Review Article

The optimal duration of dual antiplatelet therapy after coronary stent implantation: to go too far is as bad as to fall short

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Abstract: Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is key for secondary prevention of recurrent coronary ischemic events and stent thrombosis. For this purpose, DAPT showed superior efficacy compared to aspirin alone, but it is also associated with an increased risk of major, and potentially fatal, bleeding. Hence, while secondary prevention with aspirin monotherapy is generally maintained for an indefinite period, the duration of DAPT after the index event is still debated. Multiple trials have challenged the guideline recommended standard of care of 12 months of DAPT duration. These studies tested on one side a treatment reduction to 6 or 3 months, and on the other side an extension of treatment beyond 12 months in order to define the optimal DAPT duration maximizing the anti-ischemic protection and minimizing bleeding. In this document we sought to summarize the existing evidence from more than 18 randomized controlled trials in the field, and discuss the benefit and risks of prolonging/shortening DAPT duration. In addition, a specific focus on treatment individualization will outline the current, evidence-based, decision-making process for optimal DAPT duration selection after coronary stenting.

Keywords: Dual antiplatelet therapy (DAPT); bleeding; coronary stenting; DAPT duration; PRECISE-DAPT

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Introduction

The association of aspirin and a P2Y12 inhibitor, or dual antiplatelet therapy (DAPT), is one of the most widely used treatments in cardiovascular medicine, with an estimated yearly indication in more than 2 million patients with myocardial infarction (MI) or treated with percutaneous coronary intervention (PCI) (1). DAPT efficiently reduces platelet aggregation, limiting the risk for stent thrombosis or vascular thrombosis at sites distant from the initially stented lesion (2). Yet, by the same mechanism DAPT increases the risk for major bleeding, which have been linked to increased morbidity and mortality (3-6). For this reason the optimal duration of treatment, which maximize efficacy by ischemic events prevention, and minimize the concomitant risks for serious bleeding complications, have been extensively explored during the last 20 years (7,8). During this period a series of technical and pharmacological advancements have been introduced and at the same time treatment decision-making have been informed by subgroup data, suggesting treatment individualization based on various patient's subsets. A summary of the available evidence from RCTs and specific subgroups will be discussed in this document.

DAPT duration after PCI: summary of the evidence from randomized controlled trials

The optimal duration of DAPT after coronary stenting has been extensively explored in 18 randomized controlled trials (9) with more than 40,000 patients included (*Table 1*) (7). Most of these studies used as a comparator the initial landmark point proposed by guidelines at that time (i.e., 12 months of treatment) (26-28), while the experimental arm was based on a reduction of treatment duration (e.g., to 3 or 6 months) or on a prolongation of the treatment duration (e.g., 24 or 30 months). Few trials make an exception due to a special design (e.g., 6 *vs.* 24 months) (19,21,29). For the purpose of a simple classification we divided these studies in two clusters:

- Trials testing reduction of DAPT duration;
- Trials testing prolongation of DAPT duration.

Reducing the duration of DAPT after coronary stenting (Figure 1)

The reduction of DAPT duration from the initial standard proposed of 12 months has been evaluated in eleven RCTs (*Table 1*) (10-15,17), three tested 3 *vs.* 12 months of treatment, eight tested 6 *vs.* 12 months. In general these studies tested the primary hypothesis that a shorter DAPT regimen was non-inferior to the standard of care in terms of ischemic events or net adverse clinical events (NACE) (i.e., ischemic and bleeding events merged in a single composite endpoint). The possibility to reduce safely treatment duration has been often tested in conjunction to specific stent designs, in order to demonstrate their safety in the context of a shorter treatment duration (30-32).

The first study published among this cluster was the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial (12). This included 1,443 patients treated with drug-eluting stent (DES) implantation and randomized to 6 *vs.* 12 months DAPT thereafter (12). Most patients were treated with everolimus-eluting stents and roughly half presented with acute coronary syndrome (ACS). The trial ultimately demonstrated non-inferiority of 6 *vs.* 12 months of DAPT with respect to the primary end point, a composite of cardiac death, MI, or ischemia-driven target vessel revascularization. TIMI major and minor bleeding, trended higher in the 12-month group, but the difference was not statistically significant [hazard ratio (HR) 0.40; 95% CI: 0.13–1.27; P=0.12) (12).

The Second Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy (SECURITY) (17) and the Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) (14) both tested among patients treated with DES, the non-inferiority of 6 *vs.* 12 months DAPT for a composite primary endpoint including both ischemic and major bleeding. Both studies were prematurely terminated due to slow enrollment but ultimately reached the pre-specified non-inferiority hypothesis. Major bleeding was rare and similar between the two study arms in both studies.

The Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial randomized 1,829 patients across 32 centers in China, to 6 *vs.* 12 months of DAPT (13). All patients were treated with DES, but the type of stent was also randomized following the factorial 2:2 design of the study, with a balanced mixture of durable-polymer *vs.* bioresorbable-polymer cobalt-chromium sirolimus eluting stents. The trial ultimately demonstrated the non-inferiority of 6 months DAPT for the primary end point of cardiac death, MI and target lesion revascularization. The rate of major bleeding was similar in the two groups (1.2% *vs.* 0.7%; P=0.21) (13).

A factorial design was also implemented in the Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions (IVUS-XPL) study (15). In this case the first randomization was based on the implementation of intravascular ultrasound guidance to complete the PCI, while the second randomization was for DAPT duration (6 *vs.* 12 months) (15). Second-generation everolimus-eluting stent was used in all 1,400 patients included in the study. At 12-months follow-up the composite of Cardiac death, MI, stroke and TIMI major bleeding was similar between patients treated for 6- or 12-month (2.2% *vs.* 2.1%; P=0.85). Interestingly, at the subgroup analysis for the primary endpoint, patients treated with intravascular ultrasound guided stent implantation benefitted more from a shorter DAPT treatment as compared to those treated with angiographic guidance alone (P_{int}=0.018) (15).

Similarly in the OPTIMAl duration of Clopidogrel after implantation of second-generation drug-eluting stents (OPTIMA-C) trial 1,368 patients undergoing biolimus-eluting or zotarolimus-eluting stent implantation have been randomized to 6 *vs.* 12 months DAPT (16). The main study

Table 1 Randomized controlled trials testing various dual antiplatelet therapy duration strategies after coronary stent implantation

Study	Year	Patients (N)	Randomization DAPT duration (months)	Clinical presentation (% ACS)	P2Y12 inhibitor implemented	Type of coronary stent implanted	Take-home message
3–6 *vs.* 12 months DAPT							
OPTIMIZE (10)	2013	3,119	3 *vs.* 12	32	Clopidogrel 100%	2nd gen DES 100%	Non-inferiority of 3 *vs.* 12 months DAPT for death, MI, stroke or major bleeding demonstrated
REDUCE	2017	1,496	3 *vs.* 12	100	Clopidogrel 40.8% Prasugrel 10.4% Ticagrelor 48.9%	2nd gen DES 100%	Non-inferiority of 3 *vs.* 12 months DAPT for death, MI, ST, stroke, TVR or bleeding demonstrated
RESET (11)	2012	2,117	3 *vs.* 12	54	Clopidogrel 100%	1st gen DES 21% 2nd gen DES 85%	Non-inferiority of 3 *vs.* 12 months DAPT for cardiac death, MI, ST, TVR, TIMI major or minor bleeding demonstrated
DAPT-STEMI	2017	861	6 *vs.* 12	100	Clopidogrel 42.0% Prasugrel 29.5% Ticagrelor 28.5%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 12 months DAPT for death, MI, any revascularization, stroke or TIMI major bleeding demonstrated
EXCELLENT (12)	2012	1,443	6 *vs.* 12	52	Clopidogrel 100%	1st gen DES 25% 2nd gen DES 75%	Non-inferiority of 6 *vs.* 12 months DAPT for cardiac death, MI or TVR demonstrated
I LOVE IT 2 (13)	2016	1,829	6 *vs.* 12	82	Clopidogrel 100%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 12 months DAPT for cardiac death, MI or TLR demonstrated
ISAR SAFE (14)	2015	4,000	6 *vs.* 12	40	Clopidogrel 100%	1st gen DES 10% 2nd gen DES 89%	Non-inferiority of 6 *vs.* 12 months DAPT for death, MI, ST, stroke, TIMI major bleeding demonstrated
IVUS XPL (15)	2016	1,400	6 *vs.* 12	49	Clopidogrel 100%	2nd gen DES 100%	Comparability of 6 *vs.* 12 months DAPT cardiac death, MI, stroke, TIMI major bleeding
OPTIMA-C (16)	2018	1,368	6 *vs.* 12	50	Clopidogrel 100%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 12 months DAPT for cardiac death, MI, or ischaemia-driven TLR demonstrated

Table 1 (*continued*)

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Study	Year	Patients (N)	Randomization DAPT duration (months)	Clinical presentation (% ACS)	P2Y12 inhibitor implemented	Type of coronary stent implanted	Take-home message
SECURITY (17)	2014	1,399	6 *vs.* 12	38	Clopidogrel 98.7% Prasugrel 0.2% Ticagrelor 0.4%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 12 months DAPT for cardiac death, MI, ST, Stroke, BARC 3 or 5 bleeding demonstrated
SMART-DATE (18)	2018	2,712	6 *vs.* 12	100	Clopidogrel 80.7% Prasugrel or Ticagrelor 19.3%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 12 months DAPT for death, MI or stroke demonstrated
6 *vs.* >12 months DAPT							
ITALIC (19)	2015	1,822	6 *vs.* 24	24	Clopidogrel 98.6% Prasugrel 1.7% Ticagrelor 0.05%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 24 months DAPT for death, MI, TVR, stroke, major bleeding demonstrated
NIPPON (20)	2016	3,307	6 *vs.* 18	33	Clopidogrel 97.5% Prasugrel 0.1% Ticlopidine 2.3%	2nd gen DES 100%	Non-inferiority of 6 *vs.* 18 months DAPT for death, MI, CVA, major bleeding demonstrated
PRODIGY (21)	2012	1,970	6 *vs.* 24	75	Clopidogrel 100%	BMS 25% 1st gen DES 25% 2nd gen DES 50%	Failed to show superiority of 24 months DAPT for death, MI, CVA
12 *vs.* >12 months DAPT							
ARCTIC INTERRUPTION (22)	2014	1,259	12 *vs.* 18–24	0	Clopidogrel 91% Prasugrel 9%	1st gen DES 41% 2nd gen DES 63%	Failed to show superiority of >12 months DAPT for death, MI, ST, stroke or TVR
DAPT (23)	2014	9,961	12 *vs.* 30	43	Clopidogrel 65.3% Prasugrel 34.7%	1st gen DES 38% 2nd gen DES 60%	Superiority of >12 months DAPT for death, MI, stroke and Def/Prob ST demonstrated
DES LATE (24)	2014	5,045	12 *vs.* 36	61	Clopidogrel 100%	1st gen DES 64% 2nd gen DES 30%	Failed to show superiority of >12 months DAPT for cardiac death, MI or stroke
OPTIDUAL (25)	2016	1,385	12 *vs.* 18–48	36	Clopidogrel 100%	1st gen DES 34% 2nd gen DES 59%	Failed to show superiority of >12 months DAPT for death, MI, stroke or ISTH major bleeding

DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; STEMI, ST-segment elevated myocardial infarction; PCI, percutaneous coronary intervention; DES, drug-eluting stent; BMS, bare-metal stent; MI, myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis; TIMI, thrombosis in myocardial infarction; BARC, Bleeding Academic Research Consortium; CVA, cerebrovascular accident; ISTH, International Society of Thrombosis and Haemostasis.

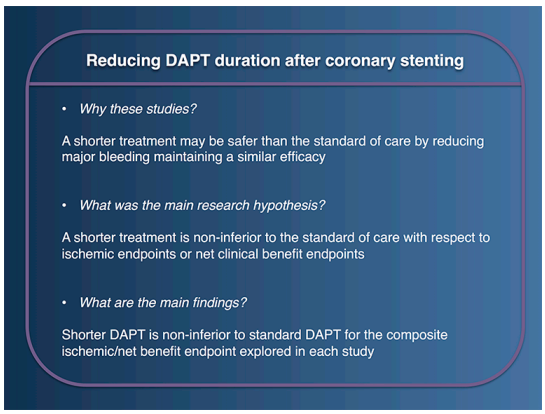

Figure 1 Summary for studies evaluating DAPT duration reduction after coronary stenting. DAPT, dual antiplatelet therapy.

hypothesis was to test non-inferiority of 6 *vs.* 12 months of DAPT for the composite primary endpoint of cardiac death, MI or ischemia driven target lesion revascularization. The primary endpoint ultimately occurred in 1.2% of patients in the short DAPT arm and 0.6% in the long DAPT arm, with the study formally meeting the pre-specifies non-inferiority margin, which was however largely exceeding the observed absolute risk difference between the two study arms (non-inferiority margin 4%) (16).

More recently two randomized trials tested a shorter DAPT duration of 6 months in patients with ACS or presenting with ST-segment elevated myocardial infarction (STEMI). The first study called SMART-DATE was executed in 31 centers in South Korea, enrolling a total of 2,712 patients undergoing PCI for an ACS (18). According to the study protocol, patients were randomized to a treatment with DAPT for 6 or 12 months. Acute presentation was balanced with roughly one-third of patients presenting with STEMI, one-third presenting with non ST-segment elevated myocardial infarction (NSTEMI) and one-third with unstable angina. The P2Y12 inhibitor most commonly implemented was clopidogrel (~80%), while ticagrelor and prasugrel became available only during the final period of enrollment. After 18 months of post-procedural follow-up the primary endpoint, a composite of all-cause death, MI, or stroke, occurred equally in the two study arms (4.7% *vs.* 4.2%) meeting the pre-specified non-inferiority hypothesis. Yet, a significant excess of MI was noted in the short DAPT arm (absolute risk difference 1%), that together with a wide non-inferiority margin for the primary study endpoint raised some concerns regarding the safety of a short DAPT regimen in ACS patients.

In line with this study, the more recent DAPT-STEMI trial (NCT01459627), presented at the transcatheter cardiovascular therapeutics congress in 2017, included 870 patients with STEMI treated with primary PCI and second-generation DES that after 6 months of uneventful treatment with DAPT were randomized to continue treatment up to 12 months or to stop P2Y12 inhibitor and continue with aspirin only. The primary study endpoint was a composite of death, MI, revascularization, stroke and major bleeding at 24 months after primary PCI. Short DAPT was found to be non-inferior as compared to the standard 12 months treatment duration (short DAPT 4.8% *vs.* long DAPT 6.6%; $P_{\text{non-inferiority}}$=0.004). Yet, due to the small sample size, the low event rate and the wide non-inferiority margin these results should be interpreted with caution.

Six months of treatment were compared to a more than 12 months treatment duration in two non-inferiority studies: ITALIC and NIPPON (20,29) trial (*Table 1*), in which patients were randomly allocated to 6 *vs.* 24 months of DAPT and 6 *vs.* 18 months of DAPT respectively. Both studies met the prespecified non-inferiority, yet the results from these studies should be interpreted with caution due to the study early termination and the wide non-inferiority margin selected, which exceeded the event rate of the experimental arm (20,29).

Ultimately three randomized studies tested an even shorter DAPT duration, lasting three months after DES implantation (10,11). The Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor ZES Implantation (RESET) and Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice (10) trials randomized 2,117 and 3,119 patients respectively after Endeavour zotarolimus-eluting stent (no longer available in the market) (10,11). In both studies the study population was at low ischemic risk, and a non-inferiority hypothesis for the NACE endpoint was tested. Ultimately both studies reached the pre-specified non-inferiority margin, showing a substantial equipoise for ischemic events in the short *vs.* long DAPT arm in the population selected.

More recently, the REDUCE trial (NCT02118870), presented at the transcatheter cardiovascular therapeutics congress in 2017, selected a population with a higher baseline ischemic risk to test the non-inferiority of 3 *vs.* 12 months of DAPT in patients with ACS treated with PCI. The 1,496 patients included in the study have been treated at index procedure exclusively with a bioabsorbable

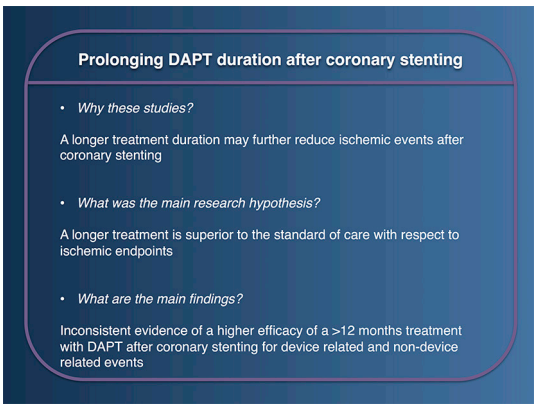

Figure 2 Summary for studies evaluating DAPT duration prolongation after coronary stenting. DAPT, dual antiplatelet therapy.

polymer DES with a luminal CD34+ antibody coating (COMBO stent). The primary endpoint was a composite of all cause death, MI, stent thrombosis, stroke, target vessel revascularization or bleeding, with a wide, 5%, non-inferiority margin. The study ultimately reached non-inferiority with an event rate of 8.2% in the short DAPT arm and 8.4% in the long DAPT arm ($P_{non\text{-}inferiority}<0.001$). More than half of the included patients have been treated with potent P2Y12 inhibitors. Yet, exploring secondary ischemic endpoints a worrisome, borderline, increase of stent thrombosis (1.2% *vs.* 0.4%; P=0.08) and all-cause mortality (1.9% *vs.* 0.8%; P=0.07) in the short DAPT arm raised some concerns regarding the efficacy of a 3-month DAPT duration among patients presenting with ACS, in line with those observed in the SMART-DATE trial.

Finally, the DETECT-OCT study explored the interesting interrelation between stent strut coverage evaluated by optical coherence tomography (OCT) and the impact of DAPT duration (33). This study was not randomized for DAPT duration, but instead assigned treatment (3 *vs.* 12 months) based on OCT findings, assigning a longer DAPT duration (i.e., 12 months) if >6% of uncovered stent strut were observed at the 3 months invasive follow-up, or a shorter DAPT duration (i.e., 3 months) in case of sufficient stent strut coverage. The composite endpoint of cardiac death, MI, stent thrombosis, and major bleeding was rare and similar in both study arms at 12 months follow-up. Despite these results regard a secondary analysis in a non-randomized study with a small sample size, the concept of an imaging guided DAPT duration is interesting and may deserve to be better explored in appropriately sized prospective studies.

Taken together, these studies were all of medium to small size, and with a relatively low event rate. In addition the relatively low period of divergence between the two treatment arms (i.e., 6 months in studies testing 6 *vs.* 12 months of DAPT and 9 months in those testing 3 *vs.* 12 months of DAPT) made these trials largely underpowered to detect differences in treatment effect for rare clinical events, which occurred less often than many had anticipated during trial design. In addition, the slight to moderate differences in inclusion criteria, type of stent used, clinical events definitions and trial design (e.g., timing of randomization could occur at the time of stent implantation or at the time of DAPT divergence) adds to the complex interpretation of the overall study results.

Prolonging the duration of DAPT after coronary stenting (Figure 2)

Four trials compared the standard of care 12 months of DAPT, with a prolonged treatment duration for up to 18–48 months (*Table 1*) (22-25). These studies globally tested the superiority hypothesis of a longer DAPT duration for ischemic endpoints including very late stent thrombosis, MI and others.

The Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation (ARCTIC INTERRUPTION) trial (22), extended follow-up of the ARCTIC study (9), based its primary hypothesis on the superiority of ≥18 months DAPT *vs.* 12 months after stent implantation (22). The study population was highly selected, including only patients undergoing elective PCI. The primary efficacy endpoint occurred in 4% of patients in both study arms, while a significant excess of bleeding was detected in the prolonged DAPT arm (22).

In the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Events (DES LATE) trial 5,045 patients free from adverse events during the first 12 months after DES implantation were included. As was observed in the ARCTIC-INTERRUPTION study, the primary endpoint of cardiac death, MI, or stroke was similar in the two study arms (24). Yet, at difference with the prior study, major bleeding were also similar between the two study arms. Also the more recent Optimal Dual Antiplatelet Therapy (OPTIDUAL) Trial, testing 48 months *vs.* 12 months of DAPT with clopidogrel after stenting, failed to show superiority of a prolonged treatment with DAPT: in fact, no difference

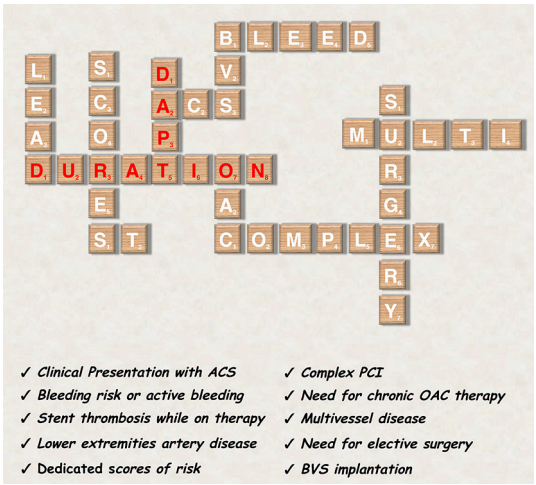

Figure 3 The DAPT duration conundrum: clinical and procedural characteristics supporting DAPT duration decision-making. DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; BVS, bioresorbable vascular scaffold; LEAD, lower extremity artery disease; OAC, oral anticoagulant; ST, stent thrombosis.

for the primary endpoint of death, MI, stroke, or major hemorrhage was detected between the two study arms (5.8% *vs.* 7.5%; HR: 0.75; 95% CI: 0.50 to 1.28), and in the same way no difference was noted when major bleeding alone were evaluated (25).

Also designed to test superiority for ischemic events of a longer treatment duration with DAPT, the PROlonging Dual antIplatelet treatment after Grading stent-induced intimal hYperplasia study (PRODIGY) trial, randomly allocated patients to a long DAPT strategy for 24 months *vs.* a short DAPT for 6 months (21). The PRODIGY trial ultimately found no difference between 6 and 24 months DAPT for the composite primary efficacy endpoint of death, MI, stroke, while it detected a significant excess of BARC 2, 3 or 5 bleeding in patients in the longer DAPT duration arm (21).

Importantly, these three trials taken separately were underpowered to detect a significant difference for more rare ischemic events (e.g., stent thrombosis). Specifically designed with this objective, the large Dual Antiplatelet Therapy (DAPT) study, included 9,961 patients treated with DES during index PCI that after an initial 12 months uneventful period of treatment (study run-in phase) were randomized to an extended treatment duration up to 30 months or to single antiplatelet therapy with aspirin (23). At difference with all previous studies, in the DAPT trial extended DAPT resulted in a 1% absolute reduction in very late stent thrombosis, a 1.6% absolute reduction of major adverse cardiovascular and cerebrovascular events (MACCE). This was driven by a 2% reduction of MI, which were in half of the cases related to a vessel different from the one initially treated during the index procedure. However, the benefit observed on the ischemic side was counterbalanced by an excess of major bleeding, with a 0.9% absolute increase in moderate or severe GUSTO bleeding and 2.6% of BARC 2, 3 or 5 bleeding (23). In addition a signal towards an increase in all-cause mortality was observed among patients treated with longer DAPT. This was later also confirmed in several meta-analyses (34-37), but was ultimately excluded in an internal revision from the American Food and Drug Administration (FDA) (38). At a more thorough evaluation of the single fatal events, most were related to cancer (39), and despite this signal was observed also in other studies (37), the authors attributed this finding to chance.

Current evidence for DAPT duration individualization

In synthesis, results from multiple RCTs suggest that prolonging treatment with DAPT is associated with a reduction of stent or non-stent related ischemic events but to a significant increase of bleeding (2). Importantly both the advantage in term of ischemic event reduction and the excess of bleeding may vary significantly based on the baseline ischemic and bleeding risk of the patient, pushing the trade-off in one direction or in the other based on the intrinsic patient characteristics. For this reason multiple studies have explored the effect on outcomes based on different DAPT duration in several subgroups (2,7,40-45). This may play an important role in treatment decision-making by individualizing the therapeutic strategy on a single patient basis. Taking into account all these variables may seem tricky (*Figure 3*), but their careful evaluation is the key for optimal treatment individualization.

Clinical presentation

The clinical presentation at the time of PCI (e.g., stable CAD or ACS) is a major determinant of the patients' baseline ischemic risk and for this reason have an important role in the selection of antiplatelet treatment duration (7,46,47). The interaction between clinical presentation and DAPT duration has been studied in a pre-specified

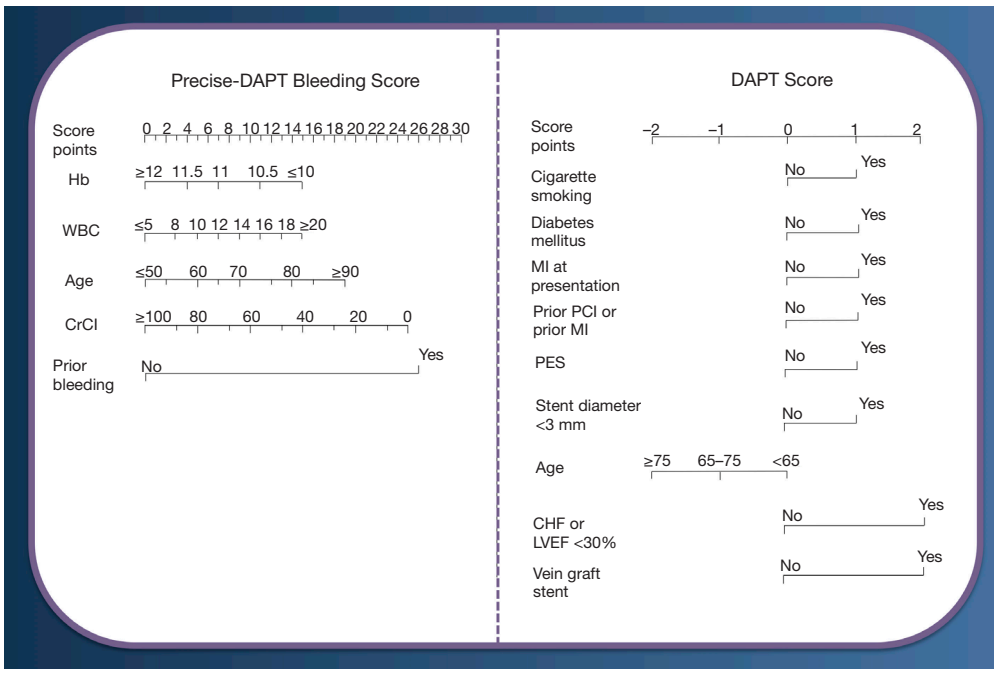

Figure 4 Dedicated clinical risk scores for DAPT duration decision-making. DAPT, dual antiplatelet therapy; Hb, hemoglobin; WBC, white blood cell count; CrCl, creatinine clearance; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; CHF, congestive heart failure; LVEF, left ventricle ejection fraction.

analysis of the PRODIGY trial (41). In this study, nearly three-quarters of the patients enrolled presented with ACS and the remaining with stable coronary artery disease (CAD). A significant heterogeneity of the effect of long *vs.* short DAPT duration was noted for NACE (P_{int}=0.024), suggesting a significant net harm from a longer DAPT in stable CAD patients (NACE in the 24-month *vs.* 6-month DAPT arm: 13.3% *vs.* 5.6%; HR 2.5, 95% CI: 1.35 to 4.69, P=0.004), and a substantial equipoise of a longer treatment duration in the ACS population (16.1% *vs.* 14.1%; HR 1.15, 95% CI: 0.88 to 1.50; P=0.29) (41).

In the larger DAPT trial, a prolonged DAPT up to 30 months significantly reduced MACCE among patients with (3.9% *vs.* 6.8%; P<0.001) but not in those without MI (4.4% *vs.* 5.3%; P=0.08) at presentation, with a positive interaction testing (P_{int}=0.03) suggesting a higher efficacy of longer DAPT among patients with MI as compared to those without (40). In addition, longer DAPT was associated with a significant increase in all-cause death among patients presenting without MI (2.1% *vs.* 1.5%; P=0.04) (40,47), but not in those with MI at presentation.

These findings are supported by a meta-analysis from 6 RCTs including 33,435 patients with prior MI, and comparing the effects of 12 *vs.* >12 months DAPT (48). Extended DAPT was associated with a significant reduction of cardiovascular death, MI or stroke (6.4% *vs.* 7.5%; ARD =1.1%; P=0.001). This benefit was observed within each component of the primary endpoint separately appraised, including a significant 15% reduction of cardiovascular death (RR 0.85, 95% CI: 0.74 to 0.98) (48). Interestingly, since most patients with MI are nowadays treated with potent P2Y12 inhibitors, it will be important to point out if the benefit of extended DAPT treatment may change based on the type of P2Y12 inhibitor used, as it was suggested in a separate study (49). Clinical guidelines support considering clinical presentation at the time of DAPT duration selection, and generally recommend 6 months of DAPT after PCI in patients with stable CAD and 12 months in patients presenting with ACS.

Risk scores

Clinical risk scores have long been used to guide the indication for oral anticoagulation in atrial fibrillation patients. Recently, specific risk scores have been validated for DAPT duration decision-making in patients undergoing PCI (*Figure 4*) (2,7,50). The concept of using a risk score to guide DAPT duration decision-making was introduced for

the first time in the PRODIGY trial (51). In this analysis, patients stratified according to the CRUSADE bleeding risk score into high (CRUSADE >40) *vs.* non-high (CRUSADE ≤40) bleeding risk categories, showed a significant interaction with the antiplatelet treatment duration. Patients deemed at high bleeding risk had a significant increase in major bleeding and red blood cell transfusion when treated with 24- versus 6-month DAPT (9.7% versus 3.7%; ARD 6%; 95% CI: 0.4% to 12.3%; P=0.04; number needed to treat to harm =17), whereas those not deemed at high bleeding risk were not exposed to a significant excess of these complications even if treated with longer DAPT duration (2.4% versus 1.6%; ARD 0.8%; 95% CI: 0.6% to 2.2%; P=0.25) (P_{int}=0.05) (51).

A specific tool for DAPT duration decision-making was developed within the DAPT trial dataset (n=11,648) to identify patients having a net benefit in terms of both ischemia and bleeding from a 30-month as compared to a 12-month treatment (52). After multivariable modeling nine clinical and procedural variables independently associated with ischemia alone or with bleeding alone were selected and included in a clinical risk score (DAPT score—*Figure 4*). This tool, which score ranges from −2 to +10, has been validated to predict the difference between the anticipated reduction in ischemic events and the anticipated increase in bleeding events with extended DAPT. Ultimately, patients with a score of 2 or more appeared to derive a net benefit from a longer treatment duration, in turn patients with a score of less than 2 did not derive such benefit, and were better addressed with a 12-month treatment duration. Yet, this tool does not allow informing early decision-making at the time of PCI to select shorter treatment durations within the first year from treatment initiation.

This aspect has been addressed by the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (53) study, which pooled data from eight RCTs including a total of 14,963 patients treated with PCI and subsequent DAPT (53). The authors aimed to explore long-term bleeding predictors while on DAPT, and develop a predicting tool to inform DAPT duration. After multivariable modeling five clinical and laboratory factors emerged as independent predictors of out-of-hospital bleeding and have been included in a novel risk score (PRECISE-DAPT—*Figure 4*). The PRECISE-DAPT score was validated in two independent external cohorts of 8,595 from the PLATO trial, and 6,172 patients from the BernPCI registry.

Among patients randomly allocated to short (3 or 6 months) or long (12 or 24 months) DAPT duration (n=10,081), patients deemed at high bleeding risk based on a PRECISE DAPT score ≥25 were associated to a significant increase of TIMI major or minor bleeding when treated with long DAPT as compared to short DAPT. Importantly, prolonging DAPT duration in this group was not associated to a benefit in terms of ischemic endpoint, hence driving the net benefit towards a shorter treatment duration. On the contrary, patients not deemed at high bleeding risk, as those with a PRECISE-DAPT score <25, did not derive a significant harm in term of bleeding events from a longer treatment duration, but instead were associated to a significant reduction of the composite ischemic endpoint of MI, definite stent thrombosis, stroke and target vessel revascularization. It is important to emphasize that these risk prediction tools has not been yet prospectively validated in the setting of a randomized clinical trial and further investigation in this field is desirable.

Stent thrombosis

Managing patients with stent thrombosis is challenging given the lack of randomized data in this group of patients. Patients suffering stent thrombosis have a higher risk of stent thrombosis recurrence (54), which appears to persist overtime. Hence, targeting these patients with longer DAPT may be reasonable to reduce the accrued risk of recurrent events overtime, if the treatment can be tolerated. In this context, is of upmost importance to explore and treat correctable causes of stent thrombosis, whether these are clinical [e.g., poor medication adherence (55), unscheduled treatment interruption/cessation (56)], or mechanical (e.g., sub-optimal stent deployment).

Lower extremities artery disease

Peripheral artery disease may often coexist in patients with CAD, and represents an important marker of further higher ischemic risk (57,58). In the CHARISMA trial comparing DAPT with aspirin alone during primary or secondary prevention, 3,096 patients qualified as having peripheral artery disease. In this patients subgroup DAPT up to a median of 28 months was associated with a lower rate of MI and hospitalization for ischemic events as compared to aspirin alone (59). In the PEGASUS trial, patients with a history of peripheral artery disease carried a 60% higher risk

of MACE (60). In this subgroup, treatment with ticagrelor 60 mg b.i.d. compared with placebo provided a robust absolute risk reduction of 5.2% at 3 years for the primary ischemic endpoint, with a significant reduction of acute limb ischemic events and a reduction of both cardiovascular and all-cause mortality (60). Similarly in the PRODIGY trial, a history of peripheral artery disease was associated with a higher risk of death and ischemic events (HR 2.80, 95% CI: 2.05 to 3.83; P<0.001), and prolonged *vs.* short DAPT significantly reduced the incidence of the primary efficacy endpoint in patients with peripheral artery disease (16.1% *vs.* 27.3%; HR 0.54, 95% CI: 0.31 to 0.95; P=0.03) but not in patients without (9.3% *vs.* 7.4%; HR 1.28, 95% CI: 0.92 to 1.77; P=0.14), with a positive interaction testing (P=0.01) (61). Longer DAPT provided a consistent benefit in these patients by also reducing definite or probable stent thrombosis and all-cause mortality (61).

Need for long-term oral anticoagulation

Patients with a need for long-term oral anticoagulation have been invariably excluded from randomized clinical trials for DAPT duration. There is a paucity of data to inform the optimal duration of DAPT in these patients (triple therapy), and whether aspirin or a P2Y12 inhibitor should be preferentially be discontinued. The ISAR-TRIPLE study enrolled 614 patients requiring oral anticoagulants (OAC) and undergoing coronary stent implantation (62). Patients were randomly assigned DAPT with aspirin and clopidogrel for 6 weeks or for 6 months, with subsequent withdrawal of clopidogrel and treatment continuation with aspirin and OAC. At 9 months of follow-up the primary endpoint of death, MI, stent thrombosis, ischaemic stroke, or TIMI major bleeding was similar between patients randomized to 6 weeks DAPT + OAC *vs.* 6 months DAPT + OAC (9.8% *vs.* 8.8%; HR 1.14, 95% CI: 0.68–1.91; P=0.63) (62). In addition, no difference for TIMI major bleeding (5.3% *vs.* 4.0%; HR 1.35, 95% CI: 0.64–2.84; P=0.44) was observed. Yet, due to the small sample size this study cannot be considered conclusive. At any rate it appear reasonable to limit as much as possible DAPT duration in patients with OAC, defining based on the competing ischemic and bleeding risk the optimal treatment strategy (7).

Complex PCI

PCI complexity has been consistently considered by interventional cardiologists as a decisive element for decisions upon DAPT duration (63,64). International guidelines have recently endorsed a standardized definition for PCI complexity (7). This is based on criteria selected in a patient-level analysis of more than 9,000 patients randomly allocated to different DAPT durations (≥12 *vs.* ≤6 months) after coronary stenting (65). The used definition was based on six elements: three vessel PCI, implantation of 3 or more stents, three or more coronary lesions, bifurcation stenting, total stent length >60 mm, treatment of a chronic total occlusion (65). The presence of at least 1 of these features qualified the procedure as a complex PCI. At follow-up, patients undergoing complex PCI had a higher crude rate of major adverse cardiovascular events (MACE) (5.0% *vs.* 2.5%; P=0.001), and continuing DAPT on a long term (≥12 months) as compared to a short term DAPT (≤6 months) significantly reduced MACE (HR 0.56, 95% CI: 0.35 to 0.89). In addition the magnitude of the benefit was directly related to the number of complex PCI elements accounted at baseline. In turn, patients not qualifying as complex PCI derived no benefit from a longer DAPT course (HR 1.01, 95% CI: 0.75 to 1.35). Yet, irrespective of PCI complexity, longer DAPT was associated with a higher risk of major bleeding (65).

Bioresorbable stent implantation

Current generation of poly-lactic acid based bioresorbable vascular scaffolds (BVS) showed a higher risk of device thrombosis as compared to metallic DESs in various clinical trials and meta-analysis (66-68). While the duration of DAPT suggested in the protocols of these studies was of 12 months, an excess of device related thrombosis was observed also in the very-late period (i.e., >12 months after implantation). The excess of very late scaffold thrombosis may be due to the slow adsorption process and the presence of scaffold remnants up to 4–5 years after implantation, representing a potential trigger for late ischemic events that could potentially be prevented by longer DAPT (69). Yet, no dedicated studies examining the optimal duration of DAPT after implantation of a BVS is currently available. Hence, based on expert consensus, international guidelines suggest extending DAPT duration beyond 12 months after BVS implantation (7).

Other two bioresorbable scaffold technologies are currently marketed in Europe. The DESsolve (Elixir Medical Corporation, Sunnyvale, California) is a poly-lactic acid based BVS with self-correcting properties and an expected adsorption time of 12 months (70). These

properties appear promising as may theoretically reduce the risk of very late scaffold thrombosis but no robust clinical data can still support this concept. At difference with the other two, the Magmaris (Biotronik, Berlin, Germany) is a metallic, magnesium-alloy, sirolimus-eluting scaffold with a higher tensile strength and an expected absorption time of 12 months (71). Interestingly, in *ex vivo* animal studies this scaffold showed lower platelet coverage and thrombus deposition as compared to both first-generation BVS (72) and to an equivalent, stainless steel sirolimus-eluting stent (73). Yet, whether these characteristics translate in a superior safety compared to other BVS remain to be demonstrated, and the clinical experience with this technology is still limited by the low number of patients included in randomized clinical trials (71). Optimal duration of DAPT with this device is unclear and is not supported by solid evidence. Clinical trials (71,74) and registries (NCT02817802) recommended at least 6 months of DAPT after magnesium-allow scaffold implantation, and clinical data up to 24 months based on a limited number of patients (n=184—84% discontinued DAPT before 24 months) did not report episodes of definite or probable scaffold thrombosis (75).

Future perspectives: will we continue treating patients with DAPT?

DAPT is one of the most important treatment options in current cardiology. The field has rapidly modified in the recent years, in fact both European and American cardiology scientific societies published a dedicated focused-update on DAPT duration (*Table 2*). Yet, many future studies have potential to further change practice.

Aspirin is the cornerstone treatment for patients with secondary prevention of cardiovascular events, and current guidelines recommended its utilization for an indefinite period of time after the index event. Utilization of low-dose aspirin on top of a P2Y12 inhibitor has proven superior to aspirin alone to prevent ischemic events after ACS or stent implantation (3). Yet, all the studies performed so far compared DAPT with single antiplatelet therapy with aspirin after coronary stent implantation, while a comparison with single antiplatelet therapy with a P2Y12 inhibitor alone was never performed. Clopidogrel alone provided superior efficacy and similar safety compared to aspirin alone in patients with atherosclerotic vascular disease in the CAPRIE trial (76). In addition potent P2Y12 inhibitors prasugrel and ticagrelor offers a more consistent and potent inhibition of platelet reactivity as compared to clopidogrel, hence potentially reducing the treatment gap for clopidogrel non-responders (4,5). In the more recent SOCRATES trial 13,199 patients with an ischemic stroke or transient ischemic attack (TIA) were randomly assigned to either ticagrelor or aspirin. The primary end point (stroke, MI, or death within 90 days) occurred in 6.7% of patients treated with ticagrelor and 7.5% of those treated with aspirin (HR, 0.89; 95% CI: 0.78–1.01; P=0.07) (77). Interestingly, there was no excess of major bleeding and intracranial hemorrhage in patients treated with ticagrelor as compared to those treated with aspirin (77).

In the same line, the MATCH trial randomized 7,599 high-risk patients with recent ischemic stroke or TIA and already on treatment with clopidogrel, to low-dose aspirin or placebo (78). Ultimately the study showed that adding aspirin on top of clopidogrel did not result in a significant reduction ischemic event, but only to an excess of major bleeding, including intracranial hemorrhage (78).

For these reasons much attention has been pointed in evaluating the efficacy and safety of a strategy with a single P2Y12 inhibition in spite of DAPT in patients undergoing coronary stent implantation (79). The GLOBAL LEADERS trial has been designed to evaluate in a PCI treated population the effects of 24-month Ticagrelor monotherapy (associated with aspirin only during the first month) compared to 12-month standard DAPT. The primary outcome was a composite of all-cause mortality or non-fatal, new Q-wave MI at 24 months. A total of 15,991 patients were randomly allocated to Ticagrelor 90 mg twice daily for 24 months plus ASA ≤100 mg for one month (Experimental arm) versus DAPT with either Ticagrelor (ACS) or Clopidogrel (stable CAD) for 12 months plus ASA ≤100 mg for 24 months (Control). The key safety endpoint was investigator-reported BARC class 3 or 5 bleeding. At 24 months of follow-up the primary endpoint was not statistically different between the two treatments tested (3.81% *vs.* 4.37%, RR 0.87, P=0.073), neither when both components of the primary endpoint were separately appraised (all cause death: 2.81% *vs.* 3.17%, RR 0.88, P=0.182). No difference for investigator-reported BARC 3 or 5 bleeding events was found (2.04% *vs.* 2.12%, RR 0.97, P=0.766). Nevertheless adherence to the experimental therapy was observed lower than those of the standard of care (78% *vs.* 93%), which may have in part impaired the statistical power of the study. Other two ongoing trials are currently investigating this strategy and may help giving a cleared picture to the field [TWILIGHT (NCT02270242)

Table 2 Duration of dual antiplatelet therapy: comparison between European Society of Cardiology (ESC) guidelines [2017] and American college of cardiology/American Heart Association (ACC/AHA) guidelines [2016]

	ESC guidelines	ACC/AHA guidelines
DAPT after PCI (SCAD)		
BMS use	6 mo.* (IA)	At least 1 mo. (IA)
	If HBR 3 mo. (IIaB)	
	If HBR 1 mo. (IIbC)	
DES use	6 mo. (IA)	At least 6 mo. (IB)
	If HBR 3 mo. (IIaB)	If HBR 3 mo. (IIbC)
	If HBR 1 mo. (IIbC)	
BVS use	At least 12 mo. (IIaC)	–
DCB use	6 mo. (IIaB)	–
DAPT after PCI (ACS)		
BMS use	12 mo.* (IA)	At least 12 mo. (IB)
	If not-HBR >12 mo. (IIbA)	If not-HBR >12 mo. (IIbA)
	If HBR 6 mo. (IIaB)	If HBR 6 mo. (IIbC)
DES use	At least 12 mo. (IA)	At least 12 mo. (IB)
	If not-HBR >12 mo. (IIbA)	If not-HBR >12 mo. (IIbA)
	If HBR 6 mo. (IIaB)	If HBR 6 mo. (IIbC)
BVS use	At least 12 mo. (IIaC)	–
DAPT after CABG (SCAD)	No indication	12 mo. (IIbB)
DAPT after CABG (ACS)	12 mo. (IC)	12 mo. (IC)
	If not-HBR** >12 mo. (IIbC)	
	If HBR 6 mo. (IIaC)	
DAPT after medically managed ACS	12 mo. (IA)	At least 12 mo. (IB)
	If not-HBR >12 mo.*** (IIbB)	If not-HBR >12 mo. (IIbA)
	If HBR at least 1 mo. (IIaC)	
DAPT in patients with an indication to OAC	1 mo. (IIaB)	–
	If HTR**** up to 6 mo. (IIaB)	

*, drug eluting stent is the preferred treatment option irrespective of intended DAPT duration; **, if at high ischaemic risk with prior myocardial infarction and CABG, who have tolerated DAPT without a bleeding complication; ***, patients with prior MI at high ischaemic risk who are managed with medical therapy alone and have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg b.i.d. on top of aspirin for longer than 12 months and up to 36 months may be considered. In Patients who are not eligible for treatment with ticagrelor, continuation of clopidogrel on top of aspirin for longer than 12 months may be considered (IIbC); ****, patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk. ACS, acute coronary syndrome; BVS, bioresorbable vascular scaffold; BMS, bare metal stent; CABG, coronary artery bypass graft; DAPT, Dual antiplatelet therapy; DEB, drug eluting balloon; DES, drug eluting stent; HBR: high bleeding risk; HTR, high thrombotic risk; OAC, oral anticoagulant; SCAD, stable coronary artery disease.

and TICO (NCT02494895)].

Conclusions

DAPT has been extensively studied for more than 20 years, opening opportunities for a thorough and evidence based treatment selection. The interpretation of the current evidence suggest that, as a general concept, longer DAPT duration is associated with a reduction of non-fatal ischemic events, but in turn increases major bleeding at a similar extent. For this reason DAPT duration should be individualized on a single patient basis, taking into account the baseline ischemic and bleeding risk status. As recommended by international guidelines clinical presentation and bleeding risk status are the main drivers of DAPT duration, together with several other factors that can further refine the risk assessment towards the maximization of the net clinical benefit.

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Footnote

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