Chapter

Dual Antiplatelet Therapy after PCI: When Could We Go Shorter?

Marcel Santaló-Corcoy, Guillaume Marquis-Gravel and Jean-François Tanguay

Abstract

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) remains an important clinical question in interventional cardiology. Several clinical and angiographic variables are associated with an increased risk for thrombotic events, and prolonged DAPT duration may improve long term clinical outcome. However, some patients also present high bleeding risk (HBR) characteristics and may require a shorter DAPT duration. The guidelines recommendations consider the data from randomized clinical trials, however numerous exclusion criteria may create gaps in the evidence leading to uncertainties, the need for expert opinion and patient level decision making. Furthermore, the stent platforms have evolved in such way that opportunities now exist to shorten duration of DAPT. This chapter will review the variables associated with ischemic and bleeding risks as well as different stent platforms to help clinicians optimize DAPT duration in patients undergoing PCI.

Keywords: percutaneous coronary intervention, stents, acute coronary syndrome, high bleeding risk, duration of antiplatelet therapy

1. Introduction

The optimal antiplatelet therapy after percutaneous coronary intervention (PCI) remains an unanswered clinical question. The last 25 years of clinical investigations has mainly been focused on the choice of P2Y12 agents and on treatment duration. Initially, the observation that bare metal stents (BMS) implantation could be associated with thrombosis, and, subsequently, the observation that first-generation drug eluting stents (DES) were associated with very-late thrombosis risk led to studies evaluating prolonged duration regimens of DAPT after PCI, but also to innovations in stent technology. However, the newer, more potent drugs (prasugrel and ticagrelor) and the advent and evolution of modern second- and third-generation DES dramatically dwindled the incidence of late and very late thrombotic complications. Thus, interest has shifted in trying to find the optimal, shortened DAPT treatment to prevent the early thrombotic complications while avoiding the late hemorrhagic events, the latter being associated with a similar risk of all-cause mortality than post-PCI recurrent myocardial infarctions [1].

Numerous trials attempted to answer these important questions, sometimes leading to discrepant results. This chapter will focus on the current evidence listed on the guidelines of main scientific societies for three groups of patients: elective PCI,

PCI in the setting of acute coronary syndromes (ACS), and PCI for patients with a coexisting indication of oral anticoagulation (OAC). For each of them we will highlight the standard recommendations for DAPT duration, as well as the main clinical, angiographic and stent-derived variables that should be used in the decision-making process to tailor a shortened DAPT therapy reflecting each patient need.

2. Latest guidelines on the topic

This document will include the latest recommendations of Canadian, American and European guidelines. Canadian scientific societies published two documents in 2018 addressing antithrombotic treatment: The Canadian Cardiovascular Society (CCS)/Canadian Association of Interventional Cardiology focused update for the use of antiplatelet therapy [2] and the CCS focused update for the management of atrial fibrillation [3]. The American College of Cardiology/American Heart Association (ACC/AHA) published a focused update on the duration of DAPT in patients with coronary artery disease (CAD) in 2016, [4] while a recent AHA/ACC/Heart Rhythm Society (HRS) focused update in the management of patients with atrial fibrillation was published in 2019 [5]. Lastly, the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) published a focused update on DAPT in 2017 [6]. However, the most recent 2020 ESC guidelines for management of ACS in patients presenting without persistent ST-segment elevation [7] and 2020 ESC/EACTS guidelines for the management of atrial fibrillation [8] will also be reviewed. A dedicated, critical comparison of the available guidelines on DAPT was published previously this year [9].

3. Evaluation of bleeding and thrombotic risk

In order to tailor optimal DAPT duration, many variables must be taken into account to ensure adequate thrombotic protection while avoiding hemorrhagic complications. To that extent, different risk scores have been derived and validated.

The PARIS risk score was one of the first tools intended to predict risks for out-of-hospital events directly modified by prolonging DAPT beyond one year (i.e. coronary thrombosis and bleeding) [10]. The aim of the DAPT score is to identify patients expected to derive benefit or harm from continuing $P2Y_{12}$ beyond 1 year. To that extent, data was gathered among patients that had not experienced any major ischemic or bleeding event 12 months after the index procedure [11]. Similarly, the CALIBER score includes patients surviving 12 months after a MI, including those not treated with PCI [12]. Hence, these three risk scores help establishing the security of long term DAPT duration.

In contrast, the PRECISE-DAPT score [13] assesses the benefit of a short (3–6 month) versus a long (12–24 month) DAPT duration. Furthermore, it allows clinicians to select DAPT duration upfront instead of at another point in time during follow-up. Of note, patients with the need of OAC were excluded from the derivation cohort. Patients undergoing elective, urgent and emergent PCI were all included in the analysis. At the time of the index PCI, an additive score is calculated by means of the presence of five clinical and biochemical variables (age, creatinine clearance, hemoglobin, white blood cell count and prior spontaneous bleeding), ranging 0 to 100 points. Patients ≥25 points were considered high bleeding risk (HBR), while <25 points were defined as non-HBR. Among HBR patients based on this score, prolonged DAPT contributed to no significant ischemic benefit, while, on the other hand, led to an increased risk of bleeding (number to harm

(NNH) = 38). In parallel, non-HBR patients benefited of a longer DAPT regimen in the form of a significant reduction in the composite endpoint of myocardial infarction (MI), definite stent thrombosis, stroke and target vessel revascularization (NNT for benefit of 68), with no significant increase in bleeding risk [13]. Results were consistent across the full spectrum of indications for PCI.

Some works have compared the accuracy of these scores head-to-head, in general showing little to no difference in their ability to predict bleeding [14–16].

More recently, the new ARC-HBR criteria have been validated at identifying patients at high bleeding risk, being more sensitive than the PRECISE-DAPT and PARIS risk scores (at the expense of specificity) [17]. Trials where these criteria are used to compare different antiplatelet durations are awaited.

It is worth noting, however, that no prediction model has been prospectively tested in the setting of a RCT.

On the other side of the coin, clinicians should be aware of certain clinical and angiographic features associated with a higher thrombotic risk in some patients, thus making it unadvisable to shorten their antiplatelet regimens. These characteristics are summarized in **Table 2**.

4. Evidence for DAPT duration after PCI in non-ACS setting

Many trials have demonstrated the non-inferiority of 6-month versus longer treatment duration amid "all-comer" patients undergoing PCI for stable and ACS settings, [18–22] and so the recommendations for elective PCI are extrapolated for the aggregated results. The ACC and ESC guidelines give strong recommendations on a standard 6-month duration of DAPT in stable patients. As for the CCS, it places greater emphasis on reduction of major CV thrombotic events vs. an increase in bleeding complications, by recommending DAPT duration from 6 up to 12 months. (**Table 1**) This is due to some metanalysis showing increased risk of ischemic outcomes with shorter DAPT durations in certain groups with high risk angiographic features (**Table 2**) [24–26].

All three guidelines suggest considering a 3-month DAPT course in patients at HBR. This comes from the experience of two trials where a zotarolimus-eluting stent was tested [27, 28]. However, due to the fact that this platform is no longer available, the recommendation stands at a weak level of evidence. The ESC guidelines also include the possibility of a 1-month period of DAPT in patients in whom 3-month DAPT poses safety concerns. This recommendation comes from two trials in which a zotarolimus-eluting Endeavor sprint stent or Biofreedom drug-coated stent reduced ischemic endpoints compared to bare-metal stent under similar DAPT duration [29, 30].

Since their publication, some new evidence supports aspirin-free strategies early after PCI: the TWILIGHT trial included high risk patients who had not had an ischemic or bleeding event after a three-month course of aspirin plus ticagrelor and randomized them to aspirin or placebo for one year. Patients with ticagrelor monotherapy had a lower clinically relevant bleeding incidence while providing no higher death or ischemic endpoints [31]. The SMART-CHOICE randomized patients to receive aspirin plus a P2Y12 inhibitor for 3 months and thereafter a P2Y12 inhibitor alone or DAPT por 12 months. The monotherapy arm resulted in noninferior rates of major adverse cardiac events [32].

The GLOBAL LEADERS trial assessed the combination of ticagrelor and aspirin for one month followed by ticagrelor alone for 23 month versus 12 months of standard DAPT followed by 12 month of aspirin alone, with neutral results [33]. Later, its ancillary substudy (GLASSY) showed the non-inferiority, but not superiority,

		DAPT duration	**Grade of recommendation**	**DAPT duration**	**Grade of recommendation**	**DAPT duration**	**Grade of recommendation**
		CCS – 2017 [3]		**ACC/AHA – 2016** [4]		**ESC – 2017** [6]	
DES-PCI for stable patients	Standard duration	6–12 months	Strong recommendation, moderate-quality evidence	6 months	Class I, level B-R	6 months	Class I, level A
	Minimal duration	3 months (HBR)	Weak recommendation, low-quality evidence	3 months (HBR or overt bleeding)	Class IIb, level C-LD	3 months (HBR)	Class IIa, level B
						1 month (if bleeding safety concern with 3-month DAPT)	Class IIb, level C
		CCS – 2017 [3]		**ACC/AHA – 2016** [4]		**ESC – 2020** [7]	
DES-PCI for ACS	Standard duration	12 months	Strong recommendation, high-quality evidence	12 months	Class I, level B-R	12 months	Class I, level A
	Minimal duration	12 months	Strong recommendation, high-quality evidence	6 months	Class IIb, level C-LD	3 months (HBR)	Class IIa, level B
						3–6 months, depending on ischemic/bleeding risk balance	Class IIa, level A

Table 1.
Standard and shortened DAPT duration according to different guidelines. Adapted and updated from [9].

Clinical [23]
Previous myocardial infarction
Diabetes mellitus
Chronic kidney disease (creatinine clearance <60 mL/min)
Previous stent thrombosis
Current smoker
Angiographic
Implantation of ≥3 stents [24]
Stented length (>60 mm) [24]
Complex lesions (bifurcation, chronic total occlusion) [24]
Left main or left anterior descending stenting [25]
Multivessel stenting [26]

Table 2.
High risk features associated with thrombotic events. Adapted from [3].

of shortened DAPT arm in a selected subpopulation of the 20 highest recruiting sites of the main trial [34]. On the other hand, the STOPDAPT-2 trial showed the benefit of 1 month of aspirin plus clopidogrel followed by clopidogrel monotherapy vs. 12 month of standard DAPT, meeting the criteria for both noninferiority and superiority [35].

5. Evidence for DAPT duration after PCI in ACS setting

The three sets of guidelines provide strong recommendation for a standard 12-month DAPT treatment after an ACS, based on the CURE trial and the PCI-CURE substudy published nearly two decades ago, in which DAPT with aspirin and clopidogrel was prescribed for 3 to 12 months after PCI [36, 37]. More recently, the pivotal prasugrel and ticagrelor trials, conducted in patients with ACS, used a 12-month default DAPT duration, furthermore establishing this approach as the standard of practice (**Table 1**) [38, 39].

5.1 Scenarios for shortened DAPT

Due to the time gap between the latest ESC guidelines on this topic and its American and Canadian counterparts, recommendations on minimal DAPT duration differ between the former and the latter (**Table 1**). The scarce evidence available at the time of the last ACC/AHA and CCS guidelines led to only weak recommendation for a 6-month DAPT on the former, while the latter holds at a 12-month recommendation. This year's ESC guidelines on the management of ACS in patients presenting without persisting ST-segment elevation includes various guidance on short DAPT.

As discussed previously, the insight from the PRECISE-DAPT study led to consider a shortened 3-month DAPT duration in patients at HBR (PRECISE-DAPT score ≥ 25) (Recommendation IIa B) [13]. What is probably more interesting, however, is the evidence gathered recently on patients at low-to-intermediate ischemic risk and low bleeding risk. The previously described TWILIGHT and SMART-CHOICE trials included a high proportion of patients presenting with ACS (64.8% and 58.2%, respectively), with the benefits of antiplatelet monotherapy

being consistent between subgroups. On the other hand, the SMART-DATE trial [40] specifically assessed 6 versus 12-month DAPT in patients with ACS. Although mortality, stroke and BARC type 2–5 bleeding did not differ between the two groups, the rate of myocardial infarction was higher in the short DAPT group. Combining the information of these three trials, the ESC guidelines suggest a 3 to 6-month DAPT therapy depending on the balance of ischemic and hemorrhagic risk in a Class IIa, level A recommendation. The recent TICO trial evaluated another aspirin-free strategy, specifically among patients undergoing PCI for an ACS [41]. Ticagrelor monotherapy after 3 months of DAPT resulted in a slight, significant reduction of the composite outcome of major bleeding and cardiovascular events at one year, compared with a ticagrelor-based 12-month DAPT.

6. Evidence of shortened DAPT duration in patients after PCI requiring lifelong oral anticoagulation

The landscape of evidence for the treatment of patients requiring lifelong oral anticoagulation after PCI has expanded notably in the last years, the main landmarks being (1) the ISAR-TRIPLE trial, where no significant difference was found in the primary endpoint of "net clinical benefit" (which included ischemic and bleeding outcomes) between 6 weeks and six months of triple therapy; [42] (2) the WOEST trial, where a dual pathway strategy (warfarin and clopidogrel) versus standard triple therapy (warfarin, clopidogrel and ASA) reduced bleeding while not increasing thrombotic events; [43] and (3) the advent of the new four direct oral anticoagulants (DOAC) and their specific trials for patients undergoing PCI,

AF patients with ACS/PCI		
Clinical setting	**Therapy regimen**	**Recommendation**
Uncomplicated or bleeding[a] > ischemic[b] risk	• TT < 1 week • OAC + P2Y12 (preferably clopidogrel) up to 12 months	I B
Ischemic[b] > bleeding[a] risk	• TT > 1 week and ≤ 1 month • OAC + P2Y12 (preferably clopidogrel) up to 12 months	IIa C
AF patients with CCS undergoing PCI		
Clinical setting	**Therapy regimen**	**Recommendation**
Uncomplicated or bleeding[a] > ischemic[b] risk	• TT ≤ 1 week • OAC + P2Y12 (preferably clopidogrel) up to 6 months	I B
Ischemic[b] > bleeding[a] risk	• TT > 1 week and ≤ 1 month • OAC + clopidogrel up to 12 months	IIa C

[a]Evaluation based on HAS-BLED score: Hypertension, Abnormal renal or liver function, Stroke or ICH history, Bleeding history or bleeding diathesis, Labile INR, Elderly (>65 years), Drugs (concomitant OAC and antiplatelet therapy, NSAIDs).
[b]Evaluation based on (1) clinical factors: diabetes, prior ACS, multivessel CAD, concomitant peripheral artery disease, premature or accelerated CAD, chronic kidney disease, ACS as clinical presentation; (2) anatomical factors: multivessel stenting, complex stenting (left main or last patent vessel stenting, chronic total occlusion intervention), prior stent thrombosis on antiplatelet treatment.
TT: Triple therapy; CCS: chronic coronary syndrome.

Table 3.
Recommendations for antithrombotic patients of AF patients undergoing PCI. Adapted from the 2020 ESC ESC/EACTS guidelines for the management of atrial fibrillation [8].

[dabigatran/RE-DUAL PCI [44]; rivaroxaban/PIONEER AF-PCI [45]; apixaban/AUGUSTUS [46]; edoxaban/ENTRUST-AF PCI [47]. The new 2020 ESC ESC/EACTS guidelines for the management of atrial fibrillation is the latest consensus document on the subject, and the only one after the publication of the four DOAC trials for AF patients undergoing PCI [8].

As a whole, these trials evaluated dual (DOAC + $P2Y_{12}$) vs. triple (VKA + $P2Y_{12}$ + aspirin) therapy. They included a notable proportion of ACS (37–52%), although the highest risk patients were underrepresented (i.e., culprit lesions in a previously stented segment). Moreover, they all used triple therapy during PCI until randomization (1–14 days post PCI) and the most commonly $P2Y_{12}$ inhibitor used was clopidogrel, as neither prasugrel or ticagrelor have evidence supporting their safety in combination with an OAC. As per outcomes, they reported a significant reduction of major/clinically significant bleeding, comparable rates of ischemic stroke, similar or non-significantly higher rates of myocardial infarction and stent thrombosis and a neutral effect on major adverse cardiac events and all-cause mortality [48]. Also, it is worth emphasizing that the AUGUSTUS trial is the only one that studied whether the advantages of dual pathway (vs. triple therapy) is independent of the type of OAC.

The ESC guidelines include four recommendations, according to the clinical presentation and the ischemic/bleeding risk balance (**Table 3**). Due to the under-representation of high ischemic risk patients on the trials, the recommendations for this population have a weak level of evidence. The evaluation of the ischemic risk is based on the presence of variables known to pose higher risk in the general population (also previously described in **Table 2**). Regarding the bleeding risk, evaluation with the AF-specific HAS-BLED risk score is recommended. This bleeding risk score has proven to be more useful at predicting bleeding risk in AF patients [49].

7. Beyond guidelines: tailored shortened DAPT durations according to stent platforms

Current guidelines include DAPT length recommendations irrespective of the DES type, encompassing the evidence of the multiple platforms in various trials. It is worth mentioning, however, some recent trials in which specific platforms have been tested in two main scenarios: one stent tested at short vs. longer DAPT durations; and two different stents compared in a short DAPT duration for patients not deemed amenable for prolonged DAPT duration. While acknowledging the limited value of a single trial, they may still be useful for tailored antiplatelet regimens. **Table 4** summarizes the current knowledge of some specific DES platforms in these two scenarios.

8. Conclusions

As new antiplatelet and anticoagulant drugs have entered the therapeutic arsenal, and as stent platforms continue to be refined through the years, established dogmas of the treatment of patients with ischemic heart disease should be reassessed. Most notably, current evidence strongly supports that for a considerable number of patients, shorter antithrombotic, aspirin-free treatment is associated not only with fewer bleeding complications, but with comparable rates of hard ischemic endpoints. Hence, a paradigm shift is underway, in which the concern should not be to find reasons to reduce the classical 12 months of DAPT. Rather, patients should be evaluated for causes *not to* receive an abbreviated aspirin-free antithrombotic

Trial	Stent platform	Population study	Study arms and DAPT therapy	Outcomes
Trials testing short vs. long DAPT durations in patients treated with new stent platforms				
GLOBAL LEADERS [33]	BioMatrix (Biosensors Europe)	All comers	Biomatrix stent 1 month DAPT ASA + ticagrelor followed by ticagrelor 12 months vs. DAPT ASA + clopidogrel (stable patients) or ASA/ ticagrelor (ACS) followed by ASA (1:1)	No superiority of the ticagrelor arm for efficacy
COBRA-REDUCE [50]	Cobra PzF (CeloNova Biosciences)	Patients taking OAC	Cobra stent vs. standard DES Cobra: DAPT 14 days, then OAC + ASA until 6 monts. Control stent: DAPT 3–6 monts. After 6 months, all received OAC + ASA	Cobra PzF stents did not achieve bleeding reduction and did not meet non-inferiority criteria with respect to thrombotic events
XIENCE 90/28 [51]	Xience (Abbott Vascular)	High bleeding risk	Xience stent DAPT 1 month and DAPT 3 months, compared to historical cohort DAPT 12 months	Non-inferior ischemic outcomes, similar rates of clinically relevant and reduction in major bleeding
EVOLVE Short DAPT [52]	Synergy (Boston Scientific)	High bleeding risk	Synergy stent 3 month DAPT vs. 12 month historical cohort	Non inferior ischemic outcomes
TICO [41]	Orsiro (Biotronik AG)	Acute coronary syndromes	Orsiro stent 3 month DAPT followed by ticagrelor monotherapy vs standard 12 month DAPT	Modest reduction of bleeding and cardiovascular events.
Trials testing different stent technologies in patients deemed for short DAPT				
LEADERS FREE [30]	Biofreedom (Biosensors Europe)	High bleeding risk	Biofreedom vs. similar BMS (1:1) 1 month DAPT ASA + clopidogrel followed by clopidogrel	Superiority of the Biofreedom stent in safety and efficacy
ONYX ONE [53]	Resolute Onyx (Medtronic)	High bleeding risk	Resolute Onyx vs. Biofreedom (1:1) 1 month DAPT followed by SAPT	Resolute Onyx non-inferior to Biofreedom in safety and effectiveness
ZEUS [29]	Endeavor (Medtronic)	High bleeding risk	Endeavor stent vs. ultra-thin BMS (1:1) 1 month DAPT	Low risk of 1-year MACE in Endeavor patients
SENIOR [54]	Synergy (Boston Scientific)	Elderly patients (>75 yo) undergoing PCI	Synergy stent vs. ultrathin BMS 1 month or 6 months DAPT, according to stable or unstable presentation	Low risk of ischemic endpoints in the Synergy arm

Table 4.
Recent trials on the performance of different stent platforms on shortened DAPT scenarios.

regimen. In order to provide the most accurate treatment regimens, a careful evaluation should be made by taking into account the clinical presentation, coexisting conditions that are prone to a higher ischemic or bleeding risk and awareness of the stent platform used.

Author details

Marcel Santaló-Corcoy, Guillaume Marquis-Gravel and Jean-François Tanguay*
Montreal Heart Institute, Université de Montréal, Montréal, Canada

*Address all correspondence to: jean-francois.tanguay@icm-mhi.org

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