Curr Treat Options Cardio Med (2019) 21: 17
DOI 10.1007/s11936-019-0721-8

Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Dual Antiplatelet Therapy: How Long Is Long Enough?

Laura Flannery, MD
Ran Liu, MD
Sammy Elmariah, MD, MPH[*]

Address
[*]Cardiology Division, Department of Medicine, Harvard Medical School, Massachusetts General Hospital, 55 Fruit St GRB 800, Boston, MA, 02114, USA
Email: SELMARIAH@mgh.harvard.edu

Published online: 30 March 2019

This article is part of the Topical Collection on *Coronary Artery Disease*

Keywords Dual antiplatelet therapy (DAPT) · P2Y12 inhibitors · Acute coronary syndrome · Coronary artery disease · Risk assessment

Abstract

Purpose of review The optimal duration of dual antiplatelet therapy (DAPT) has been a topic of considerable interest in recent years, as the risk of stent thrombosis has decreased with newer generation stents and the impact of significant bleeding events on clinical outcomes is increasingly apparent. The purpose of this review is to highlight the landmark studies examining short-duration (6 months or less) and extended-duration (greater than 12 months) DAPT as well as provide information about prediction tools to help guide individualized patient treatment decisions.
Recent findings Short-duration DAPT is acceptably safe when clinically necessary, though recent trials demonstrate non-significant trends towards increased risk of ischemic events with shorter durations. Extended-duration DAPT clearly confers a reduced risk of subsequent ischemic events but at an increased risk of bleeding.
Summary Understanding the perceived ischemic and bleeding risks for each individual patient is paramount in deciding targeted DAPT duration. For patients at a higher bleeding risk with a low ischemic risk, short-duration DAPT (6 months) is acceptable. For patients with continued ischemic risk factors and a low bleeding risk, extended-duration DAPT (up to 30 months) is recommended. The PRECISE DAPT and DAPT prediction tools are helpful in making this determination.

Introduction

Dual antiplatelet therapy (DAPT) is essential after acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI). DAPT has been shown to reduce the risk of recurrent ischemic events, including cardiac death, myocardial infarction (MI) both related and unrelated to the stent, and stroke. However, this comes at the expense of an increased risk of clinically significant bleeding. The question of how long a patient should remain on DAPT is one that clinicians encounter on a daily basis. The objective is to choose a length of treatment that maximizes the benefit of reducing recurrent ischemic events while minimizing the risk of bleed. However, this is not easily determined.

Current guidelines stratify the recommendations for DAPT duration according to type of coronary artery disease (CAD) and type of therapy received [1, 2]. According to the ACC/AHA guidelines, for patients with stable CAD who receive PCI, a minimum of 6 months of DAPT is recommended for drug-eluting stents (DES) and a minimum of 1 month of DAPT is recommended for bare metal stents (BMS). The P2Y12 inhibitor recommended in stable CAD is clopidogrel. For patients with acute coronary syndrome (ACS; non-ST or ST elevation MI), a minimum of 12 months of DAPT is recommended regardless of PCI with DES, PCI with BMS, or medical therapy only. Clopidogrel, ticagrelor, and prasugrel are acceptable P2Y12 inhibitors after PCI in ACS, although ticagrelor and prasugrel are preferred. Only clopidogrel or ticagrelor are recommended for medically managed ACS. The current ESC guidelines, while similar, endorse the consideration of shortened DAPT duration after PCI with either DES or BMS for patients deemed to possess high bleeding risk (1–3 months in stable CAD and 6 months in ACS). The ESC guidelines also recommend 12 months of DAPT for bioresorbable stents (third- and fourth-generation stents).

The general consensus has been to prescribe 6 to 12 months of DAPT, unless an interim bleeding event or urgent surgery warrants earlier cessation or a recurrent ischemic event warrants prolongation. However, there has been great interest in determining whether shorter or longer DAPT duration in the absence of an inciting event is clinically beneficial. This review is comprehensive of the major studies on this topic but will specifically highlight the studies since 2016 that have addressed both short and extended-duration DAPT as well as review the prediction tools available to personalize targeted DAPT duration to individual patients.

Evidence for short-duration DAPT

Five non-inferiority studies compared shorter term DAPT to the standard 12-month treatment: RESET (2012) and OPTIMIZE (2013) evaluated 3 months of DAPT and EXCELLENT (2012), SECURITY (2014), and ISAR SAFE (2015) evaluated 6 months of DAPT [3–7] (Table 1). PRODIGY (2012) and ITALIC (2015) compared 6 months of DAPT to an extended duration of 24 months of DAPT [8, 9]. Each study demonstrated non-inferiority with composite primary endpoints of either ischemic-only or combined ischemic and bleeding events, although they were not adequately powered to detect statistically significant differences in the individual endpoints or in some instances even in the primary composite endpoints. Subsequent meta-analyses concluded that rates of ischemic events with shorter term DAPT were comparable to those seen with longer DAPT duration but with reduced bleeding risk [10–12].

It is important to highlight that the majority of patients in the aforementioned studies received PCI for stable CAD, thereby driving the guideline recommendations for a minimum of 6 months in this population. These studies also predominantly utilized second-generation DES. More recent studies have narrowed their focus to patients with ACS who therefore possess higher ischemic risk (DAPT STEMI, SMART-DATE, and REDUCE) or to patients with

Table 1. Studies on short-duration DAPT

Study	Short vs. long duration of DAPT (months)	% ACS	% Newer DES*	Type of P2Y12 inhibitor	Sample size	Design	Primary endpoint	Results short vs. long
RESET (2012)	3 vs. 12	59%	29%	Clopidogrel	2148	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events (cardiac death, MI, stent thrombosis, target vessel revascularization, major bleeding)	4.7% vs. 4.7% ($p_{NI} < 0.01$)
OPTIMIZE (2013)	3 vs. 12	35%	100%	Clopidogrel	3119	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events death, MI, stroke, major bleeding	6.0% vs. 5.8% ($p_{NI} = 0.002$)
EXCELLENT (2012)	6 vs. 12	51%	75%	Clopidogrel	1443	Non-inferiority, randomization at time of PCI	Combined ischemic events (cardiac death/MI/ischemia-driven TVR)	4.8% vs. 4.3% ($p_{NI} = 0.001$)
SECURITY (2014)	6 vs. 12	28%	100%	Clopidogrel	1399	Non-inferiority, randomization at time of PCI	Combined ischemic events (cardiac death, MI, ST, or stroke)	4.5% vs. 5.7% ($p_{NI} \leq 0.05$)
ISAR SAFE (2015)	6 vs. 12	40%	89%	Clopidogrel	4000	Non-inferiority randomization at DAPT discontinuation	Combined ischemic and bleeding events (death/MI/ST/stroke/major bleeding)	1.5% vs. 1.6% (pNI < 0.001)
DAPT STEMI (2017)	6 vs. 12	100% (STEMI Only)	100%	Prasugrel, ticagrelor, clopidogrel	870	Non-inferiority, randomization at DAPT discontinuation	Combined ischemic and bleeding events (all-cause mortality, MI, revascularization, stroke, and TIMI major bleeding)	4.8% vs. 6.6% (pNI = 0.004)
SMART-DATE (2018)	6 vs. 12	100%	100%	Clopidogrel, prasugrel, ticagrelor	2712	Non-inferiority, randomization at time of PCI	Ischemic-only events (all-cause mortality, MI, and stroke)	4.7% vs. 4.2% (pNI = 0.027)
REDUCE (2017)	3 vs. 12	100%	100% Bioresorbable polymer-coated stent	Prasugrel or ticagrelor over clopidogrel	1496	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events (all-cause death, MI, stent thrombosis, stroke, target vessel revascularization, or bleeding)	Free from composite endpoint 91.7% vs. 91.5%, (pNI < 0.001)
I-LOVE-IT 2 (2016)	6 vs. 12	64%	100% Bioresorbable polymer-coated stent	Clopidogrel	907	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events (cardiac death, target vessel MI)	7.5% vs. 6.3% ($p = 0.32$)

Table 1. (Continued)

Study	Short vs. long duration of DAPT (months)	% ACS	% Newer DES*	Type of P2Y12 inhibitor	Sample size	Design	Primary endpoint	Results short vs. long
IVUS-XPL (2017)	6 vs. 12	49%	100%	Clopidogrel	1400	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events (cardiac death, MI, stroke, or major bleeding	2.2% vs. 2.1% ($p = 0.85$)
GLOBAL LEADERS (2018)	1 vs. 12 (with different monotherapy)	47%	100%	Ticagrelor, clopidogrel	15,991	Superiority, randomization at time of PCI	Ischemic-only events (all-cause mortality non-fatal Q-wave MI)	3.81% vs. 4.37% ($p = 0.073$)

*Any DES other than Cypher Sirolimus (Cordis, Warren, NJ, USA), Taxus Paclitaxel (Boston Scientific, Natick, MA, USA), and Endeavor Zotarolimus (Medtronic Inc., Santa Rosa, California, USA) is defined as "newer DES"

third- and fourth-generation bioresorbable polymer-coated stents (I-LOVE-IT 2 and REDUCE) [13, 14, 15•, 16].

The DAPT STEMI trial (2017) studied patients who received DES for STEMI [15•]. Patients who were free from ischemic or bleeding events at 6 months post-DES were randomized to cessation of DAPT (total 6 months) vs. continuing DAPT for a total of 12 months. At 24 months post-PCI, there was no significant difference in the primary composite endpoint of combined ischemic and bleeding events (all-cause mortality, MI, revascularization, stroke, and TIMI major bleeding; 4.8% vs. 6.6%, p for non-inferiority = 0.004). The SMART-DATE trial (2018) had a similar objective; however, it was open label, included all ACS events, and randomized patients at the time of PCI rather than after an event-free period [13]. Short-duration DAPT (6 months) was found to be non-inferior to 12 months of DAPT for the composite primary endpoint of ischemic-only events (4.7% vs. 4.2%, p for non-inferiority = 0.027). However, the study noted a trend towards higher risk of repeat MI with 6 months of DAPT (MI, 1.8% vs. 0.8%, $p = 0.02$; non-target vessel MI, 0.8% vs. 0.2%, $p = 0.07$). There was no difference in bleeding, although there was a trend towards decreased bleeding in the 6-month group (2.7% vs. 3.9%, $p = 0.09$).

Both REDUCE (2017) and I-LOVE-IT 2 (2016) evaluated even shorter duration DAPT in patients who received bioresorbable polymer-coated stents, comparing 3 and 6 months of DAPT, respectively, to 12 months [14, 16]. Both studies found that shorter duration DAPT was non-inferior with respect to the composite endpoint of ischemic and bleeding events. However, the REDUCE trial, which exclusively included ACS patients, demonstrated non-significant trends suggesting an increased risk of all-cause mortality and stent thrombosis in the 3-month group (1.9% vs. 0.8%, $p = 0.07$; 1.2% vs. 0.4%, $p = 0.08$; respectively).

IVUS-XPL (2017) evaluated DAPT duration in a population receiving long coronary stents given the association of longer stents with increased ischemic events [17]. The primary focus of this study was to evaluate intravascular ultrasound-guided vs. angiography-guided PCI for patients who have long coronary lesions, but patients were also randomized at the time of PCI to 6 vs. 12 months of DAPT. Approximately half the patients had ACS. There was no significant difference in the composite endpoint of ischemic and bleeding events (cardiac death, MI, stroke, or major bleeding; 2.2% for 6 month DAPT vs. 2.1%, $p = 0.85$).

The GLOBAL LEADERS trial (2018) investigated short-duration DAPT followed by monotherapy with ticagrelor rather than aspirin. Specifically, patients received ticagrelor and aspirin for 1 month followed by 23 months of ticagrelor monotherapy vs. standard 12 months DAPT (with clopidogrel for stable CAD or ticagrelor for ACS) followed by aspirin monotherapy for 12 months [18]. Ticagrelor monotherapy failed to show superiority to the conventional approach in the primary composite endpoint of all-cause mortality or non-fatal Q-wave MI (3.81% vs. 4.37%, ratio 0.87 [95% CI 0.75–1.01]; $p = 0.073$). In terms of safety, there was no difference in major or fatal bleeding (Bleeding Academic Research Consortium criteria grade 3 or 5, 2.04% vs. 2.12%; rate ratio 0.97 [95% CI 0.78–1.20]; $p = 0.77$). The ongoing TWILIGHT study is also evaluating the benefit of ticagrelor monotherapy compared to DAPT [18]. The study specifically enrolls patients at high risk for either ischemic or bleeding events (must meet at least one clinical and one angiographic criteria

that increases risk, such as female gender, chronic kidney disease, long target lesion, and bifurcation target lesion), with the hypothesis that ticagrelor monotherapy will associate with reduced bleeding risk while maintaining non-inferiority in preventing ischemic events [19].

In summary, several studies suggest that shorter duration (6 months, and in one instance 3 months) DAPT results in comparable rates of composite ischemic events and comparable rates of bleeding when compared to 12 to 24 months of DAPT. However, it is important to highlight that SMART-DATE and REDUCE demonstrated trends suggesting increased risk of ischemic events in ACS patients receiving shortened courses of DAPT. Additional studies are needed to further evaluate these individual endpoints before shorter term DAPT can be consistently endorsed. However, these studies suggest acceptable safety in discontinuing DAPT after 3–6 months when the clinical scenario necessitates doing so.

Additional trials are underway that evaluate the safety of very short-duration DAPT (1–3 months). The XIENCE 28, Onyx One, EVOLVE Short DAPT, and XIENCE 90 trials [18–21] are fundamentally based on the observation that the majority of stent thrombosis occurs within the first 30 days post-PCI [22]. These single-arm studies target patients possessing high bleeding risk. Going even further, the COBRA-REDUCE trial is evaluating 14 days of DAPT in patients who also require chronic oral anticoagulation and are receiving a nanocoated coronary stent, which have demonstrated evidence of reduced inflammation, neointimal hyperplasia, and thrombogenicity in preclinical studies [23, 24]. In our opinion, these studies will inform decisions for patients who have bleeding events or are in need of surgery with high risk of bleeding complication, rather than serving as a standard approach for DAPT duration after PCI.

Evidence for extended-duration DAPT

For patients that successfully complete 12 months of DAPT without a significant ischemic or bleeding event, several studies have investigated the safety and efficacy of continuing DAPT beyond 12 months. Table 2 summarizes 7 notable randomized clinical trials evaluating extended-duration DAPT: PRODIGY, ITALIC, DES LATE, ARTIC-Interruption, DAPT, and in recent years, OPTIDUAL, and PEGASUS-TIMI 54 [8, 9, 25, 26].

The PRODIGY (2012) and ITALIC (2015) trials compared 24 months of DAPT to 6 months of therapy, with randomization performed at the time of PCI [8, 9]. DES LATE (2014) and ARCTIC-Interruption (2014), on the other hand, randomized patients 12 months after DES implantation to either cessation of DAPT at that time point or continued DAPT for an additional 24 months in DES LATE or 6 to 18 months in ARTIC-Interruption [25, 26]. Each of these studies demonstrated comparable rates of ischemic events or of composites of ischemic and bleeding events. The PRODIGY and ARTIC-Interruption trials also demonstrated increased risk of bleeding with extended therapy.

The DAPT study (2014) evaluated extended-duration DAPT (30 months) vs. 12 months of therapy using a randomized, double-blinded, placebo-controlled study design and was the only trial statistically powered to

Table 2. Studies on extended-duration DAPT

Study (year)	Short vs. long duration of DAPT (months)	% ACS	% Newer DES*	Type of P2Y12 inhibitor	Sample size	Design	Primary endpoint	Results short vs. long
PRODIGY (2012)	6 vs. 24	74%	50%	Clopidogrel	1970	Superiority, randomization 1 month post-PCI	Ischemic-based events (death, MI, stroke)	10.0% vs. 10.1%, ($p = 0.91$)
ITALIC (2015)	6 vs. 24	25%	100%	Clopidogrel	1850	Non-inferiority, randomization at time of PCI	Combined ischemic and bleeding events (death, MI, stroke, target vessel revascularization, or major bleeding)	1.5% vs1.6% (pNI = 0.0002)
DES LATE	12 vs. 24	60.7%	34.2%	Clopidogrel	5045	Non-inferiority, randomization at DAPT discontinuation	Combined ischemic events (death, MI, stroke)	2.4% vs. 2.7% ($p = 0.75$)
ARCTIC-Interruption	12 vs. 24	12.1%	63%	Clopidogrel, prasugrel	1259	Non-inferiority, randomization at DAPT discontinuation	Combined ischemic events (death, MI, stent thrombosis, stroke, and urgent revascularization)	4.3% vs. 3.8% ($p = 0.58$)
DAPT (2014)	12 vs.30	42.6%	47.2%	Clopidogrel, prasugrel	9961	Superiority, randomization at DAPT discontinuation	Major adverse cardiovascular and cerebrovascular events; stent thrombosis	4.1 vs. 2.1% for MACCE; 1.4% vs. 0.4% for stent thrombosis ($p < 0.001$)
OPTIDUAL (2015)	12 vs. 48	36%	59%	Clopidogrel	1385	Superiority, randomization at DAPT discontinuation	Death/MI/ CVA/ bleeding	7.5% vs. 5.8% ($p = 0.17$)
PEGASUS-TIMI 54 (2015)	21 vs.	100%	–	Ticagrelor	21,162	Superiority, randomization 1–3 years after MI	Combined ischemic events (cardiovascular death, MI, or stroke)	7.85% for ticagrelor 90 mg BID, 7.77% for ticagrelor 60 mg BID, and 9.04% for placebo (P = 0.008; P = 0.004)

*Any DES other than Cypher Sirolimus (Cordis, Warren, NJ, USA), Taxus Paclitaxel (Boston Scientific, Natick, MA, USA), and Endeavor Zotarolimus (Medtronic Inc., Santa Rosa, California, USA) is defined as "newer DES"

specifically study the impact of DAPT duration on rates of stent thrombosis [27]. The study randomized patients who were free from ischemic or bleeding events at 12 months post-PCI (majority DES) and had been compliant with DAPT to placebo or continuation of P2Y12 inhibitor for an additional 18 months (total 30 months of DAPT). Continuation of P2Y12 inhibitor was associated with significantly lower incidence of major adverse cardiovascular and cerebrovascular events (HR, 0.71; 95% CI, 0.59–0.85; $P < 0.001$) as well as a significantly lower incidence of the co-primary endpoint of stent thrombosis (HR, 0.29; 95% CI, 0.17–0.48; $P < 0.001$). There was a lower incidence of MI (HR, 0.47; 95% CI, 0.37–0.61; $P < 0.001$) and many of the prevented MI were non-ST-related MI (1.8 vs. 2.9%; HR, 0.59; $P < 0.001$). This comes at the expense of higher rates of moderate or severe GUSTO bleeding (HR, 1.61; 95% CI, 1.21–2.16; $P = 0.001$) but no significant difference in severe or fatal bleeds. In subgroup analysis, the study results were found to be consistent regardless of whether the initial presentation was ACS or stable CAD, although the reduction in major adverse cardiovascular and cerebrovascular events was greater for those whose initial presentation was ACS [28].

The OPTIDUAL trial (2016) sought to evaluate the safety and efficacy of very extended-duration DAPT of 48 months to 12 months of DAPT [29]. Similar to the DES LATE, ARTIC-Interruption, and DAPT trial designs, patients who had received a DES and were free from major ischemic or bleeding events after 12 months were randomized to continuation of DAPT (approximately 48 months DAPT) vs. aspirin alone (total 12 months of DAPT). Compared to the DAPT trial, a higher percentage of the patients received DES for ACS (approximately 70%). Because of slow enrollment, the study was stopped early and was consequently underpowered to reach its primary outcome, which was a composite endpoint of ischemic and bleeding events (all-cause death, MI, stroke, major bleeding; 5.8% for 48 month DAPT vs. 7.5% for 12-month DAPT, $p = 0.17$). However, it did demonstrate a non-significant trend towards decreased composite endpoint of ischemic-only events with extended-duration DAPT (death, MI, or stroke was 4.2% for 48 month DAPT vs. 6.4% for 12-month DAPT, $p = 0.06$) without an increase in major bleeding (2.0% in both groups, $p = 0.95$).

The aforementioned studies on extended DAPT primarily utilized clopidogrel or prasugrel as the P2Y12 inhibitor of choice and were all exclusively in post-PCI patients. In PEGASUS-TIMI 54 (2015), patients with prior ACS (qualifying event in the past 1–3 years) and at least one additional cardiovascular risk factor (age 65 years or older, diabetes requiring medication, a second MI, multivessel disease, or chronic kidney disease) were randomized to ticagrelor (either 90 mg BID or 60 mg BID) or placebo [30]. Although not a PCI trial, 83% of enrolled patients enrolled in PEGASUS-TIMI 54 had undergone PCI at the time of the qualifying MI. Patients were enrolled an average of 1.7 years after the qualifying MI, and consequently, most patients had experienced a cessation of the initial DAPT course post-PCI and were on aspirin monotherapy. The primary outcome of a composite endpoint of ischemic events (cardiovascular death, MI, or stroke) was lower in either of the ticagrelor groups as compared to placebo (Kaplan–Meier rates at 3 years were 7.85% for ticagrelor 90 mg BID, 7.77% for ticagrelor 60 mg BID, and 9.04% for placebo; hazard ratio for ticagrelor 90 mg BID vs. placebo 0.85; 95% [95% CI 0.75 to 0.96], $P = 0.008$; hazard ratio for ticagrelor 60 mg BID vs. placebo 0.84; [95% CI

0.74 to 0.95], $P = 0.004$). Both doses of ticagrelor also significantly reduced the individual endpoints of MI as well as of death from coronary heart disease, MI, or stroke. This came at the expense of higher rates of TIMI major bleeding (Kaplan–Meier rates at 3 years were 2.60% for ticagrelor 90 mg BID, 2.30% for ticagrelor 60 mg BID, and 1.06% for placebo; hazard ratio for ticagrelor 90 mg BID vs. placebo, 2.69 [95% CI 1.96 to 3.70], $P < 0.001$; hazard ratio for ticagrelor 60 mg BID vs. placebo 2.32 [95% CI, 1.68 to 3.21], $P < 0.001$).

Overall, recent trials provide compelling evidence that extended-duration DAPT, defined as greater than 12 months, confers a lower risk of ischemic events but higher bleeding risk. This is regardless of if DAPT is started post-PCI for an ACS event or stable angina, though the benefit/risk ratio appears to be higher in ACS or in those with additional cardiovascular risk factors. This is also regardless of choice of P2Y12 inhibitor. The reduced ischemic risk is independent of the stent, as evidenced by the patients without PCI in the TIMI-54 trial and the reduction in non-stent-related MI in the DAPT study. However, extended-duration DAPT also clearly reduces stent thrombosis as demonstrated by the DAPT study. Nonetheless, it is important to recognize that extended-duration DAPT also has a clear impact bleeding events, which also is associated with a high risk of mortality [31].

Prediction scores for DAPT duration

So how does one apply these trial results clinically? DAPT clearly reduces ischemic risk but at the cost of an increased risk of bleeding. The targeted DAPT duration must be individualized to each patient and must be based on the perceived risk of both ischemic and bleeding events. To this end, several validated prediction scores have been developed to guide this decision (Fig. 1).

At the time of PCI and DAPT initiation, the PRECISE DAPT score can guide consideration of a shorter DAPT duration for patients with high bleeding risk. The PRECISE DAPT score focuses solely on prediction of out-of-hospital bleeding in patients treated with DAPT [32]. This score was derived from a cohort of 8 randomized clinical trials and validated using the PLATO trial and Bern PCI Registry. The score uses 5 factors to estimate a patient's bleeding risk: age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding. A score ≥ 25 is deemed high bleeding risk. When the score was applied to patients randomized to short-duration (3–6 months) vs. long-duration (12–24 months) DAPT, increased bleeding with prolonged DAPT was observed in patients with a high score (≥ 25), but not in those with lower risk scores ($p_{\text{interaction}} = 0.007$). While ischemic benefits of prolonged DAPT were only observed in the lower risk score group, the primary limitation of this score is that the ischemic risk is not considered.

Patients should be re-evaluated clinically at subsequent follow-up visits for the occurrence of an interim significant bleeding or ischemic event, need for concurrent oral anticoagulation, compliance concerns, or cost considerations. In the absence of compelling clinical rationale to continue or discontinue thienopyridine therapy, the risks and benefits of each approach should be discussed with patients to reach a shared decision. The DAPT score, a validated prediction rule to evaluate the benefit and harm of DAPT at 1 year post-PCI, can be helpful in guiding this discussion [33]. The DAPT score was derived using the

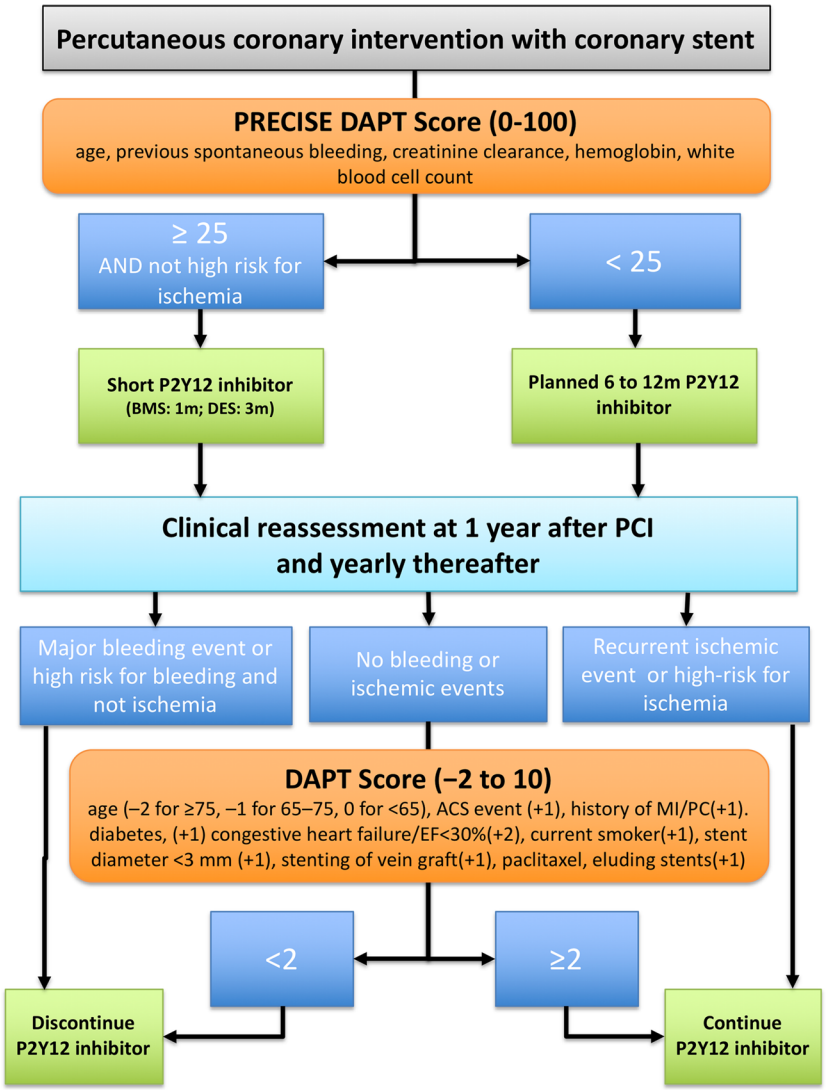

Fig. 1. Percutaneous coronary intervention with coronary stent.

DAPT study population and was validated internally as well as externally using the PROTECT trial. The score is unique in that it weighs ischemic risk against bleeding risk in order to identify patients with greater than expected harm or benefit with prolongation of DAPT beyond 1 year after PCI. From an initial 37 candidate variables, 9 variables were ultimately included in the score. Eight variables in the calculator signify an increase in ischemic risk: ACS at the time of index presentation, history of MI or PCI prior to the index presentation, diabetes, congestive heart failure or ejection fraction < 30%, current smoker (within last 2 years), paclitaxel-eluting stents, stent diameter < 3 mm, or stenting of a saphenous vein graft. The only factor found to contribute independently to bleeding risk was age 65 or older. The score can range from – 2 to 10, with a score of + 2 or higher indicating a higher ischemic/bleeding event ratio and therefore expected benefit from extended DAPT. It is important to

note that the majority of the factors are patient-dependent rather than stent or procedurally related, commensurate with the fact that the majority of the benefit of prolonged DAPT is preventing non-stent-related MI with current generation stents.

In summary, the decision about goal DAPT duration hinges on balancing the risk of increased bleeding events and the benefit of reducing ischemic events for each individual patient. We propose that, in agreement with the current guidelines, the default goal DAPT treatment should be 6 to 12 months.

However, studies of both short-duration and extended-duration DAPT have suggested benefit with acceptable safety of alternate durations in the appropriate clinical settings. It is paramount that the goal DAPT duration be a moving target that is constantly re-evaluated as a patient's bleeding and ischemic risks evolve. Validated prediction tools, specifically the PRECISE DAPT and the DAPT scores, can help guide clinical decision-making.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no 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.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2016;68(10):1082–115.
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213–60.
3. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, 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(15):1340–8.
4. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310(23):2510–22.

5. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086–97.
6. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, 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(3):505–13.
7. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36(20):1252–63.
8. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125(16):2015–26.
9. Didier R, Morice MC, Barragan P, Noryani AAL, Noor HA, Majwal T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: final results of the ITALIC trial (is there a life for DES after discontinuation of clopidogrel). JACC Cardiovasc Interv. 2017;10(12):1202–10.
10. Montalescot G, Brieger D, Dalby AJ, Park SJ, Mehran R. Duration of dual antiplatelet therapy after coronary stenting: a review of the evidence. J Am Coll Cardiol. 2015;66(7):832–47.
11. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol. 2015;65(11):1092–102.
12. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015;65(13):1298–310.
13. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet. 2018;391(10127):1274–84.
14. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. Circ Cardiovasc Interv. 2016;9(2):e003145.
15.• Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, et al. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. BMJ. 2018;363:k3793

This prospective, randomized trial demonstrates that 6 months of DAPT for patients with STEMI and therefore high ischemic risk is non-inferior to the standard 12 months of therapy.

16. American College of Cardiology. TCT17 Presentation Slides | REDUCE 2017, November 1 [Available from: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=D7E42D5E9C4E4699AF190266BC07E47B.
17. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, et al. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. JACC Cardiovasc Interv. 2016;9(14):1438–46.
18. US National Library of Medicine Clinical Trials. XIENCE 28 Global Study 2018, December 6, [Available from: https://clinicaltrials.gov/ct2/show/NCT03355742.
19. US National Library of Medicine Clinical Trials. A randomized controlled trial with resolute Onyx in one month dual antiplatelet therapy (DAPT) for high-bleeding risk patients (Onyx ONE) 2018, October 11 [Available from: https://clinicaltrials.gov/ct2/show/NCT03344653.
20. US National Library of Medicine Clinical Trials. XIENCE 90: a safety evaluation of 3-month DAPT after XIENCE implantation for HBR patients.: US National Library of Medicine Clinical Trials; 2018, December 6. [Available from: https://clinicaltrials.gov/ct2/show/NCT03218787.
21. US National Library of Medicine Clinical Trials EVOLVE Short DAPT Study 2018, September 20 [Available from: https://clinicaltrials.gov/ct2/show/NCT02605447.
22. Silber S, Kirtane AJ, Belardi JA, Liu M, Brar S, Rothman M, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. Eur Heart J. 2014;35(29):1949–56.
23. US National Library of Medicine Clinical Trials. Randomized trial of COBRA PzF stenting to reduce duration of triple therapy (COBRA-REDUCE). 2018, December 14.
24. Cutlip DE, Garratt KN, Novack V, Barakat M, Meraj P, Maillard L, et al. 9-Month clinical and angiographic outcomes of the COBRA Polyzene-F NanoCoated Coronary Stent System. JACC Cardiovasc Interv. 2017;10(2):160–7.
25. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362(15):1374–82.
26. Collet JP, Silvain J, Barthelemy O, Range G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014;384(9954):1577–85.

27. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155–66.
28. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. J Am Coll Cardiol. 2015;65(20):2211–21.
29. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J. 2016;37(4):365–74.
30. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372(19):1791–800.
31. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Cohen DJ, Steg PG, et al. Mortality following cardiovascular and bleeding events occurring beyond 1 year after coronary stenting: a secondary analysis of the dual antiplatelet therapy (DAPT) study. JAMA Cardiol. 2017;2(5):478–87.
32. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389(10073):1025–34.
33. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016;315(16):1735–49.