Current Cardiology Reports (2022) 24:277–293
https://doi.org/10.1007/s11886-022-01645-0

INTERVENTIONAL CARDIOLOGY (SR BAILEY AND T HELMY, SECTION EDITORS)

Antiplatelet Therapy in Patients Undergoing Elective Percutaneous Coronary Intervention

Mohammad Alkhalil[1,2,3] · Vladimír Džavík[1] · Deepak L. Bhatt[4] · Roxana Mehran[5] · Shamir R. Mehta[6]

Accepted: 11 November 2021 / Published online: 16 March 2022

Abstract

Purpose of review The evidence for use of dual antiplatelet therapy (DAPT) for patients undergoing percutaneous coronary intervention (PCI) in the elective setting is relatively sparse and is based on data from more than two decades ago. We will review the evidence supporting the use of DAPT with focus on stable patients undergoing elective PCI, including the role of potent P_2Y_{12} inhibitors, modified DAPT durations, and more recently, aspirin discontinuation.

Recent findings Clopidogrel is the recommended P_2Y_{12} inhibitor in the elective PCI setting. The benefit of more potent P_2Y_{12} inhibitors such as ticagrelor or prasugrel in stable patients is unproven, but their use might be reasonable in those with high clinical or angiographic features of increased ischemic risk without increased risk of bleeding. Moreover, extending DAPT beyond 12 months is associated with a reduction in ischemic events but also increased bleeding. In contrast, shortening DAPT (3–6 months) reduces bleeding compared with 1 year of treatment, but it is also probably associated with increased ischemic events, mainly in higher-risk patients undergoing complex PCI. Recently, early aspirin discontinuation at 3 months (and perhaps as early as 1 month) following PCI reduces bleeding, with no evidence to suggest an increase in ischemic events.

Summary Clopidogrel is the P_2Y_{12} inhibitor of choice, while more data are required to support the use of more potent P_2Y_{12} inhibitors in stable patients. The duration of DAPT should be tailored to individual patient ischemic and bleeding risks. New strategies, such as early aspirin discontinuation, are promising to reduce bleeding risk without increase in ischemic risk.

Keywords Clopidogrel · Ticagrelor · Prasugrel · Coronary artery disease · PCI · Bleeding risk

This article is part of the Topical Collection on *Interventional Cardiology*

✉ Shamir R. Mehta
smehta@mcmaster.ca

1 Division of Cardiology, Peter Munk Cardiac Centre, Toronto General Hospital, Toronto, Canada

2 Cardiothoracic Centre, Freeman Hospital, Newcastle-upon-Tyne, UK

3 Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, UK

4 Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA

5 Icahn School of Medicine at Mount Sinai, New York, NY, USA

6 Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Abbreviations

ALPHEUS	Assessment of Loading With the P_2Y_{12} Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting
ACS	Acute coronary syndrome
BARC	Bleeding Academic Research Consortium
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
COMMIT	ClOpidogrel and Metoprolol in Myocardial Infarction Trial
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies

CREDO	Clopidogrel for the Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
DAPT	Dual antiplatelet
HOST-EXAM	Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention
MI	Myocardial infarction
PARIS	Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients
PCI	Percutaneous coronary intervention
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 54
SASSICAIA	Strategies of Loading With Prasugrel Versus Clopidogrel in PCI-Treated Biomarker Negative Angina
STEMI	ST-elevation myocardial infarction
THEMIS	Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study
TICO	Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome
TWILIGHT	Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention

Introduction

The role of antiplatelet therapy was recognized early as a therapeutic strategy to mitigate the risk of stent thrombosis after PCI [1, 2]. It is almost a quarter of a century since the publication of the first randomized clinical trial that demonstrated the benefit of DAPT therapy over oral anticoagulation using warfarin in patients undergoing PCI with stents [2]. Likewise, the use of DAPT was also associated with a significant reduction in stent thrombosis compared to aspirin only [1]. Notably, the benefits of DAPT were not merely related to stented segments, but a significant reduction in MI was also reported highlighting the beneficial role of DAPT in non-stented segments [1–3]. The CURE trial was an early landmark randomized trial, establishing the benefit of adding clopidogrel to aspirin in patients with ACS without ST-segment elevation [4]. The benefit of clopidogrel was clear and consistent in patients undergoing PCI [5], as well as those undergoing CABG surgery and in those treated without revascularization [6]. In the COMMIT trial, clopidogrel resulted in a significant reduction of hard clinical outcomes (death and reinfarction) in patients presenting with STEMI [7]. By contrast, in patients undergoing elective PCI for stable ischemic heart disease, there is a paucity of adequately powered clinical trials evaluating antiplatelet therapy. There are even less data supporting the use of the more potent P_2Y_{12} inhibitors, ticagrelor, or prasugrel in the elective PCI setting. In this article, we review the role of DAPT following PCI in patients with stable ischemic heart disease undergoing PCI and provide further insights into the role of more potent P_2Y_{12} inhibitors, DAPT duration, and novel approach of aspirin discontinuation following PCI.

Role of Aspirin, Clopidogrel, and Potent P_2Y_{12} Inhibitors in Elective PCI

Short-term aspirin and long-term warfarin (up to 9 months) were initially used to reduce the risk of stent thrombosis after PCI [8]. This regimen fell out of favor after the importance of antiplatelet therapy was recognized as key to preventing thrombosis at the site of disrupted endothelium following PCI [9, 10]. Moreover, the need for DAPT, as opposed to a single antiplatelet after coronary stenting, was highlighted in a meta-analysis combining existing major randomized trials [1, 11, 12•]. The odds of death or MI was reduced by almost 80% when using aspirin and ticlopidine compared to aspirin alone [1]. Similarly, the odds of death or MI was halved using aspirin and ticlopidine when compared to aspirin and oral anticoagulation [1].

Nonetheless, the safety profile of ticlopidine limited its use and clopidogrel was demonstrated to be a better alternative [13]. While data supporting the incremental benefit of adding clopidogrel to aspirin are well established in patients with acute coronary syndromes [4, 5, 7], clopidogrel has not been well studied as adjunctive treatment in elective coronary stenting. The CREDO trial evaluated the effects of preloading and long-term therapy with clopidogrel added to aspirin, in 2,116 patients undergoing PCI or at high likelihood of undergoing PCI [14]. One-year treatment with clopidogrel reduced the composite of death, MI, or stroke by 27% compared with one-month of clopidogrel [14]. Importantly, the CREDO trial had 33% stable patients (350 patients in each group), with consistent effects of long-term DAPT in this group. The CHARISMA trial included 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel plus low-dose aspirin or placebo plus low-dose aspirin for a median of 28 months [15]. There was no differential treatment effect according to previous PCI history

challenging inference of antiplatelet strategy of symptomatic atherothrombosis to the elective setting (Table 1) [15].

The advent of potent P_2Y_{12} inhibitors, prasugrel and ticagrelor, improved ischemic outcomes in patients with ACS at the cost of more bleeding, compared with clopidogrel [16, 17]. Evidence supporting the use of these more potent P_2Y_{12} inhibitors in the elective setting is relatively sparse. There have been no adequately powered randomized trials of prasugrel versus clopidogrel in patients with stable CAD undergoing PCI (Table 1).

Recently, the THEMIS trial assessed the potential role of adding ticagrelor to aspirin compared with placebo and aspirin in 19,220 stable patients with diabetes [18]. Patients with previous MI or stroke were excluded from the study. The combination of ticagrelor and aspirin compared with placebo and aspirin reduced the composite of cardiovascular death, MI, or stroke by 10% (7.7% vs. 8.5%; HR 0.90; 95%CI, 0.81 to 0.99) [18]. Ticagrelor reduced the primary endpoint by 15% in patients with previous PCI (7.3% vs. 8.6%; HR 0.85; 95% CI, 0.74 to 0.97) with no difference between the two groups in patients without previous PCI history [19•]. These ischemic benefits were offset by increased risk of major bleeding from 1.1% to 2% in those with previous PCI. Nonetheless, ticagrelor improved the net benefit (defined as all-cause mortality, myocardial infarction, stroke, fatal bleeding, and intracranial hemorrhage) in patients with previous PCI (9.3% versus 11%), whereas there were no net benefit in patients without previous PCI (11.1% versus 10.5%) ($P_{interaction} = 0.012$) [19•]. Based on the results from THEMIS and THEMIS-PCI, the US Drug and Food Administration (FDA) approved the use of ticagrelor to reduce the risk of ischemic events, in high-risk patients with CAD. While data from THEMIS and THEMIS-PCI explicitly included diabetic patients, expanding the indication to use ticagrelor to 'high-risk' patients remained unsupported by existing evidence. Additionally, the long-term use of ticagrelor in THEMIS would reopen the debate regarding the optimal duration of using DAPT in patients with stable CAD.

Recently, ticagrelor has been assessed as alternative to clopidogrel ALPHEUS trial [20]. This was an open label multicentral trial that randomized 1,910 stable patients to receive either ticagrelor or clopidogrel following elective PCI [20]. There was no difference in procedural MI (the primary endpoint) or major bleeding between ticagrelor and clopidogrel groups [20]. Importantly, the study was not powered to detect difference in clinical events.

Duration of Dual Antiplatelet Treatment in Elective PCI

Data from small randomized trials were conflicting regarding extending DAPT beyond 12 months (Table 2) [21–23]. The DAPT trial was designed and powered to address this question. It included 9,961 patients who had undergone coronary stenting and only tolerated one year of DAPT without ischemic or bleeding events [24]. Patients, of which 57% had stable clinical presentation and one-third received prasugrel, were randomized to continue thienopyridine drug (clopidogrel or prasugrel) and aspirin or to receive placebo and aspirin. After 18-month follow-up, continuing DAPT reduced a composite endpoints of death, MI, or stroke by 29% (4.3% versus 5.9%, HR 0.71; 95% CI, 0.59 to 0.85) (Table 2) [24]. Extending DAPT reduced the risk of stent thrombosis (0.4% versus 1.4%, $P < 0.001$) and MI related to non-stented segments (1.8% vs. 2.9%, $P < 0.001$) [24]. These effects were consistent irrespective of previous MI history [24]. Importantly, extending DAPT was associated with increased rate of all-cause mortality (2% vs. 1.5%, $P = 0.05$) which was mainly driven by a significant difference in non-cardiovascular mortality (1% vs. 0.5%, $P = 0.002$). Additionally, prolonging DAPT caused a significant increase in moderate or severe bleeding which was evident irrespective of previous MI history ($P_{interaction} = 0.34$) [24].

Further evidence supporting the role of prolonging DAPT but with a caveat of increased bleeding risk came from the PEGASUS-TIMI 54 trial [25]. It randomized, in a double-blind 1:1:1 fashion, 21,162 patients to receive ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, and placebo in addition to low dose aspirin for a median of 33 months. The design of the PEGASUS trial had two distinctive features to separate it from the DAPT trial, although they both address a relatively similar hypothesis. Firstly, it targeted patients who had MI 1 to 3 years before enrolment, unlike the DAPT trial whereby it had a wider spectrum of CAD presentation. This time frame is beyond the recommended duration of DAPT following ACS and patients are no longer considered having unstable coronary presentation. Secondly, the PEGASUS trial did not exclude those patients who sustained bleeding or ischemic events prior to adding thienopyridine to aspirin; nonetheless, it excluded patients if they had a bleeding disorder, a history stroke, gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days [25]. The combination of aspirin and ticagrelor (60 mg twice daily) resulted in 16% reduction in a composite endpoints of cardiovascular death, MI, or stroke (7.8% versus 9.0%, HR 0.84; 95% CI, 0.74 to 0.95) but was associated with a higher rate of major bleeding (2.3% versus 1.1%, $P < 0.001$) [25]. The effect of ticagrelor was consistent irrespective of time from qualifying MI to randomization, previous history of PCI, or the presence of multivessel CAD. [25, 26].

The cumulative evidence from DAPT, PEGASUS, and other trials including meta-analyses highlight the reduction in ischemic events with extending DAPT [24, 25, 27]. Combining data from the reported subgroups analyses targeting

Table 1 Antiplatelet therapy in patients with stable coronary artery disease

Study	Cohort	PCI (%)	Experiment	Comparator	Intervention	Follow-up	Efficacy	Bleeding risk
CREDO 2002 [14]	Elective PCI or high likelihood of undergoing PCI	86%	Clopidogrel & aspirin	Aspirin & placebo	At 28 days post-PCI, clopidogrel was continued, whereas the control group received placebo (both groups received aspirin & clopidogrel for 4 weeks).*	12 months	Death, MI & stroke RR 0.73 95%CI (0.56 to 0.96)	TIMI major bleeding RR 1.32 95%CI (0.97 to 1.80)
CHARISMA 2006 [15]	Clinically evident vascular disease or multiple risk factors	23%	Clopidogrel & aspirin	Aspirin & placebo	Any established indication for clopidogrel, including post-revascularization, was excluded	28 months	Cardiovascular death, MI & stroke RR 0.93 95%CI (0.83 to 1.05)	Severe GUSTO bleeding RR 1.25 95% (0.97 to 1.61)
ASCET 2012 [64]	Angiographically documented CAD	73%	Clopidogrel	Aspirin	Aspirin-treated stable CAD to stay on aspirin or change to clopidogrel	24 months	Death, MI, stroke and unstable angina RR 0.97 95%CI (0.66 to 1.42)	Major bleeding[$] RR 2.52 95%CI (0.49 to 12.96)
JUMBO TIMI-26 2005 [65]	Patients undergoing elective or urgent PCI	100%	Prasugrel	Clopidogrel	After diagnostic angiogram, subjects were randomized to either clopidogrel or prasugrel (3 regimens were tested low dose 40 mg loading dose followed by 7.5 mg daily, intermediate dose 60 mg loading dose followed by 10 mg daily, or high dose 60 mg loading dose followed by 15 mg daily	1 month	Death, MI, stroke, unstable angina requiring hospitalization or clinical target vessel thrombosis HR 0.76 95%CI (0.46 to 1.24)	TIMI major bleeding HR 0.58 95%CI (0.10 to 3.46)
PRASFIT 2014 [66]	Elective PCI	100%	Prasugrel	Clopidogrel	Patients were randomized to prasugrel (20 mg loading dose followed by 3.75 mg daily) an optimal dose for Japanese patients and was administered 6–96 h before PCI	6–12 months	Cardiovascular death, MI, or stroke RR 0.60 95%CI (0.32 to 1.14)	TIMI major bleeding (0% vs. 2.2%)

Table 1 (continued)

Study	Cohort	PCI (%)	Experiment	Comparator	Intervention	Follow-up	Efficacy	Bleeding risk
PEGASUS 2015 [25]	Stable patients with previous MI	83%	Ticagrelor & aspirin	Placebo & aspirin	Patients with previous MI (1–3 years) and additional risk factor based on age ≥ 65, diabetes mellitus, recurrent spontaneous MI, multivessel CAD, or CKD (CrCl < 60 ml/min)	33 months	Cardiovascular death, MI, or stroke HR 0.84 95%CI (0.74 to 0.95) [$$]	TIMI major bleeding HR 2.32 95%CI (1.68 to 3.21)[$$]
DACAB 2018 [67]	Elective CABG	-	Ticagrelor & aspirin	Aspirin	Antiplatelet therapy started within 24 h post-CABG	12 months	Cardiovascular death, MI & stroke RR 033 95%CI (0.09 to 1.22)	TIMI major bleeding (1.8% vs.0%)
DACAB 2018 [67]	Elective CABG	-	Ticagrelor	Aspirin	Antiplatelet therapy started within 24 h post-CABG	12 months	Cardiovascular death, MI & stroke RR 044 95%CI (0.14 to 1.44)	TIMI major bleeding (1.2% vs.0%)
TiCAB 2019 [68]	CABG for stable or ACS presentation	-	Ticagrelor and placebo	Aspirin and placebo	Antiplatelet therapy started within 24 h, and ideally within 6 h	12 months	Cardiovascular death, MI, stroke & repeat revascularization HR 1.19 95%CI (0.87 to 1.62)	BARC ≥ 4 for peri-procedural and hospital stay-related bleedings and BARC ≥ 3 for post-discharge bleedings HR 1.17 95%CI (0.71–1.92)
THEMIS 2019 [18, 19]	Stable CAD and type II diabetes	58%	Ticagrelor & aspirin	Placebo & aspirin	Previous MI or stroke were excluded. The presence of stable CAD defined as history of PCI, CABG, or angiographic stenosis of ≥ 50% in ≥ one coronary artery	40 months	Cardiovascular death, MI & stroke HR 0.90 95%CI (0.81 to 0.99)	TIMI major bleeding HR 2.32 95%CI (1.82 to 2.94)
EUCLID 2017 [69]	Patients with symptomatic PVD	54%	Ticagrelor	Clopidogrel	Subgroup analysis of patients with PVD and concomitant CAD	30 months	Cardiovascular death, MI, or stroke HR 1.02 95%CI (0.87 to 1.19)	TIMI major bleeding HR 1.06 95%CI (0.66 to 1.69)
Zheng et al., 2019 [70]	Patients undergoing PCI for bifurcation lesions	100%	Ticagrelor	clopidogrel	Retrospective analysis with propensity score matching	12 months	Cardiac death, MI, or stroke HR 0.40 95%CI (0.22 to 0.75)	BARC ≥ 3 major bleeding HR 0.71 95%CI (0.19 to 2.67)

[*]The experimental group received 300 mg loading dose of clopidogrel compared to placebo in the control group; [$]Major bleeding defined as intracranial bleeding, bleeding requiring transfusion of blood or surgical intervention; [$$]Hazard ratio for 60 mg ticagrelor versus placebo. BARC: Bleeding Academic Research Consortium, CAD: coronary artery disease, CKD: chronic kidney disease, CrCL: creatinine clearance, GUSTO: Global Strategies for Opening Occluded Coronary Arteries, HR: hazard ratio, MI: myocardial infarction, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction

Table 2 Duration of dual antiplatelet therapy for patients with stable coronary artery disease

Study	Stable patients (%)	Experiment	Comparator	Efficacy	Bleeding risk	Change in absolute thrombotic risk	Change in absolute bleeding risk
REAL-LATE/ ZEST-LATE 2010 [21]	38%	Aspirin & clopidogrel. Randomization occurred at 12 months after stenting in patients who had been free of thrombotic or bleeding events. 83% remained on clopidogrel after 24 months of randomization	Aspirin only. 4% were taking clopidogrel at 24 months after randomization	24 months of cardiac death or MI HR 1.65 95%CI (0.80 to 3.36)	TIMI major bleeding HR 2.96 95%CI (0.31 to 28.46)	+0.6% (1.8% vs. 1.2%)	+0.1% (0.2% vs. 0.1%)
DES LATE 2014 [23]	39%	Aspirin & clopidogrel. Randomization occurred at 12 months after stenting in patients who had been free of thrombotic or bleeding events. 79% remained on clopidogrel after 24 months of randomization	Aspirin only. 8% were taking clopidogrel at 24 months after randomization	24 months cardiac death, MI, or stroke HR 0.94 95%CI (0.66 to 1.35).[$] In the stable subgroup HR 0.92 95%CI (0.53 to 1.61).[$]	TIMI major bleeding HR 0.71 95%CI (0.42 to 1.20).[$]	+0.2% (2.6% vs. 2.4%)	+0.3% (1.4% vs. 1.1%)
ARCTIC-Interruption 2014 [22]	74%	Aspirin & clopidogrel or prasugrel. Randomization occurred at 12 months after commencing dual antiplatelet. 77% remained on thienopyridine at median follow up of 17 months	Aspirin only. 17% were on thienopyridine at median follow up of 17 months	Death, MI, stent thrombosis, stroke, urgent revascularization HR 1.17 95%CI (0.68 to 2.03).[$] In the stable subgroup HR 1.13 95%CI (0.59 to 2.15).[$]	STEEPLE major bleeding HR 0.15 95%CI (0.02 to 1.20).[$]	0% (4% vs. 4%)	+0.9% (1% vs. < 0.1%)
OPTIDUAL 2016 [71]	53%	Aspirin & clopidogrel. Randomization occurred at 12 months after stenting in patients who had been free of thrombotic or bleeding events. Median follow up was 34 months	Aspirin only (median follow-up was 34 months)	Death, MI, or stroke HR 0.64 95%CI (0.40 to 1.02)	TIMI major bleeding risk difference 0 95%CI (-0.8 to 0.8)	-2.2% (4.2% vs. 6.4%)	0% (0.6% vs. 0.6%)

Table 2 (continued)

Study	Stable patients (%)	Experiment	Comparator	Efficacy	Bleeding risk	Change in absolute thrombotic risk	Change in absolute bleeding risk
DAPT 2014 [72]	57%	Aspirin & clopidogrel or prasugrel. Randomization occurred at 12 months after stenting in patients who had been free of thrombotic or bleeding events. 79% remained on thienopyridine at 30-month follow-up	Aspirin only	Death, MI, or stroke HR 0.71 95% CI (0.59 to 0.85). In the clopidogrel subgroup HR 0.80 95%CI (0.64 to 1.01)	GUSTO moderate or severe bleeding HR 1.61 95%CI 1.21 to 2.16)	-1.6% (4.3% vs. 5.9%)	+0.9% (2.5% vs. 1.6%)
EXCELLENT 2012 [58]	48%	Aspirin & clopidogrel for 6 months. Randomization occurred before PCI. Median duration of dual antiplatelet 190 (181 to 260) days	Aspirin & clopidogrel for 12 months	12 months cardiac death, MI, or ischemia-driven target vessel revascularization HR 1.14 95%CI (0.70 to 1.86) In the stable subgroup HR1.61 (0.8 to 3.21)	TIMI major bleeding HR 0.50 95%CI (0.09 to 2.73)	+0.5% (4.8% vs 4.3%)	-0.3% (0.3% vs. 0.6%)
RESET 2012 [59]	45%	Aspirin & clopidogrel for 3 months. Randomization occurred before PCI. Duration of dual antiplatelet was 93 ± 28 days	Aspirin & clopidogrel for 12 months	12 months death, MI, or stent thrombosis RR 0.73 95%CI (0.29 to 1.81). In the stable subgroup RR 0.80 95%CI (0.49 to 1.31).*	Academic Research Consortium major bleeding RR 0.33 95%CI (0.07 to 1.65)	-0.5% (0.8% vs. 1.3%)	-0.4% (0.2 vs. 0.6%)
OPTIMIZE 2013 [60]	68%	Aspirin & clopidogrel for 3 months. Randomization occurred before PCI. 6% remained on clopidogrel at 12 months	Aspirin & clopidogrel for 12 months	12 months death, MI, or stent thrombosis HR 1.11 95%CI (0.79 to 1.55). In the stable subgroup HR 1.04 95%CI (0.72 to 1.49).*	Modified major REPLACE-2 and severe of life-threatening GUSTO bleeding HR 0.71 95%CI (0.32 to 1.60)	+0.5% (4.7% vs. 4.2%)	-0.3% (0.6% vs. 0.9%)
SECURITY 2014 [73]	62%	Aspirin & clopidogrel for 6 months. Randomization occurred after PCI. 34% remained on clopidogrel at 12 months	Aspirin & clopidogrel for 12 months	12 months cardiac death, MI, stroke, definite or probable stent thrombosis RR 1.21 95%CI (0.72 to 2.02)	BARC type 3 or 5 bleeding RR 0.53 95%CI (0.16 to 1.75)	+0.8% (4.5% vs. 3.7%)	-0.5% (0.6% vs. 1.1%)

Table 2 (continued)

Study	Stable patients (%)	Experiment	Comparator	Efficacy	Bleeding risk	Change in absolute thrombotic risk	Change in absolute bleeding risk
ISAR-SAFE 2015 [61]	48%	Aspirin & placebo for 6 months. Randomization occurred 6 months after PCI	Aspirin and clopidogrel for 6 months	9 months (15 months post-PCI) death, MI, definite or probable stent thrombosis, or stroke HR 0.87 95%CI (0.51 to 1.47). In the stable subgroup at index PCI HR 1.00 95%CI (0.49 to 2.04).*	TIMI major bleeding HR 0.80 95%CI (0.21 to 2.98)	-0.2% (1.3% vs. 1.5%)	-0.1% (0.2% vs. 0.3%)
I-LOVE-IT 2 2016 [62]	18%	Aspirin & clopidogrel for 6 months. Randomization occurred before PCI. 7% remained on clopidogrel at 12 months	Aspirin & clopidogrel for 12 months	18 months cardiac death, target-vessel MI, target-lesion revascularization RR 1.19 95%CI (0.84 to 1.68). In the stable subgroup HR 1.05 95%CI (0.59 to 1.89).*	BARC ≥ 3 bleeding RR 1.88 95%CI (0.75 to 4.71)	+1.2% (7.5% vs. 6.3%)	+0.5% (1.3% vs. 0.8%)
IVUS-XPL 2016 [63]	51%	Aspirin & clopidogrel for 6 months. Randomization occurred before PCI. 9% remained on clopidogrel at 12 months	Aspirin & clopidogrel for 12 months	12 months cardiac death, MI, or target-lesion revascularization HR 1.40 95%CI (0.84 to 2.34). In the stable subgroup HR 1.17 95%CI (0.39 to 3.49).*	TIMI major bleeding HR 0.71 95%CI (0.23 to 2.25)	+1.4% (5.2% vs. 3.8%)	-0.3% (0.7% vs. 1%)
OPTIMA-C 2018 [74]	49%	Aspirin & clopidogrel for 6 months. Randomization occurred before PCI. 11% remained on clopidogrel > 6 months	Aspirin & clopidogrel for 12 months	12 months cardiac death, target-vessel MI, target-lesion revascularization HR 2.02 95%CI (0.61 to 6.72)	TIMI major bleeding HR 1.00 95%CI (0.06 to 16.02)	+0.6% (1.2% vs. 0.6%)	0 (0.1% vs. 0.1%)

*Relative risk for the net clinical benefits of thrombotic and bleeding risk; $hazard ratio of aspirin only versus aspirin & clopidogrel. BARC: Bleeding Academic Research Consortium, CAD: coronary artery disease, GUSTO: Global Strategies for Opening Occluded Coronary Arteries, HR: hazard ratio, MI: myocardial infarction, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction

stable patients with no previous MI is illustrated in Fig. 1A. In a total of 10,761 stable patients, extending DAPT more than 12 months reduced major adverse events by 21% (95% CI; 0.65 to 0.96) although these benefits were mainly derived from the DAPT study (Fig. 1A) [22–24].

Yet, the increased risk of bleeding limited the use of prolong DAPT in everyday clinical practice. Moreover, improvements in stent design including decrease in struts thickness coupled with using more biocompatible or biodegradable polymer have considerably reduced early and late stent thrombogenicty [28]. Furthermore, data from optical coherence tomography studies illustrated that most of the struts were sufficiently covered as early as three months after the implantation of drug-eluting stents [29]. These findings questioned the mandatory use of DAPT for one year and presented a new paradigm whether shorter duration of DAPT may provide adequate ischemic protection with less bleeding risk. Numerous studies, including meta-analyses, have tested this hypothesis and provided an evidence that shortening DAPT (3 to 6 months) was not associated with increased ischemic risk and rather 40–50% reduction in major bleeding [30, 31]. Importantly, these studies were rather heterogeneous with various clinical presentation, DAPT duration, and stent types adding further challenges when interpreting their findings [30–32]. Recently, Khan et al. have conducted a large study-level meta-analysis of 24 randomized-controlled trials investigating the optimal duration of DAPT in 79,073 stable and ACS patients [33]. The authors highlighted the lack of significant differences in the risk of MI, mortality, or major bleeding between short term (< 6 months) or mid-term (6 months) compared to 12-month DAPT [33]. Combining data from published subgroups focusing on stable patients is presented in Fig. 1B. Data from 7,941 stable patients suggest that shortening DAPT was not associated with increased risk of adverse ischemic events when compared to 12-month DAPT [rate ratio (RR) 1.03, 95% CI (0.82 to 1.30)] (Fig. 1B).

Balancing Ischemic and Bleeding Risks

Emerging evidence suggested that shortening DAPT may not be suitable for all PCI procedures. In a pooled analysis of 6 randomized control trials, less than 6-month DAPT was associated with 64% increase in ischemic events when compared with 12 months of DAPT in PCI procedures with complex angiographic features [RR 1.64; 95% CI (1.07 to 2.50)] [34]. Importantly, ischemic events were comparable between the two group in patients with non-complex PCI procedures

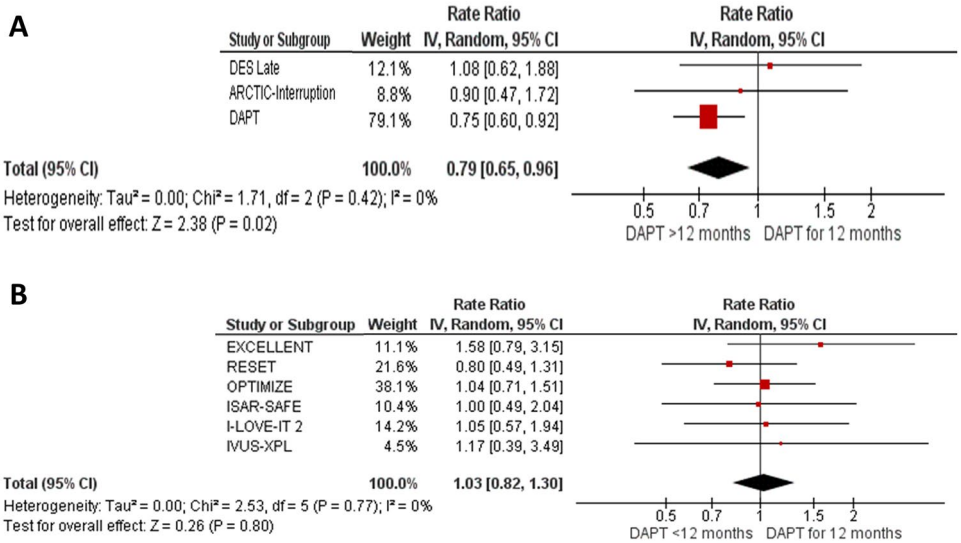

Fig. 1 (A) Meta-analysis of major randomized clinical trials using reported subgroup analyses of stable patients comparing extended DAPT (> 12 months) versus DAPT for 12 months. (B) Meta-analysis of major randomized clinical trials using reported subgroup analyses of stable patients comparing short DAPT (< 12 months) versus DAPT for 12 months. DES late (optimal duration of clopidogrel therapy with DES to reduce late coronary arterial thrombotic event); [23] the ARCTIC (Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting)-Interruption trial; [22] the DAPT (Dual Antiplatelet Therapy) trial [24]. The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial; [58] the RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) trial; [59] the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial; [60] the ISAR-SAFE (Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial; [61] the I-LOVE-IT 2 (Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization) trial; [62] the IVUS-XPL (The Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) trial [63]

($P_{interaction} = 0.01$), although the lack of difference may be related to the limited power and follow-up of the included studies. Nonetheless, this pooled meta-analysis may suggest a potential role for shortening DAPT in a selected group of PCI procedures. The differential effect of procedural complexity was consistent across patients with stable versus ACS subgroups [34]. The increase in the bleeding risk was evident in patients subjected to 12 months irrespective of the procedural complexity [34]. Similar findings were reported in patients with multivessel disease with almost threefold increase in the risk of MI when comparing 6 months against 12-month DAPT [35]. Clinical features, such as chronic kidney disease, are also considered as high-risk features for ischemic events, but similarly, they also reflect substrates of high bleeding risk and their net clinical benefit is not well established [36–38]. Therefore, determining ischemic risk based on clinical and angiographic features should also be coupled with an estimation of bleeding risk to tailor antiplatelet therapy. Notably, the PARIS registry demonstrated that patients with high bleeding risk are also those with high ischemic risk and highlighted that DAPT cessation was higher in patients who are considered at high bleeding risk [39]. Numerous risk score models were developed to aid decision making regarding the duration of antiplatelet therapy [40–42]. These models varied in the number of included clinical and angiographic variables, estimating bleeding risk versus net benefits of ischemic and bleeding risks, and decision regarding extending versus shortening DAPT. The DAPT score was tested in a large nationwide study including more than 40,000 patients in Sweden [43]. It did not adequately discriminate ischemic or bleeding risk challenging its generalizability to real-world patients [43]. On the other hand, the PRECISE-DAPT score was demonstrated to be a useful tool in highlighting patients with high bleeding risk that negates clinical benefits when extending DAPT [44]. Importantly, the DAPT score was developed for patients who had 12 months of DAPT, while the PRECISE-DAPT score was developed to early examine duration of DAPT after coronary stenting. Costa *et el* compared long versus short DAPT according to ischemic (angiographic features) and bleeding (using PRECISE-DAPT score) risks from pooled individual patients data of 8 randomized control trials [44]. The authors showed that long-term DAPT reduced ischemic events only in patients without high risk bleeding features in both complex [absolute risk difference (ARD) –3.86%; 95% CI (–7.71 to + 0.06)] and non-complex PCI [ARD –1.14%; 95% CI (–2.26 to –0.02)] strata [44]. On the other hand, prolong DAPT had comparable ischemic events in patients with high-risk bleeding features irrespective of PCI complexity [complex PCI, ARD + 1.30%; 95% CI (–6.99% to + 9.57%)] and [non-complex PCI, ARD + 1.45%; 95% CI (–1.84% to + 4.72%) [44]. Notably, the increase in bleeding risk when prolonging DAPT was only evident in patients with high-risk bleeding features [44]. Collectively, the main determinant of extending DAPT should be the presence of high bleeding risk rather than high ischemic risk. This recommendation would be particularly useful when there is concordance in bleeding and ischemic risks. More recently, a novel strategy has been tested to reduce bleeding risk, whereby interrupting DAPT was performed by discontinuing aspirin while maintaining P_2Y_{12} inhibitor.

Mitigating Bleeding Risk, Aspirin Discontinuation

Potent P_2Y_{12} inhibitors that provide fast and consistent antiplatelet effects were suggested as a potential strategy to preempt the mandatory role of aspirin following PCI [45]. Five randomized control trials were designed to test the safety and efficacy of aspirin withdrawal following PCI. One trial targeted ACS patients (TICO trial), while the remaining four included a spectrum of CAD presentations and ticagrelor was tested in two of these studies (Table 3) [46–50].

The GLOBAL-LEADERS trial randomized 15,968 patients after diagnostic coronary angiography but before PCI procedure into aspirin and ticagrelor for 1 month followed by 23 months of ticagrelor monotherapy versus standard therapy (aspirin and clopidogrel for stable patients or aspirin and ticagrelor for ACS followed by aspirin) [48]. The primary endpoint of all-cause mortality or new Q-wave MI was comparable between the experimental and standard groups (3.81% versus 4.37%, P = 0.073) [48]. At 2 years, major bleeding events were similar between the early-aspirin discontinuation and the DAPT groups (2.04% versus 2.12%, P = 0.77) [48]. The results were consistent in patients with ACS or stable angina [48]. In contrast, the TWILIGHT trial randomized 7,119 patients who tolerate DAPT without ischemic or bleeding events for 3 months after their PCI procedures to stop aspirin or to continue DAPT [47]. At 1-year post-randomization, the incidence of the primary endpoint of BARC type 2, 3, and 5 was 4.0% in the placebo plus ticagrelor group compared to 7.1% in the aspirin plus ticagrelor group (HR, 0.56; 95% CI 0.45 to 0.68) [47]. Major bleeding events (BARC 3 or 5) were halved using aspirin-free compared with standard strategy (1% versus 2%; HR, 0.49; 95% CI, 0.33 to 0.74) [47]. The rate of death, MI, or stroke was identical between the two groups (3.9% versus 3.9%) which was also consistent in stable and ACS presentations [47]. The apparent discordant results between the TWILIGHT and GLOBAL-LEADERS trials were likely resided in the different designs between the two trials as highlighted above. Importantly, ticagrelor was used in an off-label fashion during the 3-month 'testing' period following PCI in stable patients of the TWILIGHT study. Overall, the use of ticagrelor for high-risk angiographic features remains unsupported and to be proven.

Table 3 Aspirin withdrawal as a strategy to reduce bleeding risk

Study	Stable patients (%)	Experiment	Comparator	Setting	Efficacy	Bleeding risk	Net clinical benefits
GLOBAL LEADERS 2018 [48]	53%	Aspirin & ticagrelor for 1 month followed by 23 months of ticagrelor monotherapy	Aspirin and either clopidogrel (for stable patients) or ticagrelor (for ACS) for 12 months followed by aspirin monotherapy for 12 months	Randomization occurred after diagnostic angiogram but before PCI	24 months death or MI 3.8% vs. 4.4%; RR 0.87 95%CI (0.75 to 1.01) In the stable subgroup 3.7% vs. 4.2%; RR 0.87 95%CI (0.71 to 1.08)	BARC bleeding grade 3 or 5 2.0% vs. 2.1%; RR 0.97 95%CI (0.78 to 1.20)	Composite of death, MI, stroke, target or non-target vessel revascularization, and BARC type 3 or 5 bleeding RR 0.93 85%CI (0.85 to 1.00)
TWILIGHT 2019 [47]	35%	Ticagrelor & placebo	Ticagrelor & aspirin	Randomization occurred after 3 months treatment with ticagrelor & aspirin in patients who had not had a major bleeding or ischemic events	12 months death, MI, or stroke 3.9% vs. 3.9%; HR 0.99 95%CI (0.78 to 1.25). In the stable subgroup 3.1% vs. 2.9%; HR 1.06 95%CI (0.67 to 1.67)	BARC bleeding grade 3 or 5 1.0% vs. 2.0%; HR 0.49 95%CI (0.33 to 0.74)	Composite of death, MI, stroke, and BARC type 3 or 5 bleeding RR 0.83 95%CI (0.68 to 1.03)
SMART-CHOICE 2019 [49]	42%	Aspirin & P2Y12 inhibitor (77% were on clopidogrel) for 3 months followed by P2Y12 inhibitor alone	Aspirin and P2Y12 inhibitor (78% were on clopidogrel) for at least 12 months	Randomization occurred at the index procedure or at a follow-up visit within 3 months after the index procedure	12 months death, MI, or stroke 2.9% vs. 2.5%; RR 1.17 95%CI (0.75 to 1.82). In the stable subgroup 2.8% vs. 2.0% HR 1.43 95%CI (0.68 to 3.00)	BARC type 3 to 5 bleeding 0.8% vs. 1.0%; RR 0.86 95%CI (0.40 to 1.86)	Composite of death, MI, stroke, and BARC type 2 to 5 bleeding RR 0.80 95%CI (0.58 to 1.11)
STOPDAPT-2 2019 [50]	62%	Aspirin & P2Y12 inhibitor (clopidogrel 60% & prasugrel 40%) for 1 month followed by clopidogrel monotherapy	Aspirin & P2Y12 inhibitor (clopidogrel 63% & prasugrel 37%) for 12 months	Randomization occurred after the index PCI procedure and before hospital discharge	12 months cardiovascular death, MI, stroke, or definite stent thrombosis 1.96% vs. 2.51%; HR 0.79 95%CI (0.49 to 1.29). In the stable subgroup 2.05% vs. 3.49%; HR 0.59 95%CI (0.33 to 1.03).*	BARC type 3 or 5 bleeding 0.54% vs. 1.81%; HR 0.30 95%CI (0.13 to 0.65)	Composite of cardiovascular death, MI, stroke, definite stent thrombosis, and TIMI major or minor bleeding HR 0.64 95%CI (0.42 to 0.98)
O'Donoghue et al., 2020 [51••]	44%	Discontinuation of aspirin 1–3 months after PCI with continued P2Y12 inhibitor monotherapy	Aspirin & P2Y12 inhibitor for 12 months	Various	Major adverse cardiovascular events that were prespecified in each trial 2.73% vs. 3.11%; HR 0.88 95%CI (0.77 to 1.02)	BARC 3 or 5 bleeding 1.22% vs. 1.81%; HR 0.60 95%CI (0.42 to 0.86)	-

*Subgroup analysis for net clinical benefits (combined ischemic and bleeding events). ACS: acute coronary syndrome, BARC: Bleeding Academic Research Consortium, CAD: coronary artery disease, HR: hazard ratio, MI: myocardial infarction, PCI: percutaneous coronary intervention

Recently, a meta-analysis that included all five major trials has shown that aspirin discontinuation after 1–3 months post-PCI was associated with 40% reduction of major bleeding [1.97% versus 3.13%; HR 0.60, 95% CI (0.45 to 0.79)] with no apparent increased risk in major adverse cardiovascular and cerebrovascular events [2.73% vs 3.11%; HR 0.88, (0.77–1.02)] [51••]. An updated analysis using published subgroups data of the four trials, excluding the TICO trial which focused on ACS population, is presented in Fig. 2 and is consistent with the overall results from the meta-analysis by O'Donoghue et al., [RR 0.90, 95% CI (0.70 to 1.16)].

These encouraging results of early aspirin withdrawal were extended to immediately stop aspirin post-PCI [52•]. In this proof of concept single-arm study, 201 patients underwent PCI for stable CAD and immediately received prasugrel treatment, without aspirin, for 3 months after PCI. Importantly, loading with aspirin and clopidogrel pre-PCI was mandatory and only after successful PCI, angiographically or using intra-vascular imaging, patients were reloaded with prasugrel without further aspirin or clopidogrel treatment. No stent thrombosis events occurred in this study [52•].

Long-Term Maintenance Antithrombotic Therapy

Switching from DAPT to a lifelong maintenance of single antiplatelet is indicated as a secondary prevention for cardiovascular disease [53]. Aspirin is the most commonly used antiplatelet therapy and is associated with 20% relative risk reduction in major coronary events including 31% reduction in MI and 13% in coronary mortality [54]. However, the potential gastrointestinal side effects, including bleeding, have steered researchers to assess whether clopidogrel would be more effective in reducing ischemic events with a better safety profile. Recently, the HOST-EXAM study has included 5,438 patients who were maintained on DAPT for 6–18 months following PCI without ischemic or major bleeding complications and subsequently were randomized to receive either clopidogrel 75 mg or aspirin 100 mg [55]. Over 24-month follow-up, clopidogrel was associated with 27% relative risk reduction in the primary endpoint of death, MI, stroke, readmission due to ACS, and BARC bleeding type 3 or greater (HR 0.73,95% CI 0·59–0·90). The thrombotic composite endpoint of cardiac death, MI, ischemic stroke, readmission due to ACS, and definite or probable stent thrombosis was similarly reduced 32% as well as major bleeding (BARC ≥ 3) by 37% when using clopidogrel [55]. The HOST-EXAM study suggested that clopidogrel monotherapy may be superior to aspirin in patients who tolerate it DAPT for at least 6 months following PCI.

An alternative strategy is the use of dual pathway inhibition with aspirin and oral anticoagulation. This is a relatively undertested approach in patients with stable coronary disease. Rivaroxaban is a selective factor Xa inhibitor that was assessed in the COMPASS trial in 27,395 patients with stable atherosclerotic vascular disease [56]. The combination of rivaroxaban (2.5 mg bd) and aspirin was associated with 24% relative risk reduction of the risk of the primary endpoint of cardiovascular death, MI, or stroke (HR 0.76; 95% CI 0.66 to 0.86) and 18% relative risk reduction in mortality compared to aspirin alone (HR 0.82; 95% CI 0.71 to 0.96) [56]. Importantly, combining rivaroxaban with aspirin resulted in reducing the primary endpoint and mortality in stable coronary patients, regardless of whether patients had previous history of PCI [57]. However, major bleeding events occurred more frequently in the combination group but without increased risk in intracranial or fatal bleeding [56, 57].

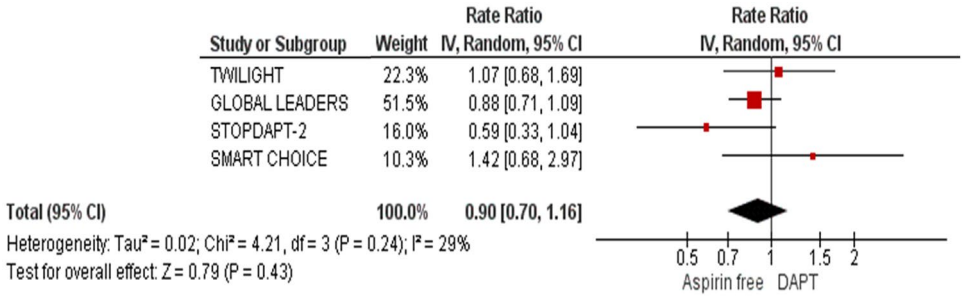

Fig. 2 Meta-analysis of major randomized clinical trials using reported subgroup analyses of stable patients comparing 1–3 months aspirin withdrawal versus DAPT for 12 months. The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial; [47] the GLOBAL LEADERS (Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs. Current-Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use) trial; [48] the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent) trial; [50] the SMART CHOICE (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) trial [49]

Table 4 Summary of DAPT following elective PCI

	Cohort	Recommendation
P_2Y_{12} Type	**Patients with previous MI** (1 year post-MI)	At 12 months, re-assess patients to identify those who tolerate potent P_2Y_{12} inhibitor following MI without bleeding events. This subgroup could continue DAPT with preference for prasugrel or ticagrelor over clopidogrel
	No previous MI	Need to determine ischemic risk and bleeding risk following PCI
	High bleeding risk	Patients should receive clopidogrel, rather than potent P_2Y_{12} inhibitor This recommendation is applicable irrespective of procedural complexity
	Low bleeding risk	Patients with low PCI complexity, Patients may be considered for potent P_2Y_{12} inhibitor (ticagrelor) in addition to aspirin Patients with high PCI complexity, Patients should be considered for potent P_2Y_{12} inhibitor (ticagrelor) in addition to aspirin
P_2Y_{12} duration	**Patients with previous MI** (1 year post-MI)	At 12 months, re-assess patients to identify those who tolerate potent P_2Y_{12} inhibitor following MI without bleeding events. This subgroup could continue DAPT for three years
	No previous MI	Need to determine ischemic risk and bleeding risk following PCI
	High bleeding risk	DAPT for 1–3 months and then aspirin or clopidogrel for life long (this combination is applicable irrespective of procedural complexity)
	Low bleeding risk	Patients with low PCI complexity, DAPT for 6 months and then aspirin or clopidogrel for lifelong Patients with high PCI complexity, DAPT for 12 months. Re-assess and if DAPT were tolerated with no bleeding events then DAPT could be extended beyond 1 year

Summary

Existing data on the role of DAPT following elective PCI have been mainly derived from subgroup analyses with relatively opposing studies on the duration and strategies on using DAPT in patients with CAD. Clopidogrel remains the most frequently used P_2Y_{12} inhibitor following elective PCI. The benefit of ticagrelor or prasugrel in stable CAD population is unproven, but their use might be reasonable in those with high clinical or angiographic features of increased ischemic risk without increased risk of bleeding. Extending DAPT beyond 12 months in patients undergoing PCI with or without ACS is associated with a reduction in ischemic events but also increased bleeding. This long-term DAPT strategy should be considered in patients with high ischemic risk who are not at increased risk of bleeding. In the DAPT trial, there was a heterogeneity of treatment effect according to thienopyridine type that was used [24]. Patients receiving prasugrel sustained larger reduction in ischemic events compared with clopidogrel, while the increase in bleeding risk was similar between prasugrel and clopidogrel. This observation alongside data from the PEGASUS trial would justify the preferred option of extending potent P_2Y_{12} beyond one-year post-MI (Table 4; Fig. 3). In contrast, shortening DAPT (3–6 months) reduces bleeding compared with 1 year of treatment, but it is also probably associated with increased ischemic events, mainly in higher-risk patients undergoing complex PCI. The novel strategy of early aspirin discontinuation at 3 months (and perhaps as early as 1 month) following PCI reduces bleeding, with no evidence to suggest an

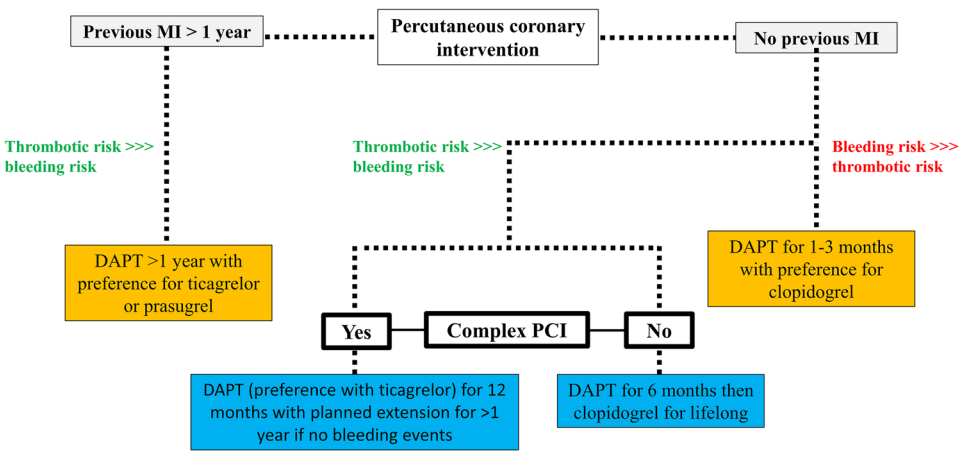

Fig. 3 Proposed flowchart for dual antiplatelet following elective percutaneous coronary intervention. Patients with previous myocardial infarction > 1 year could be considered for extending dual antiplatelet duration, up to 3 years, if they were considered at a low bleeding risk. Patients without previous history of myocardial infarction, factoring bleeding and ischemic risks should guide decision regarding duration and type of antiplatelet therapy

increase in ischemic events. This strategy should be considered as a harm mitigation strategy, especially in patients at higher risk of bleeding from DAPT.

Conclusions

Following PCI, antiplatelet strategies have evolved over the last 4 decades since the first angioplasty procedure. While extending DAPT mitigates ischemic events, this comes with a caveat of increasing bleeding risk. Strategies to reduce bleeding risk have focused on shortening DAPT which may be effective in a selected group of patients without apparent increase in ischemic events. Early aspirin withdrawal is a promising strategy that helps reducing bleeding risk while maintaining ischemic protection.

Compliance with Ethical Standards

Conflict of Interest Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, DRS.LINQ (stock options), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda.

Dr. Mehran reports institutional research payments from Abbott, Abiomed, Alleviant Medical, AMPharma, Applied Therapeutics, Arena, AstraZeneca, BAIM, Bayer, Beth Israel Deaconess, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CellAegis, CeloNova, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Duke University, Element Science, Humacyte, Insel Gruppe AG, Janssen, Magenta, Medtronic, Novartis, OrbusNeich, Philips, Vivasure, Zoll; personal fees from Boston Scientific, California Institute for Regenerative Medicine (CIRM), Cine-Med Research, Janssen, WebMD; consulting fees paid to the institution from Idorsia Pharmaceuticals, Medtronic, Novartis, Philips; Equity < 1% in Applied Therapeutics, Elixir Medical, STEL, CONTROLRAD (spouse); Scientific Advisory Board for AMA, ACC (BOT Member), SCAI (Women in Innovations Committee Member), Biosensors (spouse); Faculty CRF (no fee).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Mehta SR, Yusuf S, Clopidogrel in Unstable angina to prevent Recurrent Events Study I. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J. 2000;21:2033–41.
2. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084–9.
3. Alkhalil M. Mechanistic Insights to Target Atherosclerosis Residual Risk. Curr Probl Cardiol 2019;24. pii:S0146–2806(19)30105–7. https://doi.org/10.1016/j.cpcardiol.2019.06.004. [Epub ahead of print].
4. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502.
5. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients

undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527–33.
6. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004;110:1202–8.
7. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1607–21.
8. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979;301:61–8.
9. Mehta J. Role of platelet antagonists in coronary artery disease: implications in coronary artery bypass surgery and balloon-catheter dilatation. Am Heart J. 1984;107:859–69.
10. Barnathan ES, Schwartz JS, Taylor L, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation. 1987;76:125–34.
11. Hall P, Nakamura S, Maiello L, et al. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. Circulation. 1996;93:215–22.
12.• Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339:1665–71. **Findings from this study suggest that treatment with aspirin and ticlopidine resulted in lower rate of stent thrombosis when compared with aspirin alone or a combination of aspirin and warfarin.**
13. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators C. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation. 2000;102:624–9.
14. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288:2411–20.
15. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706–17.
16. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
17. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.
18. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. N Engl J Med. 2019;381:1309–20.
19.• Bhatt DL, Steg PG, Mehta SR, et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. Lancet. 2019;394:1169–80. **Findings from this study suggets that adding ticagrelor to aspirin in stable diabetic patients with previous history of PCI improved net clinical benefit, in contrast to patients without previous history of PCI.**
20. Silvain J, Lattuca B, Beygui F, et al. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. Lancet. 2020;396:1737–44.
21. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362:1374–82.
22. Collet JP, Silvain J, Barthelemy O, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014;384:1577–85.
23. Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. Circulation. 2014;129:304–12.
24. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371:2155–66.
25. PEGASUS- TIMI Steering Committee Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791–800.
26. Furtado RHM, Nicolau JC, Magnani G, et al. Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54. Eur Heart J. 2020;41:1625–32.
27. Palmerini T, Bruno AG, Gilard M, et al. Risk-benefit profile of longer-than-1-year dual-antiplatelet therapy duration after drug-eluting stent implantation in relation to clinical presentation. Circ Cardiovasc Interv. 2019;12:e007541.
28. Gibson CM. Going polymer free and dual antiplatelet free earlier: The coevolution of stent and pharmacotherapy. J Am Coll Cardiol. 2017;69:172–5.
29. Kim JS, Jang IK, Fan C, et al. Evaluation in 3 months duration of neointimal coverage after zotarolimus-eluting stent implantation by optical coherence tomography: the ENDEAVOR OCT trial. JACC Cardiovasc Interv. 2009;2:1240–7.
30. Yin SH, Xu P, Wang B, et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. BMJ. 2019;365:l2222.
31. Ziada KM, Abdel-Latif AK, Charnigo R, Moliterno DJ. Safety of an abbreviated duration of dual antiplatelet therapy (=6 months) following second-generation drug-eluting stents for coronary artery disease: A systematic review and meta-analysis of randomized trials. Catheter Cardiovasc Interv. 2016;87:722–32.
32. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015;65:1298–310.
33. Khan SU, Singh M, Valavoor S, et al. Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents: A Systematic Review and Network Meta-Analysis. Circulation. 2020.
34. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;68:1851–64.
35. Lee SY, Hong MK, Shin DH, et al. Association between duration of dual antiplatelet therapy and angiographic multivessel disease on outcomes in patients treated with newer-generation drug-eluting stents. Circ Cardiovasc Interv. 2016;9.
36. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Can J Cardiol. 2018;34:214–33.
37. Bundhun PK, Yanamala CM, Huang F. Should a prolonged duration of dual anti-platelet therapy be recommended to patients with diabetes mellitus following percutaneous coronary intervention? A systematic review and meta-analysis of 15 studies. BMC Cardiovasc Disord. 2016;16:161.
38. Mavrakanas TA, Chatzizisis YS, Gariani K, et al. Duration of dual antiplatelet therapy in patients with CKD and drug-eluting stents: a meta-analysis. Clin J Am Soc Nephrol. 2019;14:810–22.
39. Sorrentino S, Sartori S, Baber U, et al. Bleeding risk, dual antiplatelet therapy cessation, and adverse events after percutaneous

coronary intervention: the Paris registry. Circ Cardiovasc Interv. 2020;13:e008226.
40. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016;315:1735–49.
41. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389:1025–34.
42. Pasea L, Chung SC, Pujades-Rodriguez M, et al. Personalising the decision for prolonged dual antiplatelet therapy: development, validation and potential impact of prognostic models for cardiovascular events and bleeding in myocardial infarction survivors. Eur Heart J. 2017;38:1048–55.
43. Ueda P, Jernberg T, James S, et al. External validation of the DAPT score in a nationwide population. J Am Coll Cardiol. 2018;72:1069–78.
44. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. J Am Coll Cardiol. 2019;73:741–54.
45. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol. 2018;15:480–96.
46. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. JAMA. 2020;323:2407–16.
47. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med. 2019;381:2032–42.
48. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet. 2018;392:940–9.
49. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the smart-choice randomized clinical trial. JAMA. 2019;321:2428–37.
50. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: The STOPDAPT-2 randomized clinical trial. JAMA. 2019;321:2414–27.
51.•• O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y12 inhibitor in patients after rercutaneous coronary intervention: A systematic review and meta-analysis. Circulation. 2020;142:538–45. **Findings from this study suggest that early discontinuation of aspirin while maintaining P2Y12 inhibitor reduces bleeding risk without increase in ischemic events.**
52.• Kogame N, Guimaraes PO, Modolo R, et al. Aspirin-free prasugrel monotherapy following coronary artery stenting in patients with stable CAD: the ASET pilot study. JACC Cardiovasc Interv. 2020. **First pilot study to show the safety of aspirin-free prasugrel monotherapy immediately following PCI in stable patients.**
53. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41:407–77.
54. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–60.
55. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet. 2021.
56. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017;377:1319–30.
57. Bainey KR, Welsh RC, Connolly SJ, et al. Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). Circulation. 2020;141:1141–51.
58. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505–13.
59. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60:1340–8.
60. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310:2510–22.
61. Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36:1252–63.
62. Han Y, Xu B, Xu K, et al. Six Versus 12 Months of Dual Antiplatelet Therapy After Implantation of Biodegradable Polymer Sirolimus-Eluting Stent: Randomized Substudy of the I-LOVE-IT 2 Trial. Circ Cardiovasc Interv. 2016;9:e003145.
63. Hong SJ, Shin DH, Kim JS, et al. 6-Month Versus 12-Month Dual-Antiplatelet Therapy Following Long Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. JACC Cardiovasc Interv. 2016;9:1438–46.
64. Pettersen AA, Seljeflot I, Abdelnoor M, Arnesen H. High on-aspirin platelet reactivity and clinical outcome in patients with stable coronary artery disease: Results from ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial). J Am Heart Assoc 2012;1:e000703.
65. Wiviott SD, Antman EM, Winters KJ, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation. 2005;111:3366–73.
66. Isshiki T, Kimura T, Ogawa H, et al. Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. Circ J. 2014;78:2926–34.
67. Zhao Q, Zhu Y, Xu Z, et al. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: A randomized clinical trial. JAMA. 2018;319:1677–86.
68. Schunkert H, Boening A, von Scheidt M, et al. Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial. Eur Heart J. 2019;40:2432-40.
69. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med. 2017;376:32–40.
70. Zheng W, Li Y, Tian J, et al. Effects of ticagrelor versus clopidogrel in patients with coronary bifurcation lesions

undergoing percutaneous coronary intervention. BioMed Res Int. 2019;2019:3170957.
71. Helft G, Steg PG, Le Feuvre C, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J. 2016;37:365–74.
72. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371:2155–66.
73. Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64:2086–97.
74. Lee BK, Kim JS, Lee OH, et al. Safety of six-month dual antiplatelet therapy after second-generation drug-eluting stent implantation: OPTIMA-C Randomised Clinical Trial and OCT Substudy. EuroIntervention. 2018;13:1923–30.