZES	12 vs. 30 m	24–36	Incidence of cardiac death, MI, ST, bleeding and DAPT compliance
GLOBAL-LEADERS (NCT01813435)	16,000		Conventional DAPT 12 m vs. ticagrelor	24	All-cause death or MI
ISAR-CAUTION [36]	3,000	DES	Abrupt vs. tapered interruption	3	Cardiac death, MI, ST, CVA, bleeding or rehospitalization due to ACS
SMART-DATE (NCT01701453)	3,000	New-generation DES	6 vs. 12 m	18	All-cause death, MI, CVA, ST or bleeding
SECURITY (NCT00944333)	4,000	Second generation DES	6 vs. 12 m	24	Definite or probable ST between 6–24 m
NIPPON (NCT01514227)	4,598	Biolimus A9 stent	6 vs. 18 m	18	All-cause death, MI, CVA or bleeding
REDUCE (NCT02118870)	1,500	Combo stent	3 vs. 12 m	12	All-cause death, MI, CVA or bleeding
DAPT-STEMI (NCT01459627)	1,100	DES	6 vs. 12 m	24	All-cause death, MI, CVA, bleeding or any revascularization

BMS bare-metal stents, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stents, *HR* hazard ratio, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *ST* stent thrombosis, *ZES* zotarolimus-eluting stent

clopidogrel therapy after DES implantation were randomized in a double-blinded fashion to either gradual discontinuation (according to a tapering schema over 4 weeks) or abrupt discontinuation (after continued clopidogrel therapy for additional 4 weeks) and followed for 3 months of the composite of cardiac death, MI, stroke, ST, major bleeding or rehospitalization. Initially, 3,000 patients planned to enroll but, the due to the slow recruitment, study was stopped prematurely after enrollment of 782 patients; at this point, tapered discontinuation of chronic clopidogrel therapy is not superior to abrupt discontinuation regarding the primary endpoint in this study.

As recent studies contain more data on the second-generation DES, clinicians are expecting that short duration of DAPT would be enough in the real world. But neither previous clinical studies nor ongoing randomized trials thus far have been designed to distinguish outcomes according to type of stents, several clinical risk profiles, lesions, and procedural complexities (i.e., ACS, diabetes mellitus, renal failure, low ejection fraction, multiple stents, long stents, left main stents, or bifurcation stents). Further larger trials with an enough statistical power to address this specific issue are required comprising all of these data to establish a firm policy for DAPT duration.

CONCLUSIONS

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor has significantly improved the outcomes of patients undergoing PCI. Because of the relative risk and benefit associated with the use of DESs and DAPT, defining the optimal duration of DAPT would be very critical in real practice. Although the latest PCI guidelines recommended at least 1 year of DAPT after DES placement, recent randomized clinical trials have demonstrated that a shorter duration of DAPT would be safe and effective than longer treatment, but these trials are still limited due to a few cardiovascular events, small-to-intermediate size of study, and inherent limitations of study designs. Upcoming results of much larger, double blind, and randomized clinical trials, with a higher use of second- and newer generation DESs will guide the physician in making informed decisions on the optimal duration of DAPT for patients receiving DES implantation. In addition, more data would be required to define the role of newer generation $P2Y_{12}$ inhibitors, including ticagrelor and prasugrel, for diverse clinical settings.

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Compliance with ethics. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315–23.

2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221–31.

3. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007;369:667–78.

4. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation. 2007;116:745–54.

5. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J. 2009;30:2714–21.

6. Roy P, Bonello L, Torguson R, et al. Temporal relation between clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009;103:801–5.

7. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115:2435–41.

8. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol. 2006;47:2108–11.

9. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008;118:1138–45.

10. Berger PB, Bhatt DL, Fuster V, et al. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Circulation. 2010;121:2575–83.

11. Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. Am J Cardiol. 2008;101:960–6.

12. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol. 2009;53:2019–27.

13. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58:44–122.

14. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31:2501–55.

15. Leon MB, Mauri L, Popma JJ, et al. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol. 2010;55:543–54.

16. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the efficacy of Xience/Promus versus Cypher to reduce late loss after stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505–13.

17. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362:1374–82.

18. Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trail. Circulation. 2014;129:304–12.

19. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60:1340–8.

20. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125:2015–26.

21. Feres F, Costa RA, Abizaid A, et al. Three vs. twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310:2510–22.

22. Pfisterer M, Brunner-La Rocca HP, Buser PT. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006;48: 2584–91.

23. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007;297:159–68.

24. Van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch stent thrombosis registry. J Am Coll Cardiol. 2009;53:1399–409.

25. Butler MJ, Eccleston D, Clark DJ, et al. The effect of intended duration of clopidogrel use on early and late mortality and major adverse cardiac events in patients with drug-eluting stents. Am Heart J. 2009;157:899–907.

26. Varenhorst C, Jensevik K, Jernberg T, et al. Duration of dual antiplatelet treatment with clopidogrel and aspirin in patients with acute coronary syndrome. Eur Heart J. 2014;35:969–78.

27. Tanzilli G, Greco C, Pelliccia F, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [two-year ClOpidOgrel need] study). Am J Cardiol. 2009;104:1357–61.

28. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J. 2012;33:3078–87.

29. Valgimigli M, Park SJ, Kim HS, et al. Benefits and risks of long-term duration of dual antiplatelet therapy after drug-eluting stenting: a meta-analysis of randomized trials. Int J Cardiol. 2013;168:2579–87.

30. Pandit A, Giri S, Hakim FA, Fortuin FD. Shorter (≤6 months) versus longer (≥12 months) duration dual antiplatelet therapy after drug eluting stents: a meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv. 2014;. doi:10.1002/ccd.25520.

31. El-Hayek G, Messerli F, Bangalore S, et al. Meta-analysis of randomized clinical trials comparing short-term versus long-term dual antiplatelet therapy following drug-eluting stents. Am J Cardiol. 2014;114:236–42.

32. Mauri L, Kereiakes DJ, Normand SL, et al. Rationale and design of the Dual Antiplatelet Therapy Study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J. 2010;160:1035–41.

33. Byrne RA, Schulz S, Mehilli J, et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. Am Heart J. 2009;157:620–4.

34. Helft G, Le Feuvre C, Georges JL, et al. Efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent: the OPTImal DUAL antiplatelet therapy (OPTIDUAL) trial: study protocol for a randomized controlled trial. Trials. 2013;14:56–61.

35. Collet JP, Cayla G, Cuisset T, et al. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. Am Heart J. 2011;161:5–12.

36. Fiedler KA, Mehilli J, Kufner S, et al. Randomised, double-blind trial on the value of tapered discontinuation of clopidogrel maintenance therapy after drug-eluting stent implantation. Intracoronary Stenting and Antithrombotic Regimen: CAUTION in discontinuing clopidogrel therapy—ISAR-CAUTION. Thromb Haemost. 2014;111:1041–9.

37. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndrome. N Eng J Med. 2009;361:1045–57.

38. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.