Irish Journal of Medical Science (1971 -) (2019) 188:453–467
https://doi.org/10.1007/s11845-018-1897-8

REVIEW ARTICLE

Oral antiplatelets in primary and secondary prevention of myocardial infarction: a review

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Received: 13 July 2018 / Accepted: 24 August 2018 / Published online: 3 September 2018

Abstract

There are a number of guidelines and articles available for the use of oral antiplatelets for primary and secondary prevention of myocardial infarction (MI). Antiplatelet medications inhibit platelet activation, aggregation, and other pathways eventually inhibiting clot formation. Aspirin and clopidogrel have been the mainstay in the management of acute coronary syndrome for about a decade. We have discussed the role of aspirin, clopidogrel, ticagrelor, and prasugrel which are the most commonly used oral antiplatelet medications in the current era. We have also considered the role of newer thrombin inhibitor vorapaxar, and dual antiplatelet therapy. In this review paper, we have summarized the continuing controversy about the use of oral antiplatelet therapy and their role in primary as well as secondary prevention of MI by describing results from major clinical trials. The safety and the efficacy of the above medications have been reviewed and described in this paper.

Keywords Aspirin · Oral antiplatelets · P2Y12 inhibitors · Prevention

Background

Cardiovascular diseases are the leading cause of death in the USA and the whole world, and it kills more people than all cancers combined. In the USA, on an average, more than 375,000 people die annually from heart diseases. More than 735,000 people suffer from heart attacks annually, and of these, about 120,000 die every year. After an episode of myocardial infarction (MI), a recurrent episode can be prevented by daily administration of beta blockers, statins, and antiplatelets [1–3]. Antiplatelets play a significant role in the secondary prevention of MI.

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Platelet is a tiny enucleate blood cell, 2–4 μm in diameter. They are formed by fragmentation from megakaryocytes in the bone marrow, and about 1×10^{11} platelets are released every day in the circulation. Platelets are smooth and discoid in resting state. Its cytoplasm contains alpha granules, dense granules, and lysosomes. Alpha granules (the most abundant) contain proteins which play a significant role in regulating thrombosis and fibrinolysis, as well as proteins including glycoprotein IIb/IIIa and P-selectin, which are expressed on cell surface following platelet activation. Dense granules contain adenosine diphosphate, adenosine triphosphate, ionized calcium, pyrophosphate, and 5HT. The release of these contents contributes to platelet activation and hemostasis. When platelets are activated, there is a change in the shape of the platelets with the platelets becoming spherical and extending finger-like projections known as pseudopodia [4]. Figure 1 shows a simplified version of platelet plug formation and steps with different oral antiplatelets (Fig. 1).

In the recent years, antiplatelet therapies for the treatment of cardiovascular diseases have advanced significantly. Various clinical trials have been published showing the safety and efficacy of antiplatelet agents either alone or in combination. In this article, we have reviewed the mechanism of action, side effects, and current clinical evidence from major clinical trials regarding the use of oral antiplatelets in the primary and secondary prevention of MI.

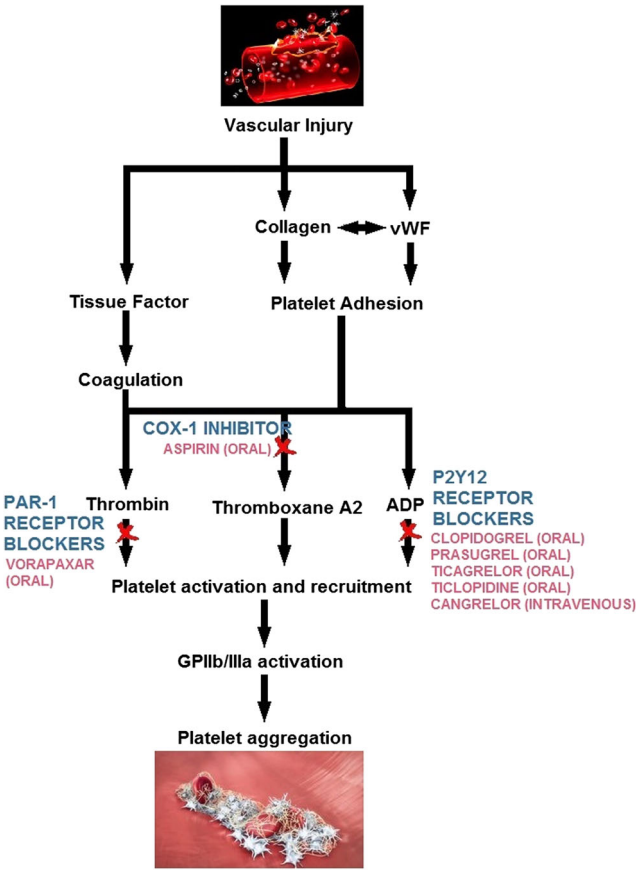

Fig. 1 Mechanism of action of various antiplatelets agents. vWF Von Willebrand factor, COX cyclooxygenase, PAR protease-activated receptor, GP glycoprotein

Aspirin

Aspirin is a widely used antiplatelet in MI. Aspirin can be used for primary prevention of cardiovascular diseases as well as secondary prevention of cardiovascular diseases [5]. The evidence of using aspirin for primary prevention is controversial, but the evidence for secondary prevention is more substantial.

Mechanism of action

Aspirin belongs to non-steroidal anti-inflammatory drug (NSAID) class. But its mechanism of action is different from other NSAIDs. All NSAIDs inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) by competitive reversible inhibition. Aspirin inhibits COX-1 and COX-2 by acetylation of COX [6]. This is irreversible inhibition. Prostaglandins are essential for the process of inflammation. Arachidonic acid is converted to prostaglandins by COX-1 and COX-2. Prostaglandin H is converted to thromboxane A2 by thromboxane A synthase. Aspirin inhibits the formation of prostaglandin H by inhibiting platelet cyclooxygenase-1 and thus the formation of Thromboxane A2 is reduced. Thromboxane A2 is a potent platelet agonist which binds to platelets and activates them as well as causes platelet aggregation by increasing expression of glycoprotein GPIIb/IIIa on the platelet cell membranes. Thromboxane A2 is also a potent vasoconstrictor and stimulates proliferation of vascular smooth muscles. Thus, by reducing thromboxane A2, aspirin decreases platelet activation as well as aggregation.

The active component of aspirin is salicylic acid. Side effects of aspirin are dose-related. Gastrointestinal bleeding is dose-related and occurs due to inhibition of COX-1 which suppresses prostaglandin E2 production which protects endothelial lining in the stomach. Salicylate toxicity occurs when the dose of aspirin is excess (> 40 mg/dl) [7], or there is a disturbance in the hepatic, renal, or metabolic system. The toxicity of aspirin is due to inhibition of Krebs cycle enzymes, oxidative phosphorylation uncoupling, and amino acid synthesis inhibition. Aspirin overdose commonly causes mixed acid-base disorder, metabolic acidosis, and respiratory alkalosis due to stimulation of the respiratory center. Salicylates are neurotoxic, and this causes tingling in ears [8]. Inhibition of Krebs cycle in CNS leads to altered mental status. Nausea and vomiting are the most common side effects, and excessive vomiting can cause dehydration and electrolyte disturbances. Aspirin overdose can also cause high heat dissipation, and this can lead to rhabdomyolysis [9] (Table 1).

Role in primary prevention

The use of aspirin for primary prevention of MI is still controversial. Many studies support the use of aspirin in reducing the risk of MI, and on the other hand, many studies show that aspirin use is not beneficial in reducing the risk of MI. For this review, we did a systematic search of the literature and included large randomized trials (more than 1000 participants) which had MI as their primary endpoint or at least a separate secondary endpoint.

In the Physician Health Study, 22,071 physicians were enrolled and followed up for a mean period of 60.2 months. This was a randomized, double-blind, placebo-controlled trial. Physicians with age between 40 and 84 were enrolled. Risk factors were distributed over a broad spectrum in the participants. Aspirin 325 mg (every other day) and placebo were randomly given to the participants. The results showed a 44% risk reduction of MI, and the benefits of aspirin for fatal and non-fatal myocardial were significant (p value < 0.00001) [10].

In the thrombosis prevention trial, aspirin reduced all ischemic heart disease (IHD) by 20% (1–35, $p = 0.04$) [11]. This was a randomized double-blinded clinical trial. The mean age of the participants was 57 years. In this study, 5499 men were included, and they were divided into four groups: active warfarin and active aspirin, active warfarin and placebo aspirin, placebo warfarin and active aspirin, and placebo warfarin and

Table 1 Description and comparison of oral antiplatelet agents

Class	Aspirin Acetyl salicylic acid	Clopidogrel Thienopyridine	Ticagrelor Cyclopentyltriazolopyridine	Prasugrel Thienopyridine	Ticlopidine Thienopyridine	Vorapaxar Himbacine analogue
Mechanism of action	Decrease platelet aggregation by inhibiting thromboxane A2	Inhibits binding of ADP to platelets and eventually inhibits activation of GPIIb/IIIa complex (2-step activation). Irreversible blockade	Direct P_2Y_{12} receptor blocker, reversible and non-competitive blockage	Inhibits binding of ADP to platelets and eventually inhibits activation of Gp_2b_{3a} complex (1-step activation). Irreversible blockade	Inhibits binding of ADP to platelets and eventually inhibits activation of Gp_2b_{3a} complex (2-step activation). Irreversible blockade	Thrombin receptor antagonist
Target	Inhibits COX-1 and COX-2 enzymes	Blocks P_2Y_{12} receptor	Blocks P_2Y_{12} receptor directly	Blocks P_2Y_{12} receptor	Blocks P_2Y_{12} receptor	Acts on PAR-1 receptor
Prodrug	No	Yes	No	Yes	No	No
Biological half-life	2–3 h for low doses, 15–30 for large doses	7–8 h (inactive metabolite)	7 h	2–15 h	12 h (single dose), 4–5 days (repeated dosing)	5–13 days
Metabolic pathway	Hepatic	Hepatic (CYP2C19)	Hepatic	Hepatic, intestinal	Hepatic	Hepatic (CYP3A4, CYP2J2)
Serious side effects	Stomach ulcer, bleeding, asthma, Reye's syndrome	Bleeding, TTP	Shortness of breath, bleeding	Bleeding, headache, back pain	Bleeding, Neutropenia and TTP	Easy bruising, bleeding, allergic reaction
Recommended dose (in mg)	LD: 150–30, MD: 75–100 QD	LD: 300, MD: 75 QD	LD: 180, MD: 90 BID	LD: 60, MD: 10 QD	LD: 500, MD: 250 BID	LD: N/A, MD: 2–5
Time to peak antiplatelet activity	~ 20–45 min	Dose dependent*	~ 2–3 h	~ 30–60 min	~ 1–3 h	~ 30–60 min

ADP adenosine diphosphate, *COX* cyclooxygenase, *PAR* protease-activated receptor, *TTP* thrombotic thrombocytopenic purpura, *LD* loading dose, *MD* maintenance dose, *QD* once a day dose, *BID* twice a day

*Dose-dependent inhibition of platelet aggregation. With higher dose, quicker peak antiplatelet activity can be achieved

placebo aspirin. Aspirin was given in the form of a controlled release formulation with a dose of 75 mg/day and warfarin was given at a dose of 2.5 mg/day, and the dose was adjusted based on INR. The mean follow-up period was 3 years. The trial was conducted in 108 group practices in UK, and men in the top 20% of the risk score distribution or the top 25% in regions with high IHD mortality rates were considered to be at high risk and were included in the trial. This study further showed that a combination of warfarin and aspirin is more effective in the reduction of IHD then either of the single drug [11]. In the group taking both warfarin and aspirin, IHD was reduced by 34% (11–51, $p = 0.006$). Major upper gastrointestinal bleed, when compared to placebo, was seven times more in warfarin and aspirin groups, eight times more in warfarin group, and five times more in aspirin group (p value < 0.05).

Hypertension Optimal Trial was a randomized, multicenter trial conducted in 26 countries. In this trial, 18,790 hypertensive patients were given with felodipine and were randomly assigned to aspirin or placebo [12]. The mean age of the participants was 61.5 years. The average follow-up time was 3.8 years. Aspirin was given in a dose of 75 mg daily in a double-blinded way. Aspirin reduced all MIs by 36% ($p =$ 0.002) [12]. Fatal bleeding was similar in the two groups, but non-fatal bleed was higher in aspirin group (1.37% vs. 0.74%, $p < 0.01$).

A sex-specific meta-analysis was performed which included 51,342 women and 44,114 men randomized to aspirin doses ranging from 100 mg every other day to 500 mg daily versus placebo for 3.7–10 years [13]. In women, aspirin reduced cardiovascular events by 12% (primarily governed by decreasing strokes), but there was no significant reduction in rates of MI or cardiovascular mortality. In men, aspirin reduced cardiovascular events by 14% ($p = 0.01$) and decreased MI by 32% ($p = < 0.001$) [13]. Aspirin therapy significantly increased the risk of bleeding in men (OR—1.72, $p < 0.001$) and women (OR—1.68, $p = 0.01$).

In Britain, healthy physicians participated in the trial for prophylactic daily aspirin (500 mg) for MI prevention [14]. This was a 6-year randomized trial in which 5139 male physicians were enrolled. The results of this trial were not promising, and it showed that Aspirin prophylaxis did not help in reducing MI occurrence rate (42.5 events/10000 person-years in aspirin group vs. 43.3 events/10000 person-years in the placebo group, $p =$ ns) [14].

Since cardiovascular events are also the leading cause of death in women, one specialized trial was done in women. This was a double-blinded, randomized, 2 by 2 factorial trial with low-dose aspirin (100 mg every other day) and vitamin E with 39,876 women participants [15]. Mean age was 70.7 years for the group taking both vitamin E and aspirin and 71.4 years for the group taking only aspirin. The patients were followed up for 2 years or until they reached the termination point. There was no significant reduction in the risk of major cardiovascular events. Also, there was no significant difference in fatal or non-fatal MI in those taking aspirin compared to those not taking aspirin [15].

Two studies were done to see the effects of aspirin for primary prevention in diabetic patients. All participants were asymptomatic. One was the prevention of progression of arterial disease and diabetes trial [16]. This trial was multicenter, randomized, double-blinded, 2 by 2 factorial, placebo-controlled trial. In this trial conducted in Scotland, 1276 adults (age > 40) with diabetes with ankle brachial pressure index of less than 0.99 were studied. This was a 2 × 2 factorial study and participants were given aspirin 100 mg daily. The mean age of the participants was 60.27 years. The mean time since diagnosis of diabetes was 6.2 years. Mean HbA1c was 7.95%. The patients were followed up for 4 years. The primary endpoint for this study was coronary heart disease or stroke or amputation above the ankle. This study showed that composite primary events in the aspirin and the non-aspirin groups were 18.2% and 18.3%, respectively ($p = 0.92$). There was no difference in rates of MI and death from coronary heart disease in those taking aspirin versus placebo [16]. The other trial was Japanese primary prevention of atherosclerosis with aspirin for diabetes study [17]. A total of 2539 diabetics were randomized with 81–100 mg aspirin or placebo. Mean age of the patients in the aspirin group was 65 years and in the placebo group was 64 years. Duration of diabetes in aspirin group was 7.3 years and in the placebo group was 6.7 years. The mean HbA1c was 7.1% in the aspirin group and 7.0% in the placebo group. The participants were followed up for a period of 3 years. The occurrence of atherosclerotic events, i.e., MI, stroke, and peripheral vascular diseases, in aspirin group was 13.6 per 1000 person-years and in the non-Aspirin group was 17.0 per 1000 person-years. Hazards ratio was 0.8 with 95% confidence interval of 0.58–1.1 (p value = 0.16). There was no significant difference in rates of MI or angina (stable and unstable) between the two groups. This study also showed that aspirin was not beneficial in the prevention of MI and cardiovascular events in patients with fairly well-controlled diabetes (HbA1c ~ 7%) [17].

In aspirin for prevention of cardiovascular events in general population trial, 3350 patients with ABI < 0.95 and no known cardiovascular disease were given 100 mg aspirin or placebo for 8.2 years [18]. There were 13.7 cardiovascular, stroke, or peripheral vascular disease events per 1000 person-years in the aspirin group and 13.3 in the placebo group. The hazards ratio was 1.03, 95% CI 0.85–1.17. Again, there was no statistical difference in the rates of fatal or non-fatal MI in the two groups. This study showed that aspirin does not reduce the risk of fatal or non-fatal MI and CV events [18].

In 2014, US FDA stated that the use of aspirin is very controversial and thus it does not recommend the use of aspirin for the primary prevention of cardiovascular diseases in the general population [19]. There is no consensus among

professional societies regarding the ideal patient population for prophylactic aspirin use for primary prevention of MI. As discussed above, the results of the randomized trials are contradictory, and there is significant heterogeneity in patient populations in those trials. The results of ongoing trials like ARRIVE, ASCEND, ASPREE, and ACCEPT-D might provide better insight regarding the ideal patient population where prophylactic aspirin use will be beneficial in the primary prevention of MI.

Currently, we propose to use low-dose aspirin (75–100 mg/day) in patients with 10-year atherosclerotic cardiovascular disease (ASCVD) risk score higher than 10%.

Role in secondary prevention

The data for the use of aspirin for the secondary prevention of MI is more substantial. Many studies have proved the beneficial use of aspirin for secondary prevention.

ISIS-2 was the first trial to show the benefits of aspirin in secondary prevention of MI [20]. This study was a multicenter, multinational, randomized, double-blinded, and placebo controlled. In this study, 17,187 patients with suspected MI were taken [20]. Aspirin reduced 26 (16 to 35) deaths per 1000 during the first 35 days. In the aspirin group, there was 9.4% of vascular deaths while in the placebo group, there was 11.8% of vascular deaths at the end of 5 weeks ($p < 0.0001$). After 1 year, the survival was 84.8% in the aspirin group and 82.7% in the placebo group, and after 2 years, it was 81.7% in the aspirin group and 80.0% in the control group ($p < 0.05$ for both).

Antithrombotic Trialists' Collaboration conducted meta-analyses of 287 studies involving 135,000 patients [21]. As per the study, after 1-month mean treatment with antiplatelet or placebo in high-risk categories, the rate of non-fatal MI was 2.6% in the antiplatelet group and 3.7% in the control group ($p < 0.0001$). The rate of vascular death was 6.8% in the antiplatelet group and 7.6% in the placebo group ($p < 0.0001$) [21]. Although this meta-analysis was before the drug-eluting stent era, there have been no randomized trials (in acute coronary syndrome (ACS) patients) in the drug-eluting stent era, where patients were randomized to aspirin versus no aspirin.

The CURRENT OASIS 7 trial (also sought to study the effect of double-dose clopidogrel vs. standard-dose clopidogrel in ACS patients) found no difference in composite events of cardiovascular death, MI, and stroke ($p = 0.61$), as well as MI ($p = 0.76$) in 25,086 ACS patients randomized to high-dose aspirin (≥ 300 mg daily) versus low-dose aspirin (75–100 mg daily). Thrombolysis in myocardial infarction (TIMI) major bleeding was not significant between the groups ($p = 0.39$); however, minor bleeding was lower in low-dose aspirin group ($p = 0.04$) [22].

In the CURE trial, aspirin was given in combination with clopidogrel in doses ranging from 75 to 325 mg in patients with ACS. The incidence of major bleeding increased as a function of the aspirin dose, both in patients treated with aspirin alone and with the combination. The risk of bleeding was lowest with doses up to 100 mg of aspirin, and there was no evidence of higher efficacy with higher doses of aspirin [23].

Both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) recommend the lifelong daily use of aspirin for secondary prevention in patients with coronary artery disease [24–27]. The ESC recommends a daily dose of 75–100 mg whereas ACC recommends a maintenance dose of 81–325 mg daily.

P2Y12 inhibitors

P2Y12 receptors are present on blood platelets. These receptors are responsible for platelet aggregation and clotting [28]. Clopidogrel, prasugrel, ticagrelor, ticlopidine, and cangrelor are P2Y12 receptor inhibitors and can be used as antiplatelets. Cangrelor is a newer agent which is administered via the intravenous route. This review focuses on oral P2Y12 agents.

Clopidogrel

Mechanism of action

Clopidogrel is a second-generation thienopyridine. Clopidogrel inhibits ADP receptor on platelet cell membranes. It is a prodrug, which requires CYP2C19 for its activation [29]. Two oxidative steps are needed to convert clopidogrel into its active metabolite. Initially, clopidogrel gets converted to 2-oxo-clopidogrel by cytochrome P450 monooxygenase-dependent metabolism. Hydrolysis of 2-oxo-clopidogrel generates active metabolite. However, the second step is still unclear and controversial [30]. Clopidogrel metabolizes in the liver by cytochrome P450 system, and it inhibits explicitly P2Y12 subtype of ADP receptor irreversibly. This is particularly important in de-activating platelet and eventually prevent cross-linking by protein fibrin [31].

Role in primary prevention

There are no trials to suggest a definite role of clopidogrel on primary prevention of MI. CHARISMA trial tested the hypothesis that long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk. Out of 15,603 patients, there were 3284 asymptomatic patients (others had established cardiovascular disease). In the asymptomatic group, the primary efficacy endpoint—a composite of the first occurrence of MI, stroke (of any cause), or death from cardiovascular causes (including hemorrhage)—was 6.6% in

clopidogrel + aspirin group versus 5.5% in aspirin alone ($p = 0.20$). The severe bleeding was similar between the two groups; however, moderate bleeding was higher in the clopidogrel group (2.1% vs. 1.3%, $p < 0.001$) [32].

Role in secondary prevention

The CURE randomized control trial studied 12,562 patients with ACS without ST-elevation for 2 years comparing clopidogrel with placebo on a background of aspirin therapy. Mean age in both groups was 64.2 ± 11.3 years. A total of 4690 patients in study group and 4724 patients in the placebo group had unstable angina at the time of randomization. Remaining 3193 patients in the study group and 3238 patients in the placebo group have suspected or associated MI. Clopidogrel (300 mg loading followed by 75 mg/day for 3–12 months, mean duration of therapy—9 months) in addition to aspirin reduced composite endpoint of non-fatal MI, stroke, or death from cardiovascular causes (9.3% vs. 11.4%, $p < 0.001$). In clopidogrel group, MI was significantly reduced (5.2% vs. 6.7%, $p < 0.001$) [33]. This reduction of ischemia can also reduce the risk of heart failure, shown by the CURE trial [33]. Benefits were noted in all the groups of patients including patients undergoing revascularization therapy and that did not. However, major (3.7% vs. 2.7%, $p = 0.001$) as well as minor (5.1% vs. 2.4%, $p = <0.001$) bleeding risk was increased with clopidogrel as compared to that with placebo. More number of people needed blood transfusion (2.8% vs. 2.2%, $p = 0.02$) after combined therapy [33]. Non-life-threatening bleeding was higher with clopidogrel (1.5% vs. 0.9%, $p = 0.002$).

The CURE PCI was a substudy of CURE trial involving 2658 cohorts. PCI was performed during the initial hospital stay in 1730 and the remaining 928 after their discharge. Patients were pre-treated with aspirin and study drug 6 days before the procedure and followed up for about 8 months [34]. Primary endpoint was a composite of mortality from cardiovascular death and MI which were significantly lower with clopidogrel (8.8% vs. 12.6%, $p = 0.002$) at the end of the study. Cardiovascular-related death and MI were lower with clopidogrel even from PCI till the end of follow-up period (6% vs. 8%, $p = 0.047$). The overall relative risk was 0.69 (95% CI—0.54-0.87). Major bleeding was not significantly higher with clopidogrel (assessed from the time of PCI to 30 days and from PCI to end of follow-up). Hence, CURE PCI study showed pre-treatment followed by long-term therapy with clopidogrel is beneficial in patients with ACS undergoing PCI. This strongly suggests a benefit of starting clopidogrel even before the patient's planned intervention without any additional bleeding risk and can be continued after PCI [34].

The CLARITY-TIMI 28 trial randomly assigned 3491 ST-elevation myocardial infarction (STEMI) patients (18–75 years of age, who presented within 12 h) to clopidogrel 300 mg loading followed by 75 mg daily versus placebo on the background of the fibrinolytic agents, aspirin and heparin (when appropriate) [35]. Patients were scheduled to undergo angiography 48 to 192 h from the start of study medication. There was a 36% relative risk reduction in rates of primary efficacy endpoint (a composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography) with clopidogrel compared to placebo (15 vs. 21.7%, $p < 0.001$). At 30 days, the composite of death, MI, and recurrent ischemia requiring revascularization was 14.1% in the placebo group and 11.6% in the clopidogrel group ($p = 0.03$). The rates of major bleeding and intracranial hemorrhage were similar between the two groups. This was the first randomized trial that showed the benefit of dual antiplatelet therapy in STEMI patients.

The CURRENT OASIS 7 trial [36] also suggested the addition of clopidogrel to aspirin is beneficial in patients undergoing PCI for ACS. A total of 25,086 patients with ACS (approximately 71% were unstable angina/non-ST-elevation myocardial infarction (NSTEMI), and 29% were STEMI) and intended early PCI were studied during this randomized controlled trial and compared double-dose (600 mg on day 1, 150 mg on days 2–7, then 75 mg daily) versus standard-dose (300 mg on day 1 then 75 mg daily) clopidogrel for 30 days post procedure. Mean age was 61.2 years in both the groups. Composite primary endpoint which included cardiovascular death, MI, or stroke was significantly higher with standard dose (4.5% vs. 3.9%, $p = 0.039$). This difference was mainly attributed to a lower rate of MI in double-dose clopidogrel (2% vs. 2.6%, relative risk reduction = 0·79 (0·64–0·96), $p = 0.018$). Secondary outcomes of cardiovascular death, MI, stroke, or recurrent ischemia (4.2% vs. 5%, relative risk reduction = 0·85 (0·74–0·98), $p = 0.025$) were also noted lower with double-dose clopidogrel [37]. TIMI defined major bleeding (defined as drop in hemoglobin ≥ 5, any fatal bleeding or intracranial bleeding) was higher with double-dose clopidogrel (1% vs. 0.7%, $p = 0.074$), but was not statistically significant. However, CURRENT defined major bleeding (defined as hemoglobin drop ≥ 5, blood transfusion requirement, leading to hypotension that requires inotropes, fatal bleeding intracranial hemorrhage, requiring surgery) rates were significantly higher with the double-dose clopidogrel (1.6% vs. 1.1%, $p = 0.009$). In this study, double-dose clopidogrel group had a 46% reduction in definite stent thrombosis.

Clopidogrel resistance

Clopidogrel resistance is defined as the failure of the molecule to inhibit the target of its action. Clopidogrel resistance is best demonstrated by the evidence of residual post-treatment P2Y12 activity by measuring ADP-induced platelet aggregation before and after treatment [38]. The prevalence of clopidogrel resistance varies from 5 to 44% depending on

various studies [38]. Pharmacokinetic and pharmacodynamic studies have demonstrated wide inter-individual variability in the concentration of active metabolite and the magnitude of platelet inhibition achieved by recommended loading and maintenance doses of clopidogrel. Although some of this variability can be explained due to genetic polymorphisms that affect the functional activity of the CYP2C19 enzyme, most of it cannot be explained by genotype or other clinical characteristics [39]. GRAVITAS trial randomized 2214 patients (60% stable angina, 40% ACS) with high on treatment reactivity 12–24 h after PCI with a drug-eluting stent to high dose (600 mg loading, 150 mg daily thereafter) versus standard dose (no additional loading, 75 mg daily) for 6 months [39]. A high-dose treatment group had a 22% absolute reduction in high on treatment reactivity at 30 days. Despite that, at 6 months, the composite primary endpoint of death from cardiovascular causes, non-fatal MI, and stent thrombosis did not differ significantly between the two groups (2.3% in each group, $p = 0.97$).

Both ACC and ESC do not recommend routine testing for platelet function of genetic testing in patients treated with clopidogrel. However, it may be considered in selected patients at high risk for poor clinical outcomes like history of stent thrombosis and stent in left main [24, 40].

Ticagrelor

Mechanism of action

Ticagrelor is a direct acting P2Y12 receptor antagonist. It binds to the P2Y12 receptor which is distinct from that of ADP, which makes the blockage reversible and noncompetitive [35]. Moreover, the drug does not need hepatic activation, which might work better for patients with genetic variants regarding the enzyme CYP2C19 [41, 42].

Role in primary prevention

There are no trials to suggest any benefit of ticagrelor in primary prevention of MI. Ticagrelor was compared to aspirin in patients with acute ischemic stroke or transient ischemic attack in SOCRATES trial, and it was compared to Plavix in patients with symptomatic peripheral arterial disease in EUCLID trial [43, 44]. There was no difference in the rates of MI between the study groups in either trial.

Role in secondary prevention

In the PLATO trial, 18,624 patients with the acute coronary syndrome were enrolled, of which 3496 patients in the ticagrelor group and 3530 patients in the clopidogrel group presented with STEMI. Of the remaining patients, 4005 in the ticagrelor group and 3950 in the clopidogrel group presented with NSTEMI, and 1549 patients in the ticagrelor group and 1563 in the clopidogrel group presented with unstable angina. Ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300 to 600 mg loading dose, 75 mg thereafter) were compared after 12 months of therapy [45]. Primary safety endpoint was composite mortality from the vascular cause, MI, or stroke which was lower with ticagrelor (9.8% vs. 11.7%, $p = <0.001$). MI rate was 5.8% in ticagrelor group and 6.9% in clopidogrel group ($p = 0.005$). Death from vascular causes was noted lower with ticagrelor at 12 months as well (4% vs. 5.1%, $p = 0.001$). No difference between ticagrelor and clopidogrel noted concerning major bleeding based on TIMI criteria ($p = 0.43$), minor bleeding ($p = 0.57$), and bleeding requiring transfusion ($p = 0.96$). However, non-CABG-related major bleeding (2.8% vs. 2.2%, $p = 0.03$) and fatal intracranial bleeding (0.1 vs. 0.01%, $p = 0.02$) were higher with ticagrelor. Dyspnea was noted in 13.8% cohorts receiving ticagrelor and 7.8% cohorts receiving clopidogrel which was significantly higher with ticagrelor ($p = <0.001$). A possible mechanism for dyspnea is believed to be inhibition of adenosine clearance by ticagrelor and hence increase in its concentration in blood. Also, inhibition of P2Y12 on sensory neurons increases the sensation of dyspnea which is also seen with other reversible inhibitors like cangrelor and elinogrel [46].

A substudy of 5216 (28% of PLATO trial participants) patients intended for non-invasive management showed similar results to the original trial [47]. The primary endpoint was lower in ticagrelor compared to that in clopidogrel (12% vs. 14.3%, HR, 0.85, $p = 0.04$). Overall mortality was lower with ticagrelor (6.1% vs. 8.2%, HR, 0.75, $p = 0.01$). The incidence of total major bleeding and non-CABG-related major bleeding was numerically higher with ticagrelor but not statistically significant [47]. A separate substudy of 7544 ACS patients with STEMI (~ 40% of PLATO trial participants) also showed similar benefits consistent with the overall study [48]. The primary endpoint occurred in 9.4% versus 10.8% of the ticagrelor and clopidogrel groups, respectively (HR, 0.87, $p = 0.07$). Ticagrelor reduced the incidence of several secondary endpoints compared with clopidogrel, including the composite of cardiovascular death and MI to 8.4% from 10.2% (HR, 0.82, $p = 0.01$), the composite of all-cause mortality, MI, and stroke to 9.8% from 11.3% (HR, 0.87, $p = 0.05$), and the composite of all arterial thrombotic events to 13.3% from 15.0% (HR, 0.87, $p = 0.03$). Ticagrelor also reduced the incidence of MI compared with clopidogrel (4.7% vs. 5.8%, $p =$ 0.03). Also, ticagrelor did not affect major bleeding [48].

Another substudy of the PLATO trial investigated the outcomes in 4662 patients with DM (~ 25% of PLATO trial participants) [49]. In patients with DM, the reduction in the primary composite endpoint (HR 0.88, 95% CI 0.76–1.03), all-cause mortality (HR 0.82, 95% CI 0.66–1.01), and stent

thrombosis (HR 0.65, 95% CI 0.36–1.17) with no increase in major bleeding (HR 0.95, 95% CI 0.81–1.12) with ticagrelor was consistent with the overall cohort and without significant diabetes status-by-treatment interactions [49].

A pre-specified subgroup analysis of the PLATO trial showed a significant interaction between treatment and region ($p = 0.045$), with less effect of ticagrelor in North America than in the rest of the world. Results of two independently performed analyses identified an underlying statistical interaction with aspirin maintenance dose as a possible explanation for the regional difference. The lowest risk of cardiovascular death, MI, or stroke with ticagrelor compared with that with clopidogrel is associated with a low maintenance dose of concomitant aspirin [50]. This is the basis for a recommendation to not exceed aspirin dose more than 100 mg when used concomitantly with ticagrelor.

The PEGASUS TIMI-54 trial tested the efficacy and safety of ticagrelor on a background of low-dose aspirin. A total of 21,162 patients who had MI 1 to 3 years earlier were enrolled and assigned either ticagrelor 90/60 mg twice daily or placebo [51]. Primary efficacy endpoint for this study was composite mortality caused by cardiovascular cause, MI, and stroke. After 3 years, the death rates were 7.85% and 7.77% in patients with 90 mg and 60 mg ticagrelor, respectively. In placebo group, it was 9.04% (p value = 0.008). Composite primary endpoint was reduced significantly with both 90-mg doses and the 60-mg dose ($p = 0.004$). However, there was no significant difference in death from any cause after adding ticagrelor to the regimen ($p = 0.14$) [51]. Primary safety endpoint was TIMI major bleeding which shown to be increased significantly with the addition of ticagrelor ($p = < 0.001$). 2.60% bleeding was noted in the ticagrelor group with 90 mg twice daily dose, 2.30% was noted in ticagrelor with 60 mg twice daily dose, and 1.06% was noted in the placebo group. Also, TIMI minor bleeding ($p = < 0.001$), bleeding requiring transfusion ($p = < 0.001$), and dyspnea ($p = < 0.001$) were noted higher with the addition of ticagrelor. Dyspnea was noted 18.93% higher with those received 90 mg twice daily and 15.84% higher with those received 60 mg twice daily within 3 years of the study period [51].

Prasugrel

Mechanism of action

Prasugrel also belongs to thienopyridine drug class and has a mechanism of action nearly similar to clopidogrel but with one-step activation compared to two-step activation for clopidogrel. CYP2C19 does not play a major role in the activation of prasugrel. After oral administration, prasugrel rapidly gets hydrolyzed to thiolactone which gets converted to its active metabolite mainly by CYP3A4 and CYP2B6. Prasugrel is a prodrug which inhibits ADP receptors by irreversibly acting on the P2Y12 receptor on platelets. The active metabolite of prasugrel prevents binding of ADP to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex and eventually platelet activation cascade.

Role in secondary prevention

There are no trials to suggest any role of prasugrel in the primary prevention of MI. TRITON-TIMI 38 trial randomized a total 13,608 patients with ACS (10,074 with unstable angina (UA)/NSTEMI and 3534 with STEMI) who were scheduled to percutaneous coronary intervention to prasugrel (60 mg loading dose and then 10 mg maintenance dose) or clopidogrel (300 mg loading dose and then 75 mg maintenance dose) [52]. Mean age in both groups was 61 years and they were followed up for 3 years from 2004 to 2007. The primary efficacy endpoint (a composite of death from cardiovascular cause, non-fatal MI, and stroke) occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (HR, 0.81; $p < 0.001$). There were also significant reductions in the prasugrel group in the rates of MI (9.7% for clopidogrel vs. 7.4% for prasugrel; $p < 0.001$), urgent target-vessel revascularization (3.7% vs. 2.5%; $p < 0.001$), and stent thrombosis (2.4% vs. 1.1%; $p < 0.001$). Non-CABG-related TIMI major bleeding (2.4% vs. 1.8%, $p = 0.03$), major/minor TIMI bleeding (5% vs. 3.8%, $p = 0.002$), bleeding requiring transfusion (4% vs. 3%, $p = <0.001$), and CABG-related TIMI major bleeding (13.4% vs. 3.2%, $p = <0.001$) occurred in significantly more patients treated with prasugrel than those treated with clopidogrel. A pre-specified subgroup analysis showed the superiority of prasugrel in both STEMI and UA/NSTEMI patients. However, the benefit was more in diabetic patients. In diabetic cohort (3146 patients), the primary endpoint occurred in 17% in clopidogrel group versus 12.2% in prasugrel group (HR, 0.70; $p < 0.001$). In non-diabetic cohort (10,462 patients), primary endpoint occurred in 10.6% in clopidogrel group versus 9.2% in prasugrel group (HR, 0.86; $p = 0.02$). Also, patients > 75 years of age and weight < 60 kg had no net benefit from prasugrel. Patients with a history of cerebrovascular events also did not have any benefit from prasugrel and had a strong trend toward a greater rate of TIMI major bleeding ($p = 0.06$) including intracranial hemorrhage. Hence, there was evidence of net harm in a patient with prior history of cerebrovascular events [52]. Thus, prasugrel is not recommended for patients > 75 years and weight < 60 kg and those with a history of prior stroke.

TRILOGY-ACS trial randomized 7243 patients with UA and NSTEMI who did not undergo revascularization to prasugrel versus clopidogrel [53]. At 17 months, there was no difference in the primary endpoint of death from cardiovascular causes, non-fatal MI, or stroke in prasugrel compared

to clopidogrel (13.9% vs. 16%, HR, 0.91; $p = 0.21$). The risk of bleeding was similar in the two groups. ACCOAST trial randomized 4033 patients with non-ST segment elevation (NSTE) ACS before or after angiography [54]. Patients scheduled to undergo angiography within 2–48 h of randomization were given prasugrel 30 mg before angiography (pre-treatment group) or placebo (control group). When intervention was indicated, an additional 30 mg prasugrel was given in the pre-treatment group and 60 mg was given in the control group. The rate of the primary efficacy endpoint, a composite of death from cardiovascular causes, MI, stroke, and urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7 did not differ significantly between the two groups (HR, 1.02; $p = 0.81$). The rate of the key safety endpoint of all TIMI major bleeding episodes through day 7 was increased with pre-treatment (HR, 1.90; $p = 0.006$). Pre-treatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days. These results did not change at 30 days [54]. Based on TRILOGY-ACS and ACCOAST trials, prasugrel is not recommended for ACS patients who are treated medically and before knowing the coronary anatomy.

The PRAGUE-18 is the only randomized trial published so far that studied head to head comparison of prasugrel versus ticagrelor in ACS patients treated with primary or immediate PCI. No difference was found in safety or efficacy between the two drugs, and the trial was stopped early due to futility [55].

Ticlopidine

Ticlopidine is a thienopyridine with the mechanism of action similar to clopidogrel, irreversibly blocking ADP receptors on the platelets [56]. Ticlopidine combined with aspirin after placement of Palmaz-Schatz stents was superior to aspirin combined with anticoagulant therapy in reducing cardiac events at 30 days in a randomized trial [57]. However, it causes rare but serious side effects of neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura (TTP). Due to better safety and tolerability profile, it was primarily replaced by clopidogrel [56]. It is a discontinued medicine in the USA.

Vorapaxar - Protease-activated receptror-1 antagonist

Mechanism of action

Thrombin activates platelets through two protease-activated receptors (PARs), PAR-1 and PAR-4 [58]. PAR-1 is activated by lower concentrations of thrombin than PAR-4 and mediates a more rapid platelet activation response. Vorapaxar is an oral competitive selective inhibitor of thrombin receptor, PAR-1. Selective PAR-1 blockade has shown to cause potent inhibition of thrombin-induced platelet aggregation but preserves primary hemostatic function [59].

Role in secondary prevention

TRACER trial enrolled 12,944 NSTE-ACS patients randomized to vorapaxar 40 mg loading and 2.5 mg daily maintenance or placebo. Aspirin and clopidogrel were administered in 97% and 87% of patients, respectively. After a median follow-up of 502 days, the primary endpoint of CV death, MI, stroke, recurrent ischemia, and urgent revascularization did not differ significantly among the groups (vorapaxar 18.5% vs. placebo 19.9%; HR 0.92, $p = 0.07$), while severe bleeding events were more frequent with vorapaxar compared to those with placebo (7.2% vs. 5.2%; HR 1.35, $p < 0.001$), with a marked increase in intracranial hemorrhage (HR, 3.39, $p < 0.001$) [59]. TRA-2P TIMI-50 trial randomized 26,449 patients with prior MI, stroke, or PVD to vorapaxar 2.5 mg daily versus placebo [60]. At 3 years, the primary endpoint of cardiovascular death, MI, or stroke had occurred in 9.3% in the vorapaxar group, as compared with 10.5% in the placebo group (HR, 0.87; $p < 0.001$). Vorapaxar was associated with an increase in intracranial hemorrhage, and the absolute increase in TIMI clinically significant bleeds (vorapaxar 15.8% vs. placebo11.1%; HR, 1.46, $p < 0.001$) was greater than the absolute reduction in ischemic events. In the subgroup of 17,779 patients with prior MI (~67% of total study population), rates of the primary endpoint over 3 years were 8.1% in the vorapaxar group versus 9.7% in the placebo group (HR, 0.80; $p < 0.0001$). TIMI clinically significant bleeding occurred in 15.1% and 10.4% of patients, respectively (HR, 1.49; $p < 0.0001$). Among patients with a history of stroke, the rate of intracranial hemorrhage in the vorapaxar group was 2.4%, as compared with 0.9% in the placebo group ($p < 0.001$). Among patients without a history of stroke, the rates of intracranial hemorrhage were lower in the two study groups (0.6% in the vorapaxar group and 0.4% in the placebo group, $p = 0.049$) [60].

Based on the above trials, vorapaxar was approved by both Food and Drug Administration (FDA) and European Medicine Agency (EMA) to reduce ischemic events in patients with prior MI. However, the benefit of vorapaxar in addition to aspirin and clopidogrel is modest and must be carefully weighed against the increase in bleeding events, including intracranial hemorrhage. Its use is contraindicated in patients with a history of cerebrovascular disease [61]. Key randomized trials investigating different durations of dual antiplatelet therapy (DAPT) have been described here (Table 2).

Table 2 Summarizing key randomized trials investigating different durations of DAPT

Study (year)	N (%ACS)	DAPT (months)	Stent type	Primary endpoint	Bleeding
RESET (2012) [62]	2117 (55%)	3 versus 12	ZES in 3 mo, SES in 12 mo	CV death, MI, ST, TVR, major or minor bleeds: 4.7% in 3 mo versus 4.7% in 12 mo ($p = 0.84$, $p_{\text{non-inferiority}} < 0.001$) (1 year after stenting)	TIMI major: 0.2% in 3 mo versus 0.6% in 12 mo, difference—$p = 0.18$
OPTIMIZE (2013) [63]	3119 (32%)	3 versus 12	E-ZES 100%	Death, MI, stroke, major bleeds: 6% in 3 mo versus 5.8% in 12 mo ($p = 0.84$, $p_{\text{non-inferiority}} = 0.002$) (1 year after stenting)	TIMI major: 0.6% in aspirin versus 0.9% in DAPT (HR 0.71, 95% CI 0.32–1.60, $p = 0.41$)
EXCELLENT (2012) [64]	1443 (52%)	6 versus 12	75% EES, 25% SES	Target vessel failure 4.8% 6 mo and 4.3% in 12 mo ($p = 0.60$; $p < 0.001$ for non-inferiority) (1 year after stenting)	TIMI major: 0.3% in 6 mo versus 0.6% in 12 mo ($p = 0.42$)
PRODIGY (2012) [65]	1970 (75%)	6 versus 24	BMS 25%, E-ZES 25%, PES 25%, EES 25%	Death, MI, stroke: 10% in 6 mo versus 10.1% 24 mo ($p = 0.91$) (2 years after stenting)	BARC type 5, 3, or 2: 3.5% in 6 mo versus 7.4% in 24 mo ($p < 0.001$)
SECURITY (2014) [66]	1399 (38%)	6 versus 12	E-ZES 41%, EES 20%, others 33%	Cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeds: 4.5% versus 3.7% in 6 mo versus 12 mo ($p = 0.469$, $p_{\text{non-inferiority}} < 0.05$) (1 year after stenting)	BARC type 3 or 5: 0.6% in 6 mo versus 1.1% in 12 mo ($p = 0.283$)
ISAR-SAFE (2015) [67]	4000 (40%)	6 versus 12	SES 8%, EES 48%, ZES 15%, BES 8%, others21%	Death, MI, ST, stroke, and TIMI major bleeds: 1.5% in 6 mo versus 1.6% 12 mo ($p = 0.70$, $p_{\text{non-inferiority}} < 0.001$) (2 years after stenting)	TIMI major bleeds: 0.2% in 6 mo versus 0.3% in 12 mo ($p = 0.74$)
ITALIC/ITALIC + (2015) [68]	1850 (23%)	6 versus 24	EES 100%	Death, MI, urgent TVR, stroke and major bleeds: 1.6% in 6 mo versus 1.5% in 24 mo ($p = 0.85$, Pnon-inferiority = 0.0002) (2 years after stenting)	Minor bleeds: 0.5% in 6 mo versus 0.4% in 24 mo ($p = 0.74$)
ARTIC-INTERRUPTION (2014) [69]	1259 (30%)	12 versus 24	First-generation DES 4.3%	Death, MI, ST, stroke, or urgent revascularization: 4% in 24 mo versus 4% in 12 mo ($p = 0.58$) (2 years after stenting)	STEEPLE major bleeds: 1% in 24 mo versus 0.5% in 12 mo ($p = 0.07$)
DAPT (2014) [70]	9961 (43%)	12 versus 30	PES 26%, SES 11%, EES 47%, ZES 12%	Death, MI, or stroke 4.3% in 30 mo versus 5.9% in 12 mo ($p < 0.001$) (33 months after stenting)	GUSTO moderate or severe bleeds 2.5% in 30 mo versus 1.6% in 12 mo ($p = 0.001$)

BARC Bleeding Academic Research Consortium, *BES* biolimus-eluting stent, *BMS* bare-metal stent, *CV* cardiovascular, *DAPT* dual antiplatelet therapy, *EES* everolimus-eluting stent, *GUSTO* global utilization of streptokinase and t-PA for occluded arteries, *MI* myocardial infarction, *N* number of patients, *PES* paclitaxel eluting stent, *SES* sirolimus-eluting stent, *ST* stent thrombosis, *STEEPLE* Safety and Efficacy of Enoxaparin in PCI patients, an International Randomized Evaluation, *TIMI* thrombolysis in myocardial infarction, *TVR* target vessel revascularization, *ZES* zotarolimus-eluting stent, *mo* months

Table 3 Guidelines for DAPT therapy in CAD patients

Duration (months)	STEMI[#]					NSE-ACS[#]				SIHD[$]	
	MT	Lytic	BMS	DES	CABG	MT	BMS	DES	CABG	BMS	DES
1										Class 1	
> 1										Class 2b	
6											Class 1**
> 6											Class 2b***
12	Class* 1	Class 1	Class 1	Class 1	Class 1	Class 1	Class 1	Class 1	Class 1		
> 12	Class 2b	Class 2b	Class 2b	Class 2b		Class 2b	Class 2b	Class 2b			

DAPT dual antiplatelet therapy, *CAD* coronary artery disease, *STEMI* ST-elevation myocardial infarction, *NSE-ACS* non-ST-elevation acute coronary syndrome, *SIHD* stable ischemic heart disease, *MT* medical therapy, *BMS* bare-metal stent, *DES* drug-eluting stent, *CABG* coronary artery bypass grafting

[#] Ticagrelor and prasugrel are preferred over clopidogrel in patients who undergo stenting in acute coronary syndrome

[$] Clopidogrel is the only P2Y12 agent studied in SIHD

*Class 2a per ESC guidelines

**Duration is 6–12 months for class 1 per ESC guidelines

***Duration > 12 months is a class 2b per ESC guidelines

Guidelines for secondary preventions [71]: ACC/AHA Guideline Update on Duration of Dual Antiplatelet Therapy (DAPT) in Coronary Artery Disease (CAD) Patients

1. Lower daily dose of aspirin (81 mg) therapy should almost always be continued indefinitely in patients with CAD.
2. In patients with stable ischemic heart disease (SIHD) treated with DAPT after drug-eluting stent (DES) implantation, P2Y12 inhibitor therapy with clopidogrel should be given for at least 6 months (class I). In patients with SIHD treated with DAPT after bare-metal stent (BMS) implantation, P2Y12 inhibitor therapy (clopidogrel) should be given for a minimum of 1 month (class I).
3. 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) (Table 3).

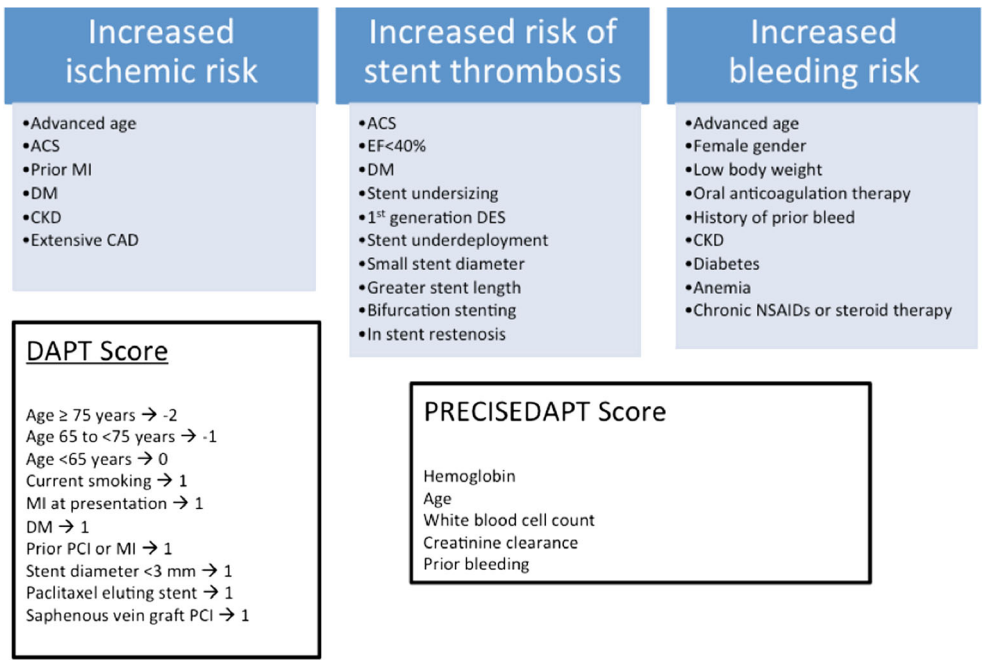

Fig. 2 DAPT and PRECISEDAPT score. ACS acute coronary syndrome, MI myocardial infarction, DM diabetes mellitus, CKD chronic kidney disease, CAD coronary artery disease, EF ejection fraction, NSAIDs non-steroidal anti-inflammatory drugs, PCI percutaneous coronary intervention

4. In patients with acute coronary syndrome (ACS) (non-ST-elevation [NSTE]-ACS or ST-elevation myocardial infarction [STEMI]) treated with DAPT after BMS or DES implantation, P2Y12 inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months (class I).
5. 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 new risk score (the "DAPT score"), derived from the Dual Anti-Platelet Therapy study, may be useful for decisions about whether to continue (prolong or extend) DAPT in patients treated with coronary stent implantation (Fig. 2).
6. In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy (class IIa). Among those who are not at high risk for bleeding complications and who do not have a history of stroke or transient ischemic attack, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y12 inhibitor therapy (class IIa).
7. In patients with ACS (NSTE-ACS or STEMI) being treated with DAPT who undergo coronary artery bypass grafting (CABG), P2Y12 inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS (class I).
8. In patients with STEMI treated with DAPT in conjunction with fibrinolytic therapy, P2Y12 inhibitor therapy (clopidogrel) should be continued for a minimum of 14 days and ideally at least 12 months (class I).
9. Elective non-cardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation. In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of P2Y12 inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y12 platelet receptor inhibitor be restarted as soon as possible after surgery (class I).

Conclusion

Antiplatelet therapy is the cornerstone for management of atherosclerotic heart disease. Aspirin therapy for primary prevention of MI is controversial and should be reserved for patients with higher risk who have multiple risk factors for coronary artery disease and have a low risk of bleeding. Lifelong therapy with aspirin is strongly recommended for secondary prevention of MI unless contraindicated. Use of second oral antiplatelet is recommended for secondary prevention of MI, usually for 6–12 months. Preference for the second agent and its duration varies based on the underlying primary event, need for PCI, and bleeding risk. It is recommended to use the newer DAPT score to guide the duration of dual antiplatelet therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hennekens CH, Dyken ML, Fuster V (1997) Aspirin as a therapeutic agent in cardiovascular disease. Circulation 96:2751–2753
2. Josan K, McAlister FA (2007) Cholesterol lowering for secondary prevention: what statin dose should we use? Vasc Health Risk Manag 3:615
3. Kezerashvili A, Marzo K, De Leon J (2012) Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it "ok" to discontinue? Curr Cardiol Rev 8:77–84
4. Ghoshal K, Bhattacharyya M (2014) Overview of platelet physiology: its hemostatic and nonhemostatic role in disease pathogenesis. ScientificWorldJournal 2014:781857
5. Ittaman SV, VanWormer JJ, Rezkalla SH (2014) The role of aspirin in the prevention of cardiovascular disease. Clin Med Res 12:147–154
6. Miner J, Hoffhines A (2007) The discovery of aspirin's antithrombotic effects. Tex Heart Inst J 34:179
7. Hill JB (1973) Salicylate intoxication. N Engl J Med 288:1110–1113
8. Sussman JB, Vijan S, Choi H, Hayward RA (2011) Individual and population benefits of daily aspirin therapy: a proposal for personalizing national guidelines. Circ Cardiovasc Qual Outcomes 4:268–75.
9. Temple AR (1981) Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 141:364–369
10. Hennekens C (1989) Final report on the aspirin component of the ongoing Physicians Health Study. N Engl J Med 321:129–135
11. Framework MRCsGPR (1998) Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 351:233–241
12. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S (1998) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 351:1755–1762
13. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL (2006) Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 295:306–313
14. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R

(1988) Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 296:313–316
15. Ridker PM, Cook NR, Lee I-M, Gordon D, Gaziano JM, Manson JE et al (2005) A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 352:1293–1304
16. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R et al (2008) The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 337:a1840
17. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N et al (2008) Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 300:2134–2141
18. Fowkes FGR, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC et al (2010) Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 303:841–848
19. Nansseu JR, Noubiap JJ (2015) Aspirin for primary prevention of cardiovascular disease. Thromb J 13:38.
20. Tinsley A, Naymagon S, Trindade AJ, Sachar DB, Sands BE, Ullman TA (2013) A survey of current practice of venous thromboembolism prophylaxis in hospitalized inflammatory bowel disease patients in the United States. J Clin Gastroenterol 47:e1–e6
21. Trialists' Collaboration A (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324: 71–86
22. Investigators CO (2010) Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010:930–942
23. Mitka M (2001) Results of CURE trial for acute coronary syndrome. JAMA 285:1828–1829
24. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F et al (2015) ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2015:ehv320
25. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA (2011) AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. Circulation 124:2458–2473
26. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA et al (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61:e78–e140
27. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr., Ganiats TG, Holmes DR Jr, et al. (2014) 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 64:e139–e228
28. Dorsam RT, Kunapuli SP (2004) Central role of the P2Y 12 receptor in platelet activation. J Clin Invest 113:340–345
29. Liu Q, Dang D-S, Chen Y-F, Yan M, Shi G-B, Zhao Q-C (2012) The influence of omeprazole on platelet inhibition of clopidogrel in various CYP2C19 mutant alleles. Genet Test Mol Biomarkers 16: 1293–1297
30. Savi P, Pereillo J, Uzabiaga M, Combalbert J, Picard C, Maffrand J et al (2000) Identification and biological activity of the active metabolite of clopidogrel. Thromb Haemost 84:891–896
31. Brown DG, Wilkerson EC, Love WE (2015) A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 72:524–534
32. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KAA (2007) Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 49:1982–1988
33. Investigators CiUAtPRET (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001:494–502
34. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK et al (2001) Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 358:527–533
35. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E (2005) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 352:1179–1189
36. Mehta SR, Tanguay J-F, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KAA, Yusuf S (2010) Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 376:1233–1243
37. Investigators C-O, Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW et al (2010) Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 363:930–942
38. Ray S (2014) Clopidogrel resistance: the way forward. Indian Heart J 66:530–534
39. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D et al (2011) Standard-vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 305:1097–1105
40. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B et al (2011) 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 58:e44–e122
41. Owen R, Serradell N, Bolos J (2007) AZD6140. Antiplatelet therapy, P2Y (12)(P2T) receptor antagonist. Drugs Future 32:845–853
42. Tantry US, Bliden KP, Wei C, Storey RF, Armstrong M, Butler K et al (2010) First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel clinical perspective. Circ Cardiovasc Genet 3:556–566
43. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KSL (2016) Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med 375:35–43
44. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, Kashyap SR (2017) Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med 376:641–651

45. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045–1057
46. Alexopoulos D, Xanthopoulou I, Perperis A, Goudevenos J, Hamilos M, Sitafidis G et al (2017) Dyspnea in patients treated with P2Y12 receptor antagonists: insights from the GReek AntiPlatElet (GRAPE) registry. Platelets:1–7
47. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S et al (2011) Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ d3527:342
48. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L, for the PLATO Study Group (2010) Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 122:2131–2141
49. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR, Wallentin L (2010) Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 31:3006–3016
50. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J, Harrington RA, Wallentin L, on behalf of the PLATO Investigators (2011) Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 124:544–554
51. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS (2015) Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 372:1791–1800
52. Sosnowski C (2008) Commentary to the article: Wiviott S D, Braunwald E, McCabe C H et al. Prasugrel versus clopidogrel in patients with acute coronary syndrome. N Engl J Med 2007; 357: 2001–15. Kardiol Pol 66:222–225 discussion 5–6
53. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG et al (2012) Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 367: 1297–1309
54. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg JM, Miller DL, Costigan TM, Goedicke J, Silvain J, Angioli P, Legutko J, Niethammer M, Motovska Z, Jakubowski JA, Cayla G, Visconti LO, Vicaut E, Widimsky P (2013) Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 369:999–1010
55. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P (2016) Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. Circulation 134:1603–1612
56. Collet JAB, Gachet C, Montalescot G (2009) P2Y12 inhibitors: thienopyridines and direct oral inhibitors. Antiplatelet therapy in ischemic heart disease, 1st edn. Wiley-Blackwell, Dallas, pp 59–76
57. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M et al (1996) A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 334:1084–1089
58. Andersen H, Greenberg DL, Fujikawa K, Xu W, Chung DW, Davie EW (1999) Protease-activated receptor 1 is the primary mediator of thrombin-stimulated platelet procoagulant activity. Proc Natl Acad Sci U S A 96:11189–11193
59. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F et al (2012) Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med 366:20–33
60. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KAA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJO, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA (2012) Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 366:1404–1413
61. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F et al (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 37:267–315
62. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y (2012) 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 60: 1340–1348
63. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV et al (2013) Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA 310:2510–2522
64. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS (2012) 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 125:505–513
65. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R, for the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators (2012) Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 125:2015–2026
66. Tarantini G, Nai Fovino L, Tellaroli P, Chieffo A, Barioli A, Menozzi A et al (2016) Optimal duration of dual antiplatelet therapy after second-generation drug-eluting stent implantation in patients with diabetes: the SECURITY (Second-Generation Drug-Eluting Stent Implantation Followed By Six- Versus Twelve-Month Dual Antiplatelet Therapy)-diabetes substudy. Int J Cardiol 207:168–176
67. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T et al (2015) ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J 36:1252–1263
68. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P,

Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC (2015) 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol 65:777–786

69. Collet JP, Silvain J, Barthelemy O, Range G, Cayla G, Van Belle E et al (2014) Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet 384:1577–1585
70. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SLT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, ver Lee P, Rinaldi MJ, Massaro JM (2014) Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 371:2155–2166
71. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA et al (2016) 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 134:e123–e155