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Coronary Artery Disease (D Feldman, Section Editor)

Dual Antiplatelet Therapy Duration After the Placement of a Drug-Eluting Stent: What Are the Data?

Jad Raffoul, MD[1]
Andrew J. P. Klein, MD, FACC, FSCAI[1,2,*]

Address
[1]Department of Internal Medicine, Saint Louis University School of Medicine, 1402 South Grand Blvd., Saint Louis, MO 63104, USA
[*,2]Department of Internal Medicine, Division of Cardiology, St. Louis VA Healthcare System - The John Cochran VA Medical Center, 915 North Grand Blvd., Saint Louis, MO 63106, USA
Email: Andrew.Klein3@va.gov

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Opinion statement

The data supporting the immediate use of dual antiplatelet therapy (DAPT) post implantation of drug-eluting stents (DESs) is irrefutable. DAPT in this early period is necessary to prevent stent thrombosis during endothelialization of the stent, a process known to be delayed when DESs are placed. In addition, DAPT helps prevent thrombosis from plaque rupture that occurs outside of the initial stented area and/or at neo-atherosclerotic lesions within a previously coated stent. The ACC/AHA current guidelines (Levine et al. J Am Coll Cardiol. 58(24):e44–122, 2011) recommend 12 months of DAPT post DES implantation. As the result of several randomized clinical trials (Task Force on Myocardial Revascularization of the European Society of Cardio-Thoracic Surgery (EACTS) et al. Eur Heart J. 31(20):2501–55, 2010) showing the safety of a shorter duration of DAPT, the European Heart Society altered their recommendations to 6–12 months of DAPT post DES implantation. However, recent data from the DAPT trial (Mauri et al. N Engl J Med. 371(23):2156–66, 2014) clearly demonstrated less ischemic events with 30 months of DAPT. This trial and others have established that an increased DAPT duration increases bleeding risk which, in turn, increases subsequent morbidity and mortality. The current conundrum lies in defining the optimal time of DAPT post DES to adequately reduce ischemic events while minimizing bleeding risks. Future studies are required to better stratify patients into low and high risk for both ischemic and bleeding risks to assess whether shorter or longer courses of DAPT are the most appropriate for any specific

patients. Until then, instead of a "one size fits all" approach to patients who receive DESs, the treating physician must consider both procedural and patient factors when deciding the optimal duration of DAPT for each patient.

Introduction

Drug-eluting stents (DESs) have been shown to reduce long-term restenosis rates as compared to bare metal stents (BMSs) [1] and have become the preferred therapy in patients undergoing percutaneous coronary intervention (PCI). The presence of an anti-proliferative agent on the DES impairs the endothelialization process. In fact, angioscopic studies have shown incomplete endothelialization 6–12 months post DES implantation [2–4], and post-mortem studies conducted 40 months after implantation have confirmed poor endothelialization in 45 % of cases [5]. The delayed endothelialization is believed to be a risk factor for stent thrombosis (ST) which, though rare, can be a fatal event. Several large trials have demonstrated the effectiveness of dual antiplatelet therapy (DAPT) to reduce stent thrombosis and reduce future cardiovascular events in patients with acute coronary syndromes (ACS) as well as post elective PCI [6–9]. DAPT also prevents thrombosis from plaque rupture in native coronary lesions that were not stented [7, 9]. Hence, the initiation of DAPT (the combination of aspirin and a P2Y12 inhibitor) is recommended for all patients with ACS, regardless of stenting, and post PCI, regardless of their presentation, i.e., ACS or stable angina (SA).

Historically, the initial recommendations for first-generation DES (sirolimus-eluting and paclitaxel-eluting stents) were for 3 and 6 months of DAPT, respectively. Several subsequent observational studies however suggested a marked increase in major adverse cardiovascular events (MACE) upon the discontinuation of DAPT after 6 months from implantation of a first-generation DES [10–13]. The results of these studies led to the current recommendation of the American College of Cardiology/American Heart Association [14] for patients to receive at least 12 months of DAPT following implantation of a DES. The European Society of Cardiology, in contrast [15], recommends 6 to 12 months of DAPT post DES implantation. This difference highlights the challenge in determining the optimal duration of DAPT as we know that prolonged DAPT is also associated with an increased bleeding risk, and these bleeding complications have been reported to increase the mortality of patients receiving longer DAPT by two to four-fold [16]. Prolonged DAPT can also impact a patient's quality of life by delaying elective surgical, dental, or endoscopic procedures [16]. This review will summarize the most recent data to help guide treating physicians make informed, patient-specific recommendations for optimal DAPT duration after a DES is placed.

Basis of current recommendations of 12 months of DAPT

The current recommendations by the ACC/AHA are based on several large observational studies demonstrating that less than 12 months of DAPT post DES is associated with worse outcomes. In an observational study of 4666 patients (all comers) from the Duke registry [10], adjusted rates of death or MI at 24 months were significantly lower when patients received 12 months of ASA plus clopidogrel compared to 6 months (3.1 vs. 7.2 %, p=0.02). In contrast, patients who received BMSs had a similar long-term mortality and rates of death/MI irrespective of the duration of DAPT at 6, 12, and 24 months [11]. In the BASKET-LATE trial [12], designed to define the incidence of cardiac death or myocardial infarction and late ST (defined as occurring between 30 days and 12 months post-stent placement) in patients (42.2 % stable angina, 57.7 % ACS) treated with a DES (first generation) (n=545) vs. BMS (n=201), patients

who stopped DAPT between 7 and 18 months had more thrombotic events with a DES (4.9 % event rate) than those who received a BMS (1.3 %). Furthermore, the discontinuation of DAPT prior to 12 months in the Dutch stent thrombosis registry [13] was a significant predictor of ST (hazard ratio 5.9, 95 % CI 1.7–19.8).

Observational data from the PREMIER registry [17] demonstrated a marked increase in cardiovascular mortality (7.5 %) in patients who stopped their DAPT within 1 month of DES placement. Mortality was also shown to be greater in patients who received 6 vs. 12 months of DAPT (5.3 vs. 2.8 %, p=0.012) in the Melbourne registry (n=2980 patients; 38.5 % SA and 61.5 % ACS) [10]. Finally, in patients presenting with ACS, which is a risk factor for ST, data from Sweden showed that less than 6 months of DAPT vs. greater than 6 months of DAPT significantly increased the risk of death, stroke, or re-infarction (hazard ratio (HR) 0.75, 95 % CI 0.59–0.95) [18]. Based on these studies, the current recommendations were made. Importantly, these registry studies involved a generation of DES (first) that are no longer clinically available and have been shown to be inferior to the current second-generation DES currently used [19]. These studies also were not randomized clinical trials and, therefore, subject to biases and confounding. Finally, many of the registries combined patients presenting with both ACS and stable angina and, thus, have both high- and low-risk patients which can influence the data.

Data for greater than 12 months of DAPT post DES

Secondary to heightened and intense public scrutiny of DESs and the risk of ST and related morbidity and mortality, some cardiologists began prescribing lifelong DAPT in the late 2000s for their patients post DES implantation even in the absence of supporting data. In an effort to better assess whether longer DAPT is indeed beneficial, the ZEST-LATE/REAL-LATE [20] studies were developed. Data were combined from these two studies to create an open-label, non-placebo-controlled study which randomized event-free patients at 12 months post DES to receive DAPT for another 12 months or aspirin alone. At 24 months, there was no difference in the composite primary endpoint of cardiac death, MI, or the risk of ST. This negative study involved different types of DESs and had an event rate of cardiac death/MI that was lower than expected (1.8 vs. 1.2 %, p=0.17) undermining its power and applicability.

Additional data negating the benefit of greater than 12 months of DAPT in patients with DESs was provided in the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY) trial [19] (Table 1), which compared four different types of DESs (first and second generation) in 2013 patients randomized to 6 vs. 24 months of DAPT. There was no difference in the primary endpoint (death from any cause, MI, or CVA) with 24 months of DAPT compared to 6 months (10.0 vs. 10.1 %, p=0.91). Furthermore, the shorter DAPT group had a significantly lower bleeding rate (HR 0.67, 95 % CI 0.47–0.95, p=0.026) [21]. Next, the DES-LATE trial [22] was designed to address whether an additional 24 months of DAPT in patients who completed 12 months of DAPT post DES without complications would reduce a composite endpoint of death from cardiac causes, myocardial infarction, or stroke compared to aspirin monotherapy. This prospective study was an open

Table 1. Major Trial highlights

Clinicaltrials.gov Identifier		PRODIGY NCT00611286		EXCELLENT NCT00698607	
Duration		**Short 6 months**	**Prolonged 24 months**	**Short 6 months**	**Prolonged 12 months**
DAPT regimen		ASA (80–160 mg)+clopidogrel (75 mg)		ASA (100–200 mg)+clopidogrel (75 mg)	
Target population		Stable CAD or any form of ACS.		At least 1 lesion diameter 2.25-4.5 mm, >50 % stenosis, and evidence of MI***; excluding LVEF≤ 25 %, LM disease >50 %, CTO, or true bifurcating lesions requiring planned 2-stent strategy.	
Study design		Randomized, 1:1:1:1 for stents (included 3rd generation BMS), 1:1 for short vs prolonged group.		Randomized 1:1 for short vs prolonged, and 3:1 for DES.	
Number of subjects		737	741	722	721
Presentation	Stable angina	250 (25.4 %)	255 (25.8 %)	353 (48.9 %)	346 (48.0 %)
	ACS	733 (74.6 %)	732 (74.2 %)	369 (51.1 %)	375 (52.0 %)
	Non-ST elevation ACS ¶	406 (41.3 %)	411 (41.5 %)	350 (48.5 %)	349 (48.4 %)
	ST-elevation ACS	327 (33.3 %)	321 (32.5 %)	19 (2.6 %)	26 (3.6 %)
Stent used	Everolimus	247 (25.1 %)	248 (25.1 %)	540 (74.8 %)	539 (74.8 %)
	Sirolimus	-	-	182 (25.2 %)	182 (25.5 %)
	Zotarolimus	245 (24.95 %)	248 (25.1 %)	-	-
	Paclitaxel	245 (24.95 %)	245 (24.8 %)	-	-
	Biolimus	-	-	-	-
	Bare metal stent (BMS)	246 (25.0 %)	246 (25.0 %)	-	-
Aim		Evaluating device-specific efficacy and safety in prolonging dual antiplatelet therapy (up to 24 months) in all-comer patients receiving BMS or a variety of DES.		Demonstrating non-inferiority with shorter duration dual antiplatelet therapy in composite of cardiac death, MI, or target vessel revascularization within 12 months after randomization.	
Primary endpoint		All-cause mortality, MI, & stroke composite.		Cardiovascular death, MI, or ID-TVR composite.	
Major conclusions		No difference in composite risk of death, MI, or CVA in BMS, PES, or EES patients across dual antiplatelet therapy groups, but significantly lower in ZES-S patients undergoing short vs prolonged dual antiplatelet therapy. Statistically higher rate of stent thrombosis at 6 months in patients who recieved PES assigned to the short arm.		No significant difference in primary endpoint composite comparing 6 to 12 months dual antiplatelet therapy (4.8 % vs 4.3 %, HR 1.14), with no clinical benefit of >6 months of therapy albeit a higher frequency of stent thrombosis. However, the study was underpowered for hard end points (death &MI) assessment.	

Table 1. (Continued)

Clinicaltrials.gov Identifier		**RESET NCT01145079**		**OPTIMIZE NCT01113372**	
Duration		**Short 3 months**	**Prolonged 12 months**	**Short 3 months**	**Prolonged 12 months**
DAPT regimen		ASA (100 mg)+clopidogrel (75 mg)		ASA (100–200 mg)+clopidogrel (75 mg)	
Target population		Angina or MI with >50 % diameter occlusion, in the setting of elective PCI only.		Stable angina, silent ischemia, unstable angina, or non-acute MI within 30 days. Exclusion criteria included anyone with elevated biomarkers at index procedure, STEMI, or rescue PCI.	
Study design		Randomized 1:1 for short vs prolonged, and E-ZES vs non-E-ZES DES, stratified patients with DMII, ACS, lesions≤24 mm and≥28 mm.		Single-blinded, randomized 1:1.	
Number of subjects		1059	1058	1563	1556
Presentation	Stable angina	471 (44.5 %)	490 (46.3 %)	935 (59.8 %)	911 (58.6 %)
	ACS	588 (55.5 %)	568 (53.7 %)	494 (31.6 %) †	502 (32.3 %) †
	Non-ST elevation ACS ¶	432 (40.8 %)	422 (39.9 %)	84 (5.4 %)	84 (5.4 %)
	ST-elevation ACS	-	-	-	-
Stent used	Everolimus	-	404 (30.0 %)	-	-
	Sirolimus	-	383 (28.5 %)	-	-
	Zotarolimus	1341 (100 %)**	559 (41.5 %)**	1563 (100.0 %)	1556 (100.0 %)
	Paclitaxel	-	-	-	-
	Biolimus	-	-	-	-
	Bare metal stent (BMS)	-	-	-	-
Aim		Evaluating safety and efficacy of E-ZES with 3 months dual antiplatelet therapy compared to patients treated with non EZES and 12 months of dual antiplatelet ("standard therapy"). Hypothesis that EZES conveyed more protection from adverse cardiovascular and cerebrovascular events.		Assessing whether short-term dual antiplatelet therapy post ZES placement is non-inferior to long-term dual antiplatelet therapy.	
Primary endpoint		Composite of death from cardiovascular causes, MI, stent thrombosis, ID-TVR, or bleeding 1 year after DES placement.		All-cause mortality, MI, stroke, & major bleeding composite.	
Major conclusions		E-ZES 3-month dual antiplatelet therapy is safe and noninferior to the standard therapy (cumulative events: 40 [4.7 %] vs 41 [4.7 %]; difference: 0.0 %), and a nonstatistically significant increased risk of major and minor bleeding.		Non-inferiority demonstrated in short vs prolonged dual antiplatelet therapy for the composite risk of death, MI, stroke, and major bleeding (6.0 % vs 5.8 % for short vs long duration; HR 1.03, P for non-inferiority 0.002), without significantly increasing the risk of stent thrombosis.	

Table 1. (Continued)

Clinicaltrials.gov Identifier		**DAPT NCT00977938**		**ISAR-SAFE NCT00661206**	
Duration		**Short 12 months**	**Prolonged 30 months**	**Short 6 months**	**Prolonged 12 months**
DAPT regimen		ASA (75–162 mg)+[clopidogrel (75 mg) or prasugrel (5–10 mg)*]		ASA (75–200 mg)+clopidogrel (75 mg)	
Target population		Enrollment of anyone eligible for PCI & DES. At randomization, excluded patients with any events (all-cause mortality, MI, stroke, repeat coronary revascularization, stent thrombosis or moderate - severe bleeding) 12 months post index procedure, discontinuation of dual antiplatelet therapy >14 days, anyone on chronic anticoagulation, & life expectancy<3 years.		Excluded patients with clinical signs/symptoms of active ischemia, STEMI/NSTEMI during the last 6 months post DES, DES to LM as index intervention, and active anticoagulation prior to enrollment.	
Study design		Double-blinded, randomized 1:1. Note that short group was an additional 18 months of placebo, and both groups had an additional 3 months of ASA along after the 30th month to assess effects discontinuation of clopidogrel.		Double-blinded, randomized 1:1 for short vs prolonged.	
Number of subjects		4658	4732	1997	2007
Presentation	Stable angina	1870 (37.8 %)	1882 (37.5 %)	48 % ‡	48 % ‡
	ACS	2103 (42.5 %)	2148 (42.8 %)	40 % ‡	40 % ‡
	Non-ST elevation ACS ¶	1592 (32.2 %)	1614 (32.2 %)	32 % ‡	32 % ‡
	ST-elevation ACS	511 (10.3 %)	534 (10.6 %)	8 % ‡	8 % ‡
Stent used	Everolimus	2358 (47.7 %)	2345 (46.7 %)	49 %	49 %
	Sirolimus	541 (10.9 %)	577 (11.5 %)	16 %	16 %
	Zotarolimus	622 (12.6 %)	622 (12.6 %)	15 %	15 %
	Paclitaxel	1316 (26.6 %)	1350 (26.9 %)	-	-
	Biolimus	-	-	8 %	8 %
	Bare metal stent (BMS)	-	-	0.40 %	0.40 %
Aim		Determine benefits and risks of continuing dual antiplatelet therapy 12 months post DES placement.		Assess the risks and costs associated with prolonged dual antiplatelet therapy, with the hypothesis that in patients undergoing PCI with DES placement, 6 months is non-inferior to 12 months of dual antiplatelet therapy.	
Primary endpoint		Coprimary efficacy end points: cumulative incidence of definite or probable stent thrombosis, and composite of death, MI, or stroke during the randomized treatment period.		Composite of death, MI, stent thrombosis (definite or probable), stroke, or TIMI major bleeding 9 months post-randomization.	
Major conclusions		Prolonged dual antiplatelet group had significantly lower risk of stent thrombosis (0.4 % vs 1.4 %; HR, 0.29), composite of adverse cardiovascular & cerebrovascular events (4.3 % vs. 5.9 %; HR 0.71), but		Study was terminated early due to lower than anticipated event rate: major adverse cardiac events was non-inferior comparing both groups (1.5 % vs. 1.6 %, p for noninferiority<0.001), as was primary end point (1.3 % vs.	

Table 1. (Continued)

Clinicaltrials.gov Identifier		**DAPT NCT00977938**		**ISAR-SAFE NCT00661206**	
Duration		**Short 12 months**	**Prolonged 30 months**	**Short 6 months**	**Prolonged 12 months**
		increased risk of bleeding (2.5 % vs. 1.6 %; HR 1.61).		1.5 %, p=0.59), as were individual endpoints of mortality, MI, stent thrombosis, and stroke. Less bleeding with short group was noted (0.3 % vs. 0.7 %, p= 0.12).	

Clinicaltrials.gov Identifier		**ITALIC NCT01476020**	
Duration		**Short 6 months**	**Prolonged 24 months**
DAPT regimen		Aspirin (75 mg/106 mg/325 mg)+clopidogrel (75 mg)/prasugrel (60 mg) /ticagrelor (90 mg)	
Target population		Aspirin non-resistant subjects who were eligible for PCI (excluding primary PCI for acute MI and left main disease) with at least 1 Xience V DES. Some xclusion criteria were patients who recieved pretreatment with abciximab, prior DES placement, major surgery within 6 weeks preceding DES placement, and medical comorbidities with associated 2 year life-expectancy.	
Study design		Multicentered, non-blinded 1:1 randomization. Aspirin sensitivity assessed by one of three methods, depending on the site of enrollement. Aspirin non-responders were excluded.	
Number of subjects		912	910
Presentation	Stable angina	375 (41.1 %)	378 (41.5 %)
	ACS	211 (23.1 %)	217 (23.8 %)
	Non-ST elevation ACS ¶	210 (23.0 %)	214 (23.5 %)
	ST-elevation ACS	1 (0.1 %)	3 (0.3 %)
Stent used	Everolimus	100 %	100 %
	Sirolimus	-	-
	Zotarolimus	-	-
	Paclitaxel	-	-
	Biolimus	-	-
	Bare metal stent (BMS)	-	-
Aim		To demonstrate non-inferiority of 6 months to 24 months dual antiplatelet therapy.	
Primary endpoint		Composite of death, MI, urgent TVR, stroke, and major bleeding, 12 months post-stenting.	
Major conclusions		Study was terminated earlier than anticipated due to recruitment issues. Data collected demonstrated no significant difference in attaining the primary end point (1.5 % vs. 1.6 %; p=0.85), as well as rates of stent thrombosis & bleeding between both groups. Non-inferiority between the groups was also	

Table 1. (Continued)

Clinicaltrials.gov Identifier	**ITALIC NCT01476020**	
Duration	**Short 6 months**	**Prolonged 24 months**
	demonstrated (absolute risk difference 0.11 %, 95 % CI −1.04 to 1.26; p=0.002 for noninferiority).	

Dual antiplatelet therapy, DAPT; EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE, Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC, Is There A LIfe for Drug-eluting Stents (DES) After Discontinuation of Clopidogrel; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study; RESET, REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation

ACS Acute coronary syndrome; *ASA* acetylsalicylic acid; *BMS* bare metal stent; *CAD* coronary artery disease; *CI* confidence interval; *CTO* chronic total occlusion; *CVA* cerebrovascular accident; *DES* drug-eluting stent; *DMII* diabetes mellitus type II; *EES* everolimus-eluting stent; *HR* hazard ratio; *ID-TVR* Ischemia-driven target vessel revascularization; *LM* left main; *LVEF* left-ventricular ejection fraction; *MI* myocardial infarction; *PCI* percutaneous coronary intervention; *STEMI* ST-elevation myocardial infarction; *TVR* target vessel revascularization

* Weight-based dosing; 5 mg if weight<60 kg, 10 mg if>60 kg

** Endeavour vs Resolute for short vs prolonged therapy group

*** Stable angina, unstable angina, recent myocardial infarction, silent ischemia, a positive functional study, or reversible changes on ECG consistent with ischemia

¶ Includes non-ST elevation MI as well as unstable angina

† Recent ACS within 30 days prior to enrollment

‡ Percentages were reported as being similar between both arms

label and randomized 5045 patients whose initial presentation included both stable angina (38 %) as well as ACS (39 % UA, 11 % NSTEMI, 12 % STEMI). At the end of the study period, the primary endpoint was no different between the 12- and 36-month groups (2.4 vs. 2.6 %) with a non-significant decrease in bleeding in the 12 month DAPT group (hazard ratio 0.71, 95 % confidence interval 0.42–1.20, p=0.20). With no difference between the two groups in terms of death from any cause, myocardial infarction, stent thrombosis, or stroke, this study would suggest that extending DAPT to 36 months provides no additional benefit and may increase the risk of bleeding.

The limitations of the DES-LATE trial included the open-label nature, the low event rate, and the fact that it included only patients who were event free at 1 year and therefore were likely more stable. In order to overcome these limitations, the DAPT trial was designed. This large multi-center international double-blinded RCT was designed to examine the impact of long-term DAPT (30 months) vs. 12 months on the prevention of adverse cardiovascular events as well as define the magnitude of bleeding risk associated with prolonged DAPT. This study was powered for the primary endpoints of stent thrombosis and major adverse cardiovascular and cerebrovascular events (MACCE) and a composite of death, non-fatal myocardial infarction, or stroke [23••]. Treatment with either clopidogrel or prasugrel was permitted. In November 2014, the DAPT trial results were released at the American Heart Association Scientific Sessions and concomitantly published [24••]. In summary, 9961 patients (initial presentation 42 % ACS, 38 % stable angina, and ~20 % other indication) were randomly assigned after 12 months of DAPT post DES to aspirin plus a thienopyridine or aspirin plus a placebo for an 18 additional months. Of the initially screened population, 23 % were excluded for a number of reasons including having had ischemic events within the first 12 months (n=2638 patients [death, MI, CVA, ST, revascularization, or bleeding]). By excluding these patients, the study excluded many patients at the highest risk of the primary endpoint, i.e., patients wherein prolonged DAPT might have provided the maximal benefit.

Over 4700 patients in both arms completed follow-up to 30 months. The DAPT study showed that compared with subjects treated with DAPT for 12 months, subjects randomized to 30 months of treatment had a significantly lower cumulative incidence of stent thrombosis (0.4 vs. 1.4 %, hazard ratio 0.29, p<0.001) and MACCE (4.3 vs. 5.9 %, hazard ratio 0.71, p<0.001). This result was primarily driven by a reduction in myocardial infarction (2.1 vs. 4.1 %, hazard ratio 0.47, p<0.001). Highlighting that DAPT reduces both ST and non-stent-related thrombosis; non-stent thrombosis-related myocardial infarction comprised 55 % of the treatment benefit (1.8 vs. 2.9 %, hazard ratio 0.59, p<0.001). There was no difference in the incidence of stroke between the two treatment arms (0.8 vs. 0.9 %, p=0.32).

The negative impact of prolonged DAPT was highlighted in the primary safety endpoint of this trial, namely bleeding. Prolonged DAPT was associated with increased moderate to severe bleeding (2.5 vs. 1.6 %, HR 1.61, 95 % CI 1.2–2.6, p=0.001), though there was no difference in GUSTO severe bleeding or BARC defined fatal bleeding (type 5 bleeding) between the two groups. More concerning was an increased risk of death from any cause in the prolonged DAPT group compared to placebo (2.0 vs. 1.5 %, HR=1.36, 95 % CI 1.00–1.85, p=0.05). The authors note that this may be related to an imbalance in cancer

prevalence and cancer-related mortality. When the 22 patients with malignancy-associated death were removed from the analysis, there was no difference in overall mortality between the two groups. How this large and influential study will impact the guidelines is unknown. The editorial accompanying this publication suggested dividing DAPT post DES into two distinct periods, i.e., a period of "mandatory" DAPT and a period wherein DAPT may be "possibly beneficial" [25•].

Approximately 20 % of the DAPT DES cohort came from the Taxus Liberté Post Approval Study (TL-PAS) which was initially designed as a post market surveillance study (n=4199) [26]. Patients who were free of events after 12 months of open-label prasugrel (n=3494) were then eligible to enter into the DAPT trial and received either placebo or prasugrel for another 18 months. Of this original cohort, 2191 patients were randomized and 97 % completed the 30-month study. This is the single largest study involving the use of prolonged prasugrel therapy and demonstrated that 30 months of prasugrel and aspirin reduced the composite endpoint (death, MI, or stroke) by a significant amount (3.7 vs. 8.8 %, HR 0.407, p<0.001) with most of the reduction being recurrent MI. With the enhanced efficacy of prasugrel, a greater than 90 % reduction in ARC-defined definite or probable ST (0.2 vs. 2.9 %, HR 0.063, p<0.001) was also shown with a longer DAPT duration. There was a trend toward GUSTO moderate to severe bleeding with the prolonged therapy (2.4 vs. 1.7 %, HR 1.438, p=0.234) with no difference in severe bleeds.

Both in the DAPT trial and within the TL-PAS sub-study, there was noted to be an acute rise in ischemic events upon cessation of DAPT (both in the 12- and 30-month groups) independent of the generation of thienopyridine and that most of these events were not stent thrombosis. In an effort to decrease this rise in events, the concept of a tapered withdrawal of DAPT has been tested. ISAR-CAUTION (NCT00640679) [27••] attempted to answer whether abrupt cessation or a progressive downgraded dosing would be better, i.e., have less ST or ischemic events, in patients in whom DAPT cessation was planned after 12 months. These patients were randomized in a double-blinded fashion to gradual discontinuation over 4 weeks or abrupt cessation and were followed for 3 months for a composite of cardiac death, MI, stroke, ST, major bleeding, or re-hospitalization. Though target enrollment was 3000 patients, the study was terminated due to slow enrollment, and only 782 patients were randomized. The tapering protocol involved a 4-week period wherein patients went from daily thienopyridine dosing to every other day for 1 week followed by every 2 days for a week followed by every 3 days for a week and finally every 4 days for a week. This tapering approach was not superior to abrupt cessation, though this study was clearly underpowered due to the low event rate and the number of subjects. Given the fact that there is a clear increase in the number of ischemic events with DAPT cessation, future studies examining how to mitigate this risk are required.

Data for a shorter duration of DAPT (<12 months)

The current European Heart Society guidelines recommend 6–12 months of DAPT following DES placement. This shorter period is based on several randomized trials that have shown the safety and efficacy of a shorter period of

DAPT in select patients. The PRODIGY trial [21] included bare metal, first- and second-generation DESs, and randomized 2000 patients to 6 or 24 months of DAPT. These patients would be considered high risk for ST, and future events given the cohort comprised 74.4 % of ACS patients. Despite this, there was no difference in the primary endpoint of death from any cause, MI, or CVA between the two groups (10.0 vs. 10.1 %, p=0.91), and there was a higher incidence of bleeding in the 24-month cohort.

The EXCELLENT trial (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) was an open-label trial comparing efficacy of Xience/Promus to Cypher stents, but also randomized patients to 6 vs. 12 months of DAPT [28]. For the 1443 patients (51.1 % ACS, 48.4 % SA) enrolled, there was no difference between the 6- and 12-month groups for the endpoint of primary target vessel failure (composite of cardiac death, MI, or ischemia-driven target vessel revascularization). Stent thrombosis tended to occur more frequently in the 6-month DAPT group than in the 12-month group (0.9 vs. 0.1 %, hazard ratio 6.02, 95 % CI 0.72–49.96, p=0.10). Despite this trend, the risk of death or myocardial infarction did not differ in the two groups (2.4 vs. 1.9 %, hazard ratio 1.21, 95 % CI 0.60–2.47, p=0.58). Additionally, there was a higher rate of target vessel failure (TVF) among diabetic patients in the 6-month group (HR 3.16, 95 % CI 1.42–7.03, p=0.005) highlighting the higher risk of these patients.

The issue of stent specificity and duration of DAPT was highlighted in the RESET (REal Safety and Efficacy of 3-month DAPT following Endeavor zotarolimus-eluting stent implantation) trial [29]. This unique study enrolled 2117 patients (53.3 % ACS, 44.7 % SA) and randomized patients to receive either Endeavor zotarolimus-eluting stents (E-ZESs) plus 3 months of DAPT or any other drug-eluting stent plus 12 months of DAPT. At 12 months, the primary composite of cardiac death, MI, ST, target vessel revascularization (TVR), or bleeding was no different between the two groups (4.7 vs. 4.7 %, p<0.001 for non-inferiority). Interestingly, the ST rate was no different between a shorter DAPT group with E-ZES stents vs. any other DES with prolonged DAPT (0.2 vs. 0.3 %, p=0.65). These results are consistent with data from the PROTECT study (NCT00476957) [30] which also showed a low ST rate with E-ZESs. These studies have raised the question of whether the safety of a shorter DAPT might be stent specific.

Stent specificity and its association with low ST rates were further raised in the Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice (OPTIMIZE, NCT01113372) trial [31]. This non-inferiority study compared 3 vs. 12 months of DAPT in 3119 patients undergoing PCI with a zotarolimus-eluting stent. These patients had either stable angina or a history of "very low-risk ACS" which was defined as unstable angina or recent (but not acute) myocardial infarction (<30 days). There was a formal recommendation not to enroll patients with elevated biomarkers. The primary endpoint (all-cause death, MI, CVA, or major bleeding) occurred in only 6.0 % of patients receiving 3 months of therapy vs. 5.8 % of patients receiving 12 months (risk difference 0.17, 95 % CI −1.52 to 1.86). MACE rates at 1 year did not differ between the groups (8.3 % in the 3 month vs. 7.4 % in the 12 month cohort (HR 1.12, 95 % CI 0.87–1.45, p=.002 for non-inferiority). Of note, between 91 and 360 days, no statistically significant association was observed for the primary endpoint between the short- and

long-term DAPT groups (2.6 vs. 2.6 %, HR 1.03, 95 % CI 0.66–1.60), MACE (5.3 vs. 4.3 %, HR 1.22, 95 % CI 0.88–1.70) or stent thrombosis (4 [0.3 %] vs. 1 [0.1 %], HR 3.97, 95 % CI, 0.44–35.49). Though not adequately powered, the low event rate in this study raises the question of whether a 3-month course of DAPT is safe in low-risk patients receiving a zotarolimus-eluting stent.

The ITALIC trial (NCT01476020) [32] was a multi-centered, prospective, open-label randomized trial that also hypothesized that 6 months of DAPT was non-inferior to 24 months of DAPT in aspirin-sensitive patients. Of the 2031 patients (1822 actually analyzed) (44 % ACS) who had received at least 1 Xience V DES, there was no difference in the primary end point (composite of all-cause mortality, MI, urgent TVR, CVA, or thrombolysis in myocardial infarction (TIMI) major bleeding) between both groups (1.5 vs. 1.6 %, p=0.85). The authors concluded that in aspirin-sensitive patients (all patients were tested), 6 months of DAPT was non-inferior to 24 months when a Xience V stent was placed. However, this study had low event rates and was not powered adequately nor was it powered for stent thrombosis. Additionally, the trial was terminated early due to slow enrollment.

Unfortunately, none of these studies were powered to compare stent thrombosis. Critics have stated that these studies were even underpowered to identify actual differences in the composite endpoints given the relatively low event rates. There were also methodological issues within the studies that have impaired the applicability of these trials [23••]. For instance, PRODIGY pooled analysis of DES and BMS which clearly differ with regard to necessary DAPT duration. Several meta-analyses have been completed using some of the aforementioned trials. The most recent meta-analysis [33•] examined the REAL/ZEST-LATE, PRODIGY, EXCELLENT, and RESET trials. These four RCTs provide a median short duration DAPT of 6.2 months (n=4081) vs. 16.8 months in the prolonged DAPT group (n=4076). There was no difference in the rate of the composite endpoint of cardiac death or myocardial infarction between the short (3.3 %) and prolonged (3.0 %) DAPT groups (OR 1.11, 95 % CI 0.81–1.43, p=0.41). In this study, an analysis [34] performed at the time of DAPT discontinuation clearly demonstrated a non-significant higher rate of ST in the shorter duration of DAPT vs. the longer period (0.35 vs. 0.20 %, p=0.22). Major bleeding was higher in the prolonged DAPT group (0.29 vs. 0.71 %, p=0.01). Another recent meta-analysis of the same trials confirmed that longer DAPT therapy did not reduce the risk of all-cause mortality (OR 0.89, 95 % CI 0.67–1.17, p=0.4, I^2=0 %), myocardial infarction (OR 1.16, 95 % CI 0.85–1.57, p=0.35, I^2=0 %), cardiac death (OR 0.88, 95 % CI 0.61–1.25, p=0.47, I^2=0 %), stent thrombosis (OR 1.29, 95 % CI 0.76–2.21, p=0.35, I^2=0 %), or cerebrovascular accidents (OR 0.73, 95 % CI 0.41–1.27, p=0.26, I^2=0 %). They also found an increase in major TIMI bleeding (OR 51, 95 % CI 0.29–0.89, p=0.02, I^2=0 %) and concluded that there is no difference in the efficacy outcomes of ≤6 and ≥12 months of DAPT in patients receiving DES stents.

Recently, a study assessing the safety of 6- vs. 12-month DAPT in second-generation DES, i.e., the SECURITY RCT trial (NCT00944333), was reported [35]. Initially designed to enroll 4000 patients, this study was prematurely

terminated because of "enrollment futility because of minimal differences in the rate of the primary endpoint between the two groups." Overall, a total of 1399 patients with stable or unstable angina or documented silent ischemia who received at least one second-generation DES were randomized. The primary composite endpoint (cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 3 or 5 bleeding at 12 months) occurred in 4.5 vs. 3.7 % (risk difference 0.8 %, 95 % CI −2.4–1.7 %, p=0.469) of patients in the 6- vs. 12-month groups, respectively. There was also no difference in the secondary endpoint (the primary endpoint + BARC type 2 bleeding) or stent thrombosis at 12 or 24 months. There was no difference in bleeding, but overall, the event rates were far less than expected, and this study was grossly underpowered. Further confounding its findings is that DAPT was still being used in 33.8 % of the 6-month group at the 12-month follow-up. This fact coupled with the low event rates and the underpowered nature of the study limit the applicability of this study. Interestingly, the authors used multivariable analysis to assess for factors that influenced the primary endpoint. They determined that several procedure-related factors (mean stent length, size, and number) and patient factors (age) were strong independent predictors highlighting that each patient's risk for adverse events likely differs [36].

The results of the ISAR-SAFE trial (NCT00661206) [37], a multi-center international study comparing 6 vs. 12 months of DAPT, were released in November 2014. This study initially planned to enroll 6000 patients to achieve a power sufficient for the primary endpoint of death, myocardial infarction, stent thrombosis, or major bleeding at 1 year. This number was determined to detect a non-inferiority difference of 2 % from an expected rate of 10 % and was not powered to detect a difference in ST alone. The trial randomized 4005 patients (6 months n=1997, 12 months n=2007) prior to early termination due to a lower than anticipated event rate. Patients enrolled in this study (24 % diabetics) were real world with various presentations (SA 48 %, ACS 52 %) and stent type (everolimus-eluting stents 49 %, zotarolimus-eluting stents 15 %, newer generation sirolimus-eluting stents 16 %, biolimus 8 %, and BMS 0.4 %). There was no difference in MACE between the 6- vs. 12-month group (1.5 vs. 1.6 %, p for non-inferiority <0.001) and the composite of death, MI, CVA, and stent thrombosis was similar (1.3 vs. 1.5 %, p=0.59). Individual endpoints included mortality (0.4 vs. 0.6 %, p=0.37), MI (0.7 vs. 0.7 %, p=0.85), stent thrombosis (0.3 vs. 0.2 %, p=0.74), and stroke (0.4 vs. 0.3 %, p=0.57). Major and minor bleeding were numerically lower with the 6-month group (0.3 vs. 0.7 %, p=0.12). BARC >2 class bleeding was significantly reduced with the abbreviated DAPT therapy (1 vs. 2 %, p=0.01). Readers should interpret these data, understanding that the trial was stopped early due to a significantly lower than expected event rate of 1.6 % vs. an anticipated 10 % rate and therefore was underpowered.

Additional considerations that impact risk

Currently, the guidelines suggest a one size fits all approach for all patients after they receive a DES. These recommendations do not take into consideration

patient or procedural variables, both of which are known to impact individual patient risks for both ST and future events such as bleeding. In fact, inconsistency in the current data investigating longer vs. shorter DAPT may derive from inclusion of patients presenting with very distinct clinical presentations (stable angina vs. acute coronary syndrome) and treatments (stent type). Future studies involving specific sub-groups are needed.

The most feared complication of an abbreviated DAPT duration is stent thrombosis (ST) and for those physicians contemplating this approach, it is critical to understand the patient, procedural, and anatomic risk factors for this potentially fatal complication. Patient-specific variables that increase the risk of ST include ACS, smoking, diabetes mellitus, renal failure, and low ejection fraction [38–41]. A pooled analysis from the SPIRIT and COMPARE trials [19] showed that younger patients (<65 years of age) have a higher risk of ST compared to their elderly colleagues (>65 years of age). Procedural variables that increase the risk of ST with DES include direct stenting during ACS, longer stent length, overlapping stents, incomplete lesion coverage, persistent slow flow, residual stenosis, and dissection [42–45]. Though intravascular ultrasound (IVUS)-guided stenting to ensure appropriate expansion has not been proven in RCTs, a propensity-score matched analysis showed that patients undergoing IVUS-guided DES placement had a lower definite ST rate at 30 days and 12 months than those wherein IVUS was not used [46]. Additionally, bifurcation stenting, treatment of in-stent restenosis, chronic total occlusion, as well as stenting in lesions with necrotic cores (as assessed by IVUS with virtual histology) appear to increase the risk of ST [40]. These procedural and patient presentation factors need to be considered when determining the optimal duration of DAPT.

There are stent-related factors that also increase the risk of ST including the anti-proliferative agent used and its dose, strut/polymer thickness, and coating technologies which are all factors that differ between stent types and the two different generations. Second-generation differ from first-generation DESs with respect to both the anti-proliferative agents (second-generation everolimus and zotarolimus vs. first-generation paclitaxel and sirolimus), the coating technologies employed toward the polymer layer, and the stent frame [47]. With advancements in technology, the second-generation stents may result in better stent apposition leading to improved endothelialization which may reduce the risk of ST [48]. With thinner struts, more endothelium may be covered. This likely contributes as much as the type of anti-proliferative drug present as lower ST rates have been seen with all of the second-generation stents [48]. Therefore, providers considering a shorter DAPT for their patients should also consider the type of stent implanted. In a pre-specified analysis from the PRODIGY trial [49], paclitaxel stents showed a significantly higher rate of definite, probable, or possible ST compared to everolimus-eluting stent, zotarolimus-eluting stents, or bare metal stents. Additionally, the OPTIMIZE trial showed non-inferiority of

a shorter DAPT (3 months) with zotarolimus-eluting stents over prolonged DAPT [31]. The PROTECT trial [30] showed no difference in ST beyond 1 year with zotarolimus-eluting stents and sirolimus-eluting stents. In contrast, the TL-PAS study [26] suggests that for the TAXUS Liberté paclitaxel-eluting stent, >30 months of DAPT is beneficial.

Future directions/areas of investigation

The current ACC/AHA guidelines [14] recommend that patients receiving DES can receive prasugrel or ticagrelor along with aspirin post ACS or stent implantation (in place of clopidogrel) based on large trials showing the enhanced efficacy of the newer agents in the reduction of ischemic events [50, 51]. The optimal duration of DAPT with these newer agents is unknown, though the TL-PAS study [26] would suggest that in patients who receive paclitaxel stent, prolonged DAPT out to 30 months should be considered. The EDUCATE trial (NCT01069003) is evaluating in a double-blind, placebo-controlled fashion the impact of 12 vs. 30 months of DAPT (clopidogrel or prasugrel + aspirin) in 2500 patients receiving the Endeavor zotarolimus-eluting stent on a composite outcome (cardiac death, MI, ST, bleeding, and DAPT compliance). The OPTIDUAL trial (NCT00822536) [52•] is ongoing and will add additional information about the long-term impact of prolonged DAPT therapy out to 48 vs. 12 months. Various permutations of DAPT are also being evaluated. The GLOBAL LEADERS study (NCT01813435) (n=16,000) will assess the safety and efficacy of 1 month of DAPT with ticagrelor and aspirin followed by 23 months of ticagrelor monotherapy vs. 12 months of DAPT with aspirin and ticagrelor upon the outcome of all-cause death or MI.

The optimal duration of DAPT with the newer bioabsorbable polymers or scaffolds is also the subject of scrutiny and debate. Though late stent thrombosis may not be an issue with these bioabsorbable stents, the delayed absorption of these scaffolds may actually require longer therapy than our current DES platforms.

Conclusion

Overall, the optimal duration of DAPT following implantation of a DES remains debatable and is dependent upon patient, procedural, and anatomical characteristics that most physicians do not consider. Current ACC/AHA and European Heart Society guidelines suggest a one size fits all approach; however, benefit vs. risk of longer DAPT or shorter DAPT is patient specific. Additionally, whether to abruptly discontinue or taper DAPT remains an important unanswered question given increased event rates following DAPT cessation. The further identification of risk factors for early and late events including trials involving the newer agents, prasugrel, and ticagrelor are needed.

Compliance with Ethics Guidelines

Conflict of Interest
Dr. Jad Raffoul and Dr. Andrew J.P. Klein each declare no potential conflict of interest.

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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