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Review

Dual antiplatelet therapy after coronary stent implantation: Individualizing the optimal duration

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ABSTRACT

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor antagonist in addition to aspirin is the antiplatelet treatment of choice in patients undergoing percutaneous coronary intervention. Despite DAPT being one of the most widely investigated treatment strategies in the cardiology field, its optimal duration after coronary stenting remains controversial. The balance between the possible benefit of preventing a thrombotic event and the risk of suffering a bleeding complication due to maintenance of therapy is of critical relevance to determine the duration of DAPT in a given patient. Indeed, extended DAPT is associated with a reduction in non-fatal ischemic outcomes, at the cost of increasing the risk of bleeding events. Of note, several factors related to the patient, the procedure, or the device implanted may influence the ischemic and/or bleeding risk profiles of a given patient. Therefore, it is reasonable to recommend that the decision on DAPT duration should be individualized on a case-to-case basis. This review aims to provide a comprehensive overview of the current status of knowledge on duration of DAPT after coronary stenting, focusing on the evidence provided mainly by randomized clinical trials, as well as to discuss the factors that may influence the individual ischemic and bleeding risk profiles for a given patient, and whether the use of risk scores may inform the decision-making process for determining DAPT duration.

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Introduction

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor antagonist in addition to aspirin remains the antithrombotic treatment of choice in patients with acute coronary syndromes or undergoing percutaneous coronary intervention (PCI) [1–6]. In spite of the large amount of evidence supporting DAPT as the cornerstone treatment in these settings [7,8], the optimal duration of DAPT in patients receiving coronary stenting is yet to be fully elucidated. In particular, there is a clear trade-off between the benefit obtained with DAPT in preventing recurrent ischemic events and an increased risk of bleeding, which is directly related to treatment length. Of note, both ischemic and bleeding events are known to have a negative impact on prognosis [9–11]. The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) have recently revised their recommendations regarding DAPT duration, underscoring the relevance of the subject [12,13].

The optimal duration of DAPT in a given patient is determined by the balance between the individual risks of presenting a recurrent ischemic event or a hemorrhagic complication due to maintained antithrombotic treatment. Therefore, a personalized approach appears to be reasonable when defining the optimal duration of therapy that should theoretically minimize the combined risk of both ischemic and bleeding adverse events. The aim of the present manuscript is to provide a comprehensive overview of the current status of knowledge on duration of DAPT, focusing on the results obtained in randomized clinical trials evaluating different strategies of DAPT duration and the available evidence regarding clinical, procedure- or device-related factors that may help weighing ischemic and bleeding risks and, thus, individualizing DAPT duration.

Optimal duration of DAPT: available evidence

Randomized clinical trials

The results of 14 randomized clinical trials comparing different strategies of DAPT duration in patients undergoing coronary stent implantation (mostly newer-generation stents) have been published to date (Fig. 1). These trials can be divided into two groups according to their hypotheses regarding the primary endpoint: (a)

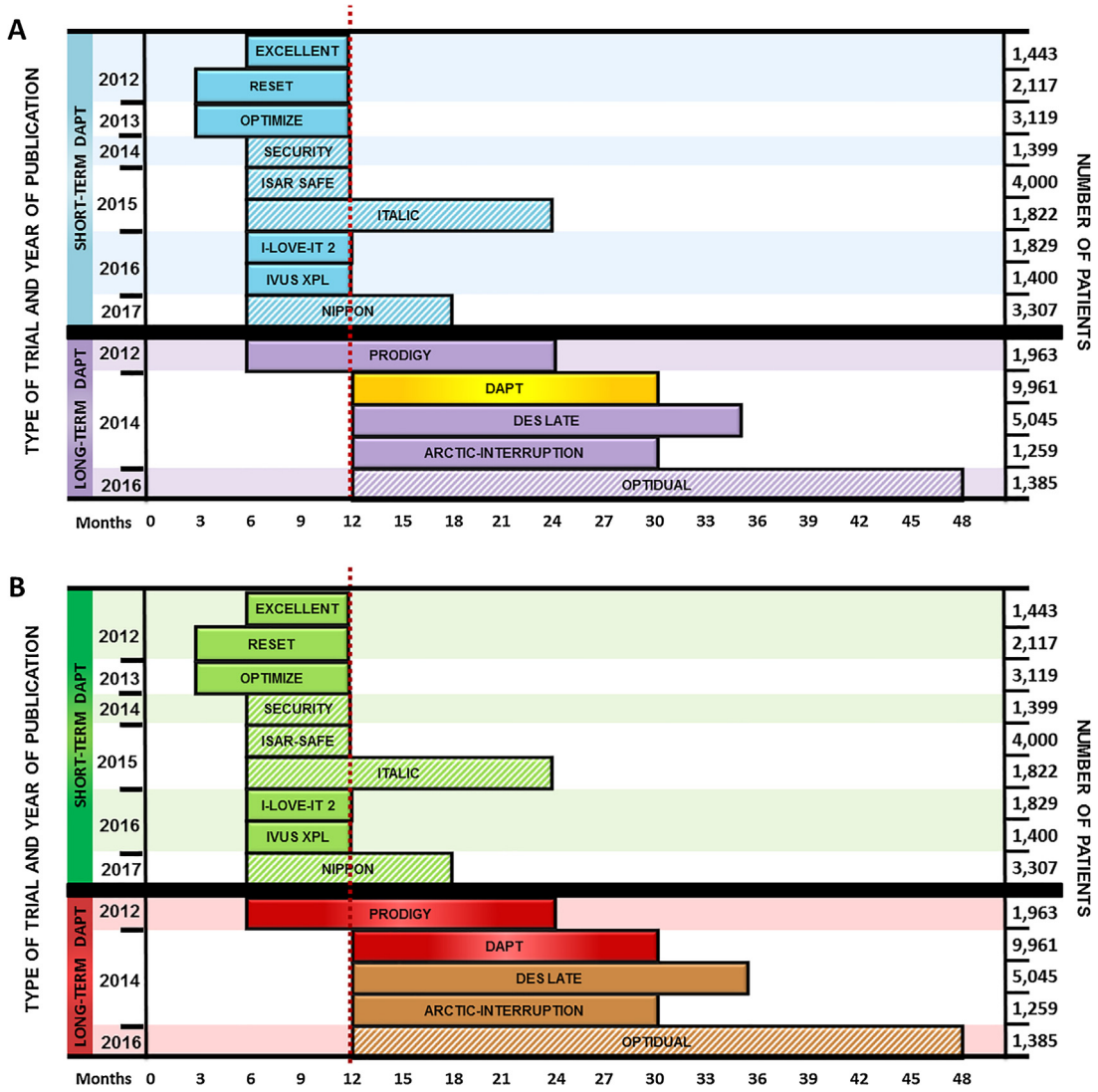

Fig. 1. Trials of DAPT duration after PCI. (A) Results for the primary endpoint. Bars colors indicate whether the hypothesis of the primary endpoint was demonstrated (blue for non-inferiority of short compared to long DAPT duration in short-term trials and orange for superiority of long compared to short DAPT duration in long-term trials) or not (purple for not confirmed superiority of long compared to short DAPT duration in long-term trials). (B) Results for the key safety endpoint of bleeding. Bars colors indicate whether a significant difference in the key safety endpoint of bleeding was observed (red for significant difference in long-term trials) or not (green for short-term trials and brown for long-term trials). White-striped bars indicate that the trial was prematurely stopped before completing the planned enrolment. DAPT, dual antiplatelet therapy.

short-term DAPT trials: these studies tested the hypothesis that a shorter DAPT duration (3 or 6 months) was non-inferior to the standard (12 months) or a prolonged (>12 months) regimen [14–22]; and (b) long-term DAPT trials: these studies evaluated the hypothesis that a longer DAPT duration (>12 months) was superior to the standard (12 months) or a shorter regimen (6 months) [23–27].

Trials investigating shorter durations of DAPT have consistently showed that such regimens may provide sufficient or at least non-inferior efficacy than longer durations in terms of preventing ischemic outcomes (Table 1) [14–22]. In addition, a numerical but not statistically significant trend towards reduced major bleeding outcomes with shorter durations was also observed in several of these investigations (Table 2). However, some may argue that these studies have limitations such as the following: (a) non-inferiority designs; (b) low-risk study populations with a relatively low proportion of acute coronary syndrome (ACS) patients and lower than expected rates of events; and (c) the fact that some of these trials were prematurely stopped before reaching the planned enrolment [17–19,22]. Overall, these issues may restrict their validity and should not allow drawing definitive conclusions and extrapolate them for all patients receiving coronary stenting. The results of the REDUCE (Randomized Evaluation of Short-term DUal Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt) trial have been recently reported (not published at the time this manuscript was written), showing non-inferiority of 3-month compared to 12-month DAPT in ACS patients treated with the Combo® stent (OrbusNeich, Hong Kong) (NCT02118870).

Five trials have evaluated if a prolonged DAPT duration (ranging from 18 to 48 months) was superior to the standard (12 months) [24–27] or a shorter length (6 months) [23]. Interestingly, all but one of these studies randomized patients to prolonged or standard DAPT duration after an initial 12-month run-in phase free of adverse events, which indicates that highly-selected subjects were included and, thus, caution must be taken when extrapolating their results to the general population [24–27]. Noteworthy, the rates of major bleeding were statistically significantly increased in the extended DAPT arm in two of these studies and numerically higher in a third one [23,24,26], which reinforces the concept that the risk of bleeding is directly related to the duration of therapy. The dual antiplatelet therapy (DAPT) trial deserves especial attention, since it is the largest randomized study evaluating DAPT duration and the single investigation that has showed evidence of benefit with a long-term strategy [24]. In brief, patients (9961 of 22,866 subjects screened) with drug-eluting stent (DES) implantation were randomized after a 12-month run-in phase without suffering any ischemic or bleeding event to continue DAPT for up 30 months or discontinue DAPT by withdrawing the $P2Y_{12}$ inhibitor (clopidogrel or prasugrel). Extended DAPT duration was associated with a significant reduction in the rates of both co-primary endpoints: major adverse cardiovascular and cerebrovascular events, a combination of death, myocardial infarction (MI), or stroke [4.3% vs. 5.9%; hazard ratio (HR) 0.71; 95% confidence interval (CI), 0.59–0.85; $p < 0.001$], and definite or probable stent thrombosis (ST) (0.4% vs. 1.4%; HR 0.29; 95% CI, 0.17–0.48; $p < 0.001$). This was at the cost of a significant increase in moderate of severe bleeding events, according to the GUSTO criteria, with prolonged therapy (2.5% vs. 1.6%; HR 1.61; 95% CI, 1.21–2.16; $p = 0.001$) [24].

Quite a few meta-analyses of the above-mentioned trials have been published in recent years [28–35]. It is noteworthy that some discrepancies have been observed among their results, which could be explained by several reasons that pose challenges when performing meta-analyses in this specific matter. In particular, the use of a particular methodological approach in a meta-analysis (e.g. traditional with binary outcomes, stratified, Bayesian, etc.) [36] or between-trials differences in bleeding definitions (Table 2) or in DAPT length strategies (e.g. 12 months duration was considered "short" or "long" depending on the study, some trials did not incorporate an arm of standard 12-month duration, etc.) need to be taken into account when interpreting the results provided. Taken together, the findings of randomized clinical trials and meta-analyses assessing DAPT duration can be summarized as follows: (a) shortened durations (3–6 months) reduce the risk of major bleeding and appear to be non-inferior in terms of ischemic events than standard regimen; (b) prolonged therapy is associated with a reduction in ischemic events (MI and ST), but at the cost of increased risk of major hemorrhagic events; and (c) it is uncertain if the trade-off between mortality due to increased bleeding events and a likely reduction in cardiac death due to decreased ischemic events may result in a negative net impact of prolonging DAPT on all-cause mortality.

Overall, the available evidence makes perfectly clear that a "one-size-fits-all" strategy is no longer valid when deciding DAPT duration. Therefore, a personalized approach is mandatory in order to select the optimal duration of therapy to maximize its benefits.

Current guidelines

The ESC and ACC/AHA practice guidelines have recently updated their recommendations regarding DAPT duration [12,13]. The publication of these two focused updates and the fact that there are some discrepancies among their recommendations underscore not only the relevance but also the complexity of the subject at hand. A summary of current guidelines recommendations on DAPT duration after PCI is provided in Table 3.

In brief, both guidelines recommend 12 months of DAPT with a $P2Y_{12}$ inhibitor (prasugrel or ticagrelor preferred to clopidogrel) in addition to aspirin in ACS patients undergoing coronary stenting, with the possibility of shortening (6 months) or prolonging DAPT duration depending on bleeding and ischemic risk. The ESC guidelines prefer ticagrelor 60 mg bid for longer than 12 months of therapy over clopidogrel or prasugrel in patients with prior MI and high ischemic risk who have tolerated DAPT without a bleeding complication due to the results of the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction) trial [37].

More discrepancies between both guidelines can be noted for patients with stable coronary artery disease (SCAD) undergoing PCI. According to the ESC guidelines, a 6-month course of DAPT with clopidogrel is generally recommended irrespective of stent type, with the exception of at least 12 months in patients treated with bioresorbable vascular scaffolds (BVS). In patients at high bleeding risk, 3 months or even just 1 month of DAPT can be an option. Prolonging DAPT up to 30 months may be considered in patients without a bleeding complication who are at low bleeding risk but high thrombotic risk [12]. The ACC/AHA guidelines give a general recommendation of 1 month and 6 months of DAPT (clopidogrel with aspirin) after bare-metal stent (BMS) and DES implantation, respectively. Prolonged DAPT may be reasonable in patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk. Conversely, a 3-month course may be considered in patients at high risk of bleeding [13].

The most remarkable feature of both guidelines is the possibility of tailoring DAPT duration, which has to be done after a careful assessment of the individual risk profile of ischemic and bleeding outcomes. Further, another important concept is that the decision for DAPT duration should not be immutable, but instead dynamic with the chance to be reassessed during the course of the initially selected regimen [13].

Table 1
Efficacy endpoints in randomized clinical trials of DAPT duration after PCI.

Trial (year)	Number of patients[a]	Hypothesis	Time of randomization	$P2Y_{12}$ antagonists	Primary endpoint definition	Primary endpoint Events (%) Association measure (95% CI)	Death of any cause Events (%) Association measure (95% CI)	CV death Events (%) Association measure (95% CI)	MI Events (%) Association measure (95% CI)	Definite or probable ST Events (%) Association measure (95% CI)	Conclusion (regarding primary endpoint)
Short-term DAPT trials											
EXCELLENT (2012)	1443	6 months non-inferior to 12 months	Index PCI	Clopidogrel	Cardiac death, MI, or ischemia-driven TVR at 12 months	4.8 vs. 4.3 HR 1.14 (0.70–1.86)	0.6 vs. 1.0 HR 0.57 (0.17–1.95)	0.3 vs. 0.4 HR 0.67 (0.11–3.99)	1.8 vs. 1.0 HR 1.86 (0.74–4.67)	0.9 vs. 0.1 HR 6.02 (0.72–49.96)	Non-inferiority confirmed
RESET (2012)	2117	3 months non-inferior to 12 months	Index PCI	Clopidogrel	CV death, MI, ST, ischemia-driven TVR, or bleeding at 12 months	4.7 vs. 4.7 DIF 0.0% (−2.5 to 2.5)	0.5 vs. 1.0 DIF −0.5% (−1.4 to 0.4)	0.2 vs. 0.4 DIF −0.2% (−0.6 to 0.3)	0.2 vs. 0.4 DIF −0.2% (−0.6 to 0.3)	0.2 vs. 0.3 DIF −0.1 (−0.5 to 0.3)	Non-inferiority confirmed
OPTIMIZE (2013)	3119	3 months non-inferior to 12 months	Index PCI	Clopidogrel	Death, MI, stroke, or major bleeding at 12 months	6.0 vs. 5.8 HR 1.03 (0.77–1.38)	2.8 vs. 2.9 HR 0.95 (0.63–1.45)	1.9 vs. 2.1 HR 0.90 (0.55–1.49)	3.2 vs. 2.7 HR 1.17 (0.77–1.76)	0.8 vs. 0.8 HR 1.08 (0.49–2.36)	Non-inferiority confirmed
SECURITY (2014)[b]	1399	6 months non-inferior to 12 months	Index PCI	Clopidogrel Prasugrel (0.2%) Ticagrelor (0.4%)	Cardiac death, MI, stroke, definite or probable ST, BARC bleeding (3 or 5) at 12 months	4.5 vs. 3.7 DIF 0.8% (−2.4 to 1.17)	1.2 vs. 1.1 DIF 0.1% (NA)	0.7 vs. 0.4 DIF 0.3% (−0.4 to 1.1)	2.3 vs. 2.1 DIF 0.2% (−1.2 to 1.7)	0.3 vs. 0.4 DIF −0.1% (−0.7 to 0.4)	Non-inferiority confirmed
ISAR-SAFE (2015)[b]	4000	6 months non-inferior to 12 months	6 months after index PCI	Clopidogrel	Death, MI, stroke, definite or probable ST, or TIMI major bleeding at 9 months after randomization	1.5 vs. 1.6 HR 0.91 (0.55–1.50)	0.4 vs. 0.6 HR 0.66 (0.27–1.63)	NA	0.7 vs. 0.7 HR 0.93 (0.44–1.97)	0.3 vs. 0.2 HR 1.25 (0.33–4.65)	Non-inferiority confirmed
ITALIC (2015)[b]	1822	6 months non-inferior to 24 months	Index PCI (excluding patients with events during the first 6 months)	Clopidogrel Prasugrel (1.6%) Ticagrelor (0.1%)	Death, MI, repeat emergency TVR, stroke, or TIMI major bleeding at 12 months	1.6 vs. 1.5 HR 1.07 (0.52–2.22)	0.9 vs. 0.8 HR 1.14 (0.41–3.15)	0.5 vs. 0.3 HR 1.67 (0.40–6.97)	0.7 vs. 0.4 HR 1.50 (0.42–5.32)	0.3 vs. 0.0 HR –	Non-inferiority confirmed
I-LOVE-IT 2 (2016)	1829	6 months non-inferior to 12 months	Index PCI	Clopidogrel	Cardiac death, target vessel MI or clinically-indicated TLR at 12 months	6.8 vs. 5.9 DIF 0.87% (−1.37 to 3.11)	1.1 vs. 1.4 DIF 0.3% (NA)	0.6 vs. 0.8 DIF 0.2% (NA)	4.4 vs. 3.9 DIF 0.5% (NA)	0.6 vs. 0.2 DIF 0.4% (NA)	Non-inferiority confirmed
IVUS XPL (2016)	1400	6 months non-inferior to 12 months	Index PCI	Clopidogrel	Cardiac death, MI, stroke, or TIMImajor bleeding at 12 months	2.2 vs. 2.1 HR 1.07 (0.52–2.22)	0.7 vs. 1.5 HR 0.50 (0.17–1.45)	0.4 vs. 0.7 HR 0.60 (0.14–2.50)	0.1 vs. 0.0 HR –	0.3 vs. 0.3 HR 1.00 (0.14–7.11)	Non-inferiority confirmed
NIPPON (2017)[b]	3307	6 months non-inferior to 18 months	Index PCI	Clopidogrel Ticlopidine (2.3%) Prasugrel (0.1%)	Death, MI, cerebrovascular events, or modified REPLACE-2 major bleeding from 6 to 18 months	2.1 vs. 1.5 HR 1.44 (0.86–2.43)	1.0 vs. 0.4 HR 2.25 (0.93–5.43)	0.5 vs. 0.2 HR NA	0.2 vs. 0.1 HR 3.07 (0.41–23.23)	0.1 vs. 0.1 HR NA	Non-inferiority confirmed

Table 1 (*Continued*)

Trial (year)	Number of patients[a]	Hypothesis	Time of randomization	$P2Y_{12}$ antagonists	Primary endpoint definition	Primary endpoint Events (%) Association measure (95% CI)	Death of any cause Events (%) Association measure (95% CI)	CV death Events (%) Association measure (95% CI)	MI Events (%) Association measure (95% CI)	Definite or probable ST Events (%) Association measure (95% CI)	Conclusion (regarding primary endpoint)
Long-term DAPT trials											
PRODIGY (2012)[c]	1963	24 months superior to 6 months	30 ± 5 days after index PCI	Clopidogrel	Death, MI, or stroke from randomization to 24 months after index PCI	10.0 vs. 10.1 HR 0.98 (0.74–1.29)	6.6 vs. 6.6 HR 1.00 (0.72–1.40)	3.8 vs. 3.7 HR 1.03 (0.66–1.61)	4.2 vs. 4.0 HR 1.06 (0.69–1.63)	1.5 vs. 1.3 HR 1.15 (0.55–2.41)	Superiority not shown
DAPT (2014)	9961	30 months superior to 12 months	12 months after index PCI (excluding patients with events in the run-in phase)	Clopidogrel Prasugrel (34.7%)	Coprimary: – Death, MI, or stroke, – Definite/probable ST, from randomization to 30 months after index PCI	4.3 vs. 5.9 HR 0.71 (0.59–0.85) 0.4 vs.1.4 HR 0.29 (0.17–0.48)	2.0 vs. 1.5 HR 1.36 (1.00–1.85)	0.9 vs. 1.0 HR 1.00 (0.66–1.52)	2.1 vs. 4.1 HR 0.47 (0.37–0.61)	0.4 vs.1.4 HR 0.29 (0.17–0.48)	Superiority confirmed
DES LATE (2014)[c]	5045	36 months superior to 12 months	12–18 months after index PCI (excluding patients with events in the run-in phase)	Clopidogrel	Cardiac death, MI or stroke at 24 months after randomization	2.4 vs. 2.6 HR 0.94 (0.66–1.35)	1.4 vs. 2.0 HR 0.71 (0.45–1.10)	0.8 vs. 1.2 HR 0.68 (0.38–1.23)	1.2 vs. 0.8 HR 1.43 (0.80–2.58)	0.5 vs. 0.3 HR 1.59 (0.61–4.09)[d]	Superiority not shown
ARCTIC-interruption (2014)	1259	18 to 30 months superior to 12 months	12 months after index PCI (excluding patients with events in the run-in phase or	contraindication to interrupt DAPT)	Clopidogrel Prasugrel (8.5%)	Death, MI, stroke or TIA, urgent coronary					
revascularization, or ST at follow-up (median: 17 months after randomization)	4.0 vs. 4.0 HR 1.17 (0.68–2.03)	1.0 vs. 1.0 HR 1.32 (0.49–3.55)	NA	1.0 vs. 1.0 HR 1.04 (0.41–2.62)	0.0 vs. 1.0 HR NA	Superiority not shown					
OPTIDUAL (2016)[c]	1385	48 months superior to 12 months	12 ± 3 months after index PCI (excluding patients with events in the run-in phase)	Clopidogrel	Death, MI, stroke, or ISTH major bleeding at follow-up (median: 33.9 months after randomization)	5.8 vs. 7.5 HR 0.75 (0.50–1.28)	2.3 vs. 3.5 HR 0.65 (0.34–1.22)	1.4 vs. 2.0 HR 0.69 (0.31–1.56)	1.6 vs. 2.3 HR 0.67 (0.31–1.44)	0.4 vs. 0.1 HR 2.97 (0.31–28.53)	Superiority not shown

BARC, Bleeding Academic Research Consortium; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; DIF, difference; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events II; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

[a] Number of patients analyzed for the primary endpoint of the trial.

[b] The trial was prematurely stopped before completing the planned enrolment.

[c] Percentage of events reported in the following order: % with short-term duration vs. % with long-term duration.

[d] Results reported just for definite stent thrombosis.

Table 2
Major hemorrhagic events according to several bleeding definitions in randomized clinical trials of DAPT duration after PCI.

Study (year)	Number of patients[a]	DAPT duration	Definition of bleeding as key safety outcome	Bleeding (key safety outcome) Events (%) Association measure (95% CI)	TIMI major Events (%) Association measure (95% CI)	GUSTO severe Events (%) Association measure (95% CI)	BARC type 3 or 5 Events (%) Association measure (95% CI)	STEEPLE major Events (%) Association measure (95% CI)
Short-term DAPT trials								
EXCELLENT (2012)	1443	6 vs.12 months	TIMI major bleeding	0.3 vs. 0.6 HR 0.50 (0.09–2.73)	0.3 vs. 0.6 HR 0.50 (0.09–2.73)	NA	NA	NA
RESET (2012)	2117	3 vs. 12 months	TIMI major and minor bleeding	0.5 vs. 1.0 DIF −0.5% (−1.2 to 0.2)	0.2 vs. 0.6 DIF −0.4% (−0.9 to 0.1)	NA	NA	NA
OPTIMIZE (2013)	3119	3 vs. 12 months	Modified major REPLACE-2[b] and severe or life-threatening GUSTO bleeding±	0.6 vs. 0.9 HR 0.71 (0.32–1.60)	NA	NA	NA	NA
SECURITY (2014)[b]	1399	6 vs. 12 months	BARC bleeding 3 or 5	0.6 vs. 1.1 DIF −0.5% (−1.4 to 0.4)	NA	NA	0.6 vs. 1.1 DIF −0.5% (−1.4 to 0.4)	NA
ISAR-SAFE (2015)[b]	4000	6 vs.12 months	TIMI major bleeding	0.2 vs. 0.3 HR 0.80 (0.21–2.98)	0.2 vs. 0.3 HR 0.80 (0.21–2.98)	NA	0.3 vs. 1.1 DIF −0.8% (NA)	NA
ITALIC (2015)[b]	1822	6 vs. 24 months	TIMI major bleeding	0.0 vs. 0.3 HR –	0.0 vs. 0.3 HR-	NA	NA	NA
I-LOVE-IT 2 (2016)	1829	6 vs. 12 months	BARC bleeding ≥3	1.2 vs. 0.7 DIF 0.5% (NA)	NA	NA	NA	NA
IVUS XPL (2016)	1400	6 vs.12 months	TIMI major bleeding	0.7 vs. 1.0 HR 0.71 (0.23–2.25)	0.7 vs. 1.0 HR 0.71 (0.23–2.25)	NA	NA	NA
NIPPON (2017)[b]	3307	6 vs.18 months	Modified REPLACE-2 criteria[c]	0.7 vs. 0.7 HR 0.94 (0.41–2.14)	NA	NA	0.7 vs. 0.7 DIF 0.1% (−0.6 to 0.7)	NA
Long-term DAPT trials								
PRODIGY (2012)	1963	6 vs. 24 months	BARC type 2, 3 or 5	3.5 vs. 7.4 HR 0.46 (0.31–0.69)	0. 6 vs. 1.6 HR 0.38 (0.15–0.97)	NA	1.9 vs. 3.4 DIF 1.5% (NA)	NA
DAPT (2014)	9961	30 vs. 12 months	Moderate or severe GUSTO bleeding	2.5 vs. 1.6 HR 1.61 (1.21–2.16)	NA	0.8 vs. 0.6 DIF 0.2% (−0.1 to 0.6)	2.7 vs. 1.5 DIF 1.2% (NA)	NA
DES LATE (2014)	5045	12 vs. 36 months	TIMI major bleeding	1.1 vs. 1.4 HR 0.71 (0.42–1.20)	1.1 vs 1.4 HR 0.71 (0.42–1.20)	NA	NA	NA
ARCTIC-interruption (2014)	1259	18–30 vs. 12 months	STEEPLE major bleeding	1.0 vs. <0.5 HR 0.15 (0.02–1.20)	NA	NA	NA	1.0 vs. <0.5 HR 0.15 (0.02–1.20)
OPTIDUAL (2016)[b]	1385	48 vs.12 months	ISTH major Bleeding	2.0 vs. 2.0 HR 0.98 (0.47–2.05)	0.6 vs. 0.6 DIF 0.0% (−0.8 to 0.8)	0.4 vs. 0.6 DIF −0.2% (−0.9 to 0.6)	2.0 vs. 2.0 DIF 0.0% (NA)	NA

BARC, Bleeding Academic Research Consortium; CI, confidence interval; DIF, difference; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; NA, not available; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; STEEPLE, Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients; TIMI, Thrombolysis in Myocardial Infarction.

[a] Number of patients analyzed for the primary endpoint of the trial.

[b] The trial was prematurely stopped before completing the planned enrolment.

[c] Intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, clinically evident bleeding causing a decrease of hemoglobin by >3 g/dl, all bleeding causing a decrease of hemoglobin by >4 g/dl, and bleeding leading to transfusion of packed red blood cells or ≥2 U of whole blood.

Table 3
Summary of current ACC/AHA and ESC guidelines recommendations for duration of dual antiplatelet therapy.

	ACS treated with PCI	SCAD treated with PCI
ACC/AHA		
General recommendation	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months. (Class I B)	In patients with SIHD treated with DAPT after BMS implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month. (Class I A) In patients with SCAD treated with DAPT after DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel) should be given for at least 6 months. (Class I B)
Shortening DAPT duration	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable. (Class IIb C)	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable. (Class IIb C)
Prolonging DAPT duration	In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable. (Class IIb A)	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable. (Class IIb A)
ESC		
General recommendation	In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT $\geq$25). (Class I A)	In patients with SCAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type. (Class I A)
Shortening DAPT duration	In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT $\geq$25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered. (Class IIa B)	In patients with SCAD considered at high bleeding risk (e.g. PRECISE-DAPT $\geq$25), DAPT for 3 months should be considered. (Class IIa B) In patients with SCAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered. (Class IIb C)
Prolonging DAPT duration	In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered. (Class IIb A) In patients with MI and high ischemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg bid for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel. (Class IIb B) In patients with ACS treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered. (Class IIa C)	In patients with SCAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered. (Class IIa C) In patients with SCAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and $\leq$30 months may be considered. (Class IIb A)

ACC, American College of Cardiology; AHA, American Heart Association; ACS, acute coronary syndrome; BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ESC, European Society of Cardiology; SIHD, stable ischemic heart disease; NSTE-ACS, non-ST elevation acute coronary syndrome; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; PCI, percutaneous coronary intervention; SCAD, stable coronary artery disease; STEMI, ST-segment elevation myocardial infarction.

Individualizing duration of DAPT

As stated previously, an individualized approach based on the balance between ischemic and hemorrhagic risks is mandatory in order to decide the length of DAPT in patients receiving coronary stenting. Multiple factors have been proposed to modify the risk of ischemic and/or bleeding events, which can be grouped together into the following categories: patient-, procedure-, or device-related factors (Fig. 2).

Patient-related factors

Numerous clinical factors have been associated with worse prognosis in patients undergoing coronary stenting (clinical presentation, age, diabetes mellitus, chronic kidney disease, smoking status, peripheral artery disease, etc.). Since intensity and optimal duration of DAPT depend on weighing the risks of atherothrombotic and hemorrhagic events, it is intuitive to assume that patients with greater ischemic risk would obtain a larger benefit of more potent and longer DAPT regimens. Among factors associated with worse prognosis, the clinical presentation (SCAD or ACS) at the time of PCI is a major determinant of adverse events, including mortality, which is the rationale behind the general recommendation of longer DAPT in ACS compared to SCAD patients endorsed by current guidelines [12,13]. The results of a subgroup analysis of the DAPT trial support this recommendation, as the reduction in major adverse cardiovascular and cerebrovascular events achieved with the 30-month prolonged DAPT was greater in patients presenting with MI (30.7%) at the time of PCI (3.9% vs. 6.8%; $p < 0.001$) compared to those without MI (4.4% vs. 5.3%; $p = 0.08$), showing a statistically significant interaction ($p = 0.03$). Despite extended DAPT increased bleeding in both groups (MI patients: 1.9% vs. 0.8%; $p = 0.005$; non-MI patients: 2.6% vs. 1.7%; $p = 0.007$), no significant interaction was observed

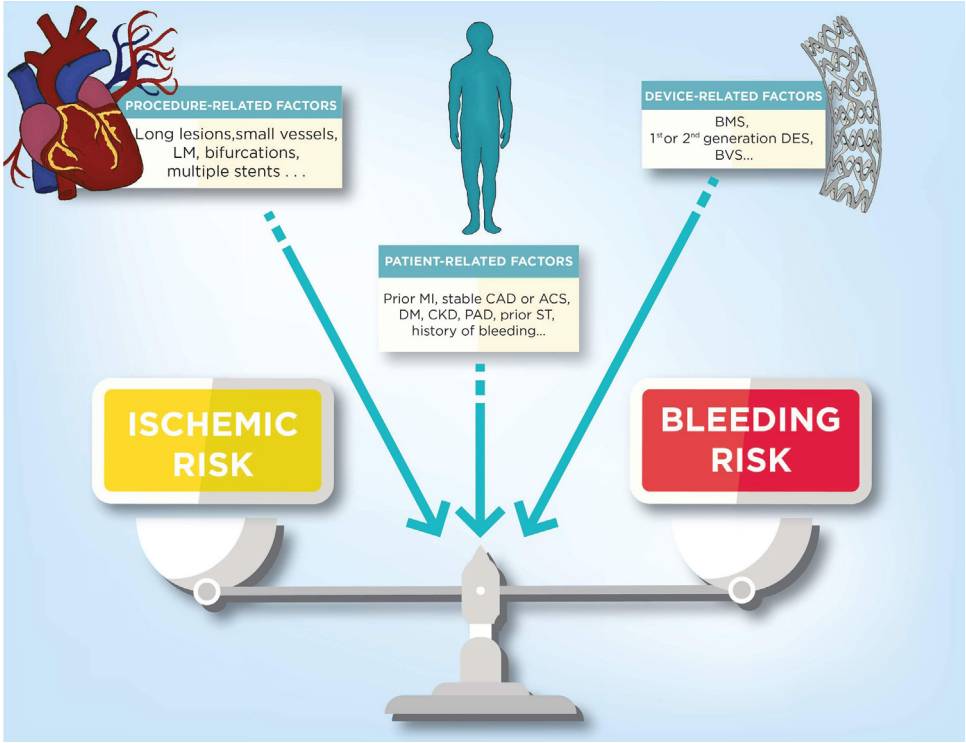

Fig. 2. Factors to consider when deciding DAPT duration after coronary stenting. ACS, acute coronary syndrome; BMS, bare-metal stent; BVS, bioresorbable vascular scaffold; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DM, diabetes mellitus; LM, left main; MI, myocardial infarction; PAD, peripheral artery disease; ST, stent thrombosis.

(p = 0.21) [38]. In line with this concept, an individual patient data (n = 11,473) meta-analysis showed that shortening DAPT to 3 months, but not to 6 months, was associated with higher rates of MI or definite or probable ST when compared to 1-year DAPT in patients with ACS (most of them with unstable angina, thus, of relative low risk), whereas no differences were found in SCAD subjects. As expected, rates of major bleeding were lower with short DAPT length, irrespective of clinical presentation [39].

The evidence for long-term DAPT in high-risk patients due to a prior MI is based mainly on the results of the PEGASUS-TIMI 54 trial and a subgroup analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial [37,40]. In brief, the CHARISMA trial compared DAPT (clopidogrel and aspirin) with aspirin monotherapy in patients (n = 15,603) deemed at high risk of suffering a cardiovascular event without finding significant differences between the two study arms in the rates of the primary endpoint (composite of cardiovascular death, MI, or stroke) at a median follow-up of 28 months [41]. However, DAPT was associated with a reduction in the primary endpoint in a prespecified subgroup analysis of patients with clinically evident atherothrombosis (6.9% vs. 7.9%; RR 0.88; 95% CI, 0.77–1.00; p = 0.046) [41]. Further, a post hoc analysis including patients with documented history of MI, stroke, or symptomatic peripheral artery disease showed a benefit among patients with prior MI (n = 3846) of long-term DAPT compared to aspirin monotherapy (6.6% vs. 8.3%; HR 0.77; 95% CI, 0.64–0.98; p = 0.03) [40]. Remarkably, the PEGASUS-TIMI 54 trial was specifically designed to investigate the potential benefit of DAPT (ticagrelor in addition to aspirin) beyond 1 year after a MI. Patients (n = 21,162) with prior history of MI 1–3 years before enrolment and an additional cardiovascular risk factor were randomized 1:1:1 to receive ticagrelor 90 mg bid, ticagrelor 60 mg bid, or placebo. The two ticagrelor doses significantly reduced the rate of the composite primary efficacy endpoint (cardiovascular death, MI, or stroke) when compared to placebo, but the 60-mg dose showed a slightly better profile in terms of bleeding than the 90-mg dose. The 60-mg dose of ticagrelor reduced the primary efficacy endpoint at 3 years compared to placebo (7.8% vs. 9.0%; HR 0.84; 95% CI, 0.74–0.95; p = 0.004), at the cost of increased major bleeding (2.3% vs. 1.1%; HR 2.32; 95% CI, 1.68–3.21; $p < 0.001$) [37]. In addition, the results of a meta-analysis comparing extended (>12 months) to standard (12 months) DAPT in high-risk patients (n = 33,435) with a history of prior MI showed that DAPT beyond 1 year decreased ischemic outcomes (including reduced individual rates of cardiovascular death, recurrent MI, and stroke) at the cost of increased risk of major bleeding [42]. Overall, these findings support the concepts that optimal DAPT duration may differ according to clinical presentation and that high-risk subgroups, such as patients with history of prior MI, may benefit more from extended courses of DAPT, but always considering the balance between ischemic and bleeding risks.

Individuals requiring long-term oral anticoagulation, mostly due to the presence of atrial fibrillation, represent a high-risk population in terms of bleeding risk. Shortening the duration of triple therapy to the indispensable minimal length to protect against ischemic events and using direct oral anticoagulants instead of vitamin k antagonists are recommendable strategies to reduce hemorrhagic events [43,44]. However, a thorough revision of the particularities of long-term antithrombotic therapy in this subset of patients is beyond the scope of this manuscript.

Procedure-related factors

The complexity of PCI procedures is also considered a relevant aspect associated with higher risk of short- and long-term ischemic events. Several factors can play a role in this relationship between coronary anatomy and/or procedural complexity and atherothrombotic risk. For instance, patients with advanced coronary artery disease are more likely to have several comorbidities (e.g. diabetes mellitus, chronic kidney disease, etc.) that may

cause in turn a more accelerated progression of atherosclerotic disease. Further, several features associated with complex procedures (e.g. large number of stents implanted, small-sized vessels, long length of stents, two-stent bifurcation techniques, calcified lesions that may cause underexpansion of the implanted devices, etc.) are known to be related with increased risk of events, particularly with ST [45,46].

It is difficult and challenging to evaluate the complexity of PCI in a given trial, and even more to compare it across different studies. However, it is worth mentioning the commendable work by Giustino and colleagues that performed a post hoc patient-level pooled analysis of randomized controlled trials with the objective to evaluate the efficacy and safety of long-term (≥1 year) versus short-term (3 or 6 months) DAPT according to the complexity of PCI [47]. A complex PCI was defined as having at least one of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. As expected, patients undergoing complex PCI had a greater risk of adverse ischemic events (composite of cardiac death, MI, or ST). Long-term DAPT significantly reduced ischemic events compared to short-term DAPT in the complex PCI group (4.1% vs 6.8%; adjusted HR 0.56; 95% CI 0.35–0.89), whereas no difference was observed in the noncomplex PCI group (2.9% vs. 2.9%; adjusted HR 0.01; 95% CI 0.75–1.35), observing a statistically significant interaction ($p = 0.01$). Long-term DAPT was associated with augmented risk of major bleeding, irrespective of PCI complexity. Noteworthy, the magnitude of the benefit achieved with long-term DAPT was progressively greater as PCI complexity increased [47]. Therefore, patients with advanced coronary artery disease and/or undergoing complex PCI procedures can be considered at higher risk of ischemic events and may benefit from prolonged DAPT.

Device-related factors

The type of implanted device (stent or bioresorbable scaffold) may also be relevant when selecting DAPT duration [48]. Current evidence suggests that the newer-generation DES are associated with a lower risk of device-related events, particularly ST, than first-generation DES or even BMS [49–51]. Despite that there are limited data evaluating if the stent type may influence DAPT duration, available information advocates that longer DAPT courses could be more favorable in patients treated with first-generation DES than in patients receiving newer-generation DES [28]. However, this concern can be considered irrelevant nowadays since first-generation DES are no longer available for clinical use. To date, there is no clear evidence to suggest that different DAPT courses should be recommended among newer-generation stents.

Several studies have recently showed that contemporary DES have greater efficacy and safety in terms of device-related events than BMS in patients with high risk of bleeding in whom a short DAPT duration was prescribed as per protocol [52–54]. It is important to note that these studies actually compared devices and not durations of therapy, since no randomized trial has evaluated to date if an abbreviated DAPT course is safer than the standard DAPT duration in patients deemed at high bleeding risk. This matter will be evaluated in the currently ongoing MASTER-DAPT trial (NCT03023020).

The introduction of BVS into clinical practice has raised concerns regarding optimal duration of DAPT when these devices are implanted. The Absorb BVS (Abbot Vascular, Santa Clara, CA, USA) was the first bioresorbable scaffold for clinical use, but its commercialization has been stopped due to the higher rates of scaffold thrombosis (especially late and very late events) associated with this device [55,56]. It has been advocated that prolonging DAPT duration may be advisable in patients treated with BVS beyond 12 months who have not suffered a bleeding event during the first year of treatment [48,57], which may be due to the observation that the majority of very late device thrombosis with the Absorb BVS occur in the absence of DAPT [55]. Further investigation is warranted in order to determine if the same concerns apply to newer generation of bioresorbable devices (e.g. polylactic acid or magnesium-alloy scaffolds).

Use of scores

Physicians often find it challenging in real-life clinical practice to identify subjects that may benefit from shorter or longer DAPT duration. In fact, one of the difficulties is that certain factors or conditions (e.g. age) are associated with both ischemic and bleeding outcomes. This has led to the development in recent years of scores specifically designed to predict these risks and, therefore, help in the decision-making process [58–60]. A detailed description of the pros and cons of these risk scores has been provided elsewhere [61]. It is worth mentioning, however, that the DAPT and PRECISE-DAPT scores have been derived from cohorts of patients from randomized clinical trials evaluating different DAPT courses and, consequently, have been specifically designed to inform and guide decision-making on DAPT duration. Hence, recent ESC guidelines recommend their use may be considered as guidance and prioritize them over other available scores [12].

In brief, the DAPT score aims to select patients who derive a benefit from prolonging DAPT (score ≥2), taking into consideration both ischemic and bleeding risks. Conversely, the PRECISE-DAPT score intends to identify patients at high risk of bleeding (score ≥25) in whom selecting a short period of DAPT may be beneficial. Although the combination of these two scores may be an appealing strategy in order to select treatment duration [36], it is important to note that these tools have a number of limitations. First and foremost, none of these predictive models have been prospectively tested in the setting of a randomized clinical trial to evaluate if a strategy based on the use of scores is actually of value [12,62]. Other issues are a moderate to good, but not optimal, accuracy of these models, or the fact that the risk of suffering an ischemic or hemorrhagic complication may change over time (e.g. some variables included in the scores are modifiable). Indeed, it must be emphasized that these scores might be helpful tools to inform decisions, but the clinical judgment must prevail based on a case-by-case careful evaluation of all factors potentially associated with ischemic and bleeding risks.

Future options

Optimization of antithrombotic therapy after coronary stenting is critical in order to improve clinical outcomes and, therefore, is the subject of intense investigation nowadays. Current efforts are focused not only in evaluating different durations of DAPT, but also in finding alternatives to conventional DAPT (aspirin in addition to a single $P2Y_{12}$ inhibitor for the specified course of dual treatment). Despite a detailed description of these investigations not being the goal of the present review, it is worth briefly mentioning several strategies that are currently being explored and/or that might become suitable alternatives for certain clinical scenarios in the near future. First, de-escalation of $P2Y_{12}$ antagonists, which consists of switching from a potent agent (prasugrel or ticagrelor) during the acute phase following ACS undergoing PCI to clopidogrel in the maintenance phase. This strategy has been recently tested in two trials [63,64], one of them guided with platelet function testing [64], with promising results in terms of safety, although further investigation is warranted in order to understand the subgroups of patients that could potentially benefit from this approach. Second, dual therapy with low-dose

rivaroxaban (instead of aspirin) in addition to a $P2Y_{12}$ inhibitor, but no differences in efficacy or safety of this strategy compared to standard DAPT with aspirin have been observed so far in ACS patients undergoing PCI [65]. Finally, several ongoing studies aim to assess if monotherapy with a $P2Y_{12}$ inhibitor (after a short period of DAPT) is superior to DAPT followed by aspirin monotherapy. The GLOBAL LEADERS (NCT01813435) and the TWILIGHT (NCT02270242) trials are evaluating this approach using ticagrelor as the $P2Y_{12}$ inhibitor of choice, whereas the STOPDAPT-2 (NCT02619760) study is testing this strategy using clopidogrel.

Conclusions

Despite DAPT being one of the most extensively studied treatment strategies in cardiology, its optimal duration after coronary stenting is yet to be determined and the decision for any given patient may be substantially different, depending on a number of factors. Several characteristics related to the patient, the procedure, or the device implanted need to be taken into account on a case-by-case basis when evaluating ischemic and bleeding risks. Noteworthy, the available evidence demands that the "one size fits-all" strategy cannot any longer be applied when deciding the duration of DAPT. Since risk profiles may change or events may occur during follow-up, it is also relevant to consider that the decision for duration can be reassessed during the course of the initially selected regimen. The use of risk scores may help the decision-making process, but clinical judgment is irreplaceable when assessing the trade-off between the potential benefit of reducing ischemic outcomes and the risk of increased bleeding associated with DAPT. Hence, an individualized approach is mandatory when deciding the optimal DAPT duration for each patient in order to maximize its benefits.

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Conflict of interest

JL Ferreiro (corresponding author) reports (a) honoraria for lectures from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics and Pfizer; (b) consulting fees from AstraZeneca, Eli Lilly Co., and Ferrer; (c) research grants from AstraZeneca. LM Lugo declares that she has no conflict of interest.

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