

Update in dual antiplatelet therapy in patients with ischemic artery disease

Srdjan Aleksandric¹, MD, MSc, Miloje Tomasevic^{1,2}, MD, PhD, Milan A. Nedeljkovic, MD, PhD^{1,3}

¹Division of Cardiology, Clinical Center of Serbia, Belgrade, Serbia, ²University of Kragujevac, School of Medicine, Kragujevac, Serbia, ³University of Belgrade, School of Medicine, Belgrade, Serbia.

Abstract

Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome, myocardial infarction, ischemic stroke/transient ischemic attack and peripheral artery disease. Dual antiplatelet therapy (low-dose aspirin plus ADP-P2Y12 receptor blockers) has become the cornerstone of therapy for the management of acute and chronic coronary artery disease and the prevention of ischemic complications associated with percutaneous coronary intervention. The newer ADP-P2Y12 inhibitors, prasugrel and ticagrelor, demonstrated superior ischemic outcomes versus clopidogrel, but there are not recommended in patients with stable coronary artery disease, unless in high-risk situations of elective stenting, such as documented stent thrombosis on clopidogrel or left main stenting. Clopidogrel is still the only ADP-P2Y12 inhibitor agent approved for patients with stable coronary artery disease undergoing percutaneous coronary intervention. The currently guidelines support the use of dual antiplatelet therapy for up to 12 months in patients with acute coronary syndrome with or without ST-segment elevation, irrespective of revascularization strategy or stent type. The recommendations for duration of dual antiplatelet therapy in patients with stable coronary artery disease undergoing percutaneous coronary intervention are 1-12 months after bare-metal stents and 6-12 months after first-generation drug-eluting stents. In a past few years, stent technology has improved and a new-generation drug-eluting stents with a safety profile has been developed. This review is focused on the most recent advances in oral antiplatelet therapy and duration of dual antiplatelet therapy in the era of new-generation drug-eluting stents.

Keywords

Antiplatelet, cardiovascular disease, coronary artery disease, stable angina, acute coronary syndrome without ST-segment elevation, ST-segment elevation myocardial infarction, percutaneous coronary intervention, coronary stents.

Introduction

Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome (ACS), myocardial infarction (MI), ischemic stroke/transient ischemic attack and peripheral artery disease (PAD)¹. Inhibition of platelet function by combined use of aspirin (acetylsalicylic acid, ASA) and ADP-P2Y12 receptor blockers is an important strategy for preventing ischemic cardiovascular (CV) events in patients with acute and chronic coronary artery disease (CAD), including those undergoing percutaneous coronary intervention (PCI)¹. Therefore, dual antiplatelet therapy (DAPT) has become the cornerstone of therapy for the management of acute and chronic CAD and the prevention of ischemic complications associated with PCI¹⁻². However, patients receiving DAPT, especially those with

ACS, remain at substantial risk of ischemic CV events because current agents do not interfere with all platelet activation pathways, allowing continued platelet activation via other pathways¹⁻². The currently available adenosine diphosphate (ADP)-P2Y12 inhibitors are irreversible thienopyridines (clopidogrel and prasugrel) and reversibly binding ticagrelor. The newer ADP-P2Y12 inhibitors, prasugrel and ticagrelor, demonstrated superior ischemic outcomes versus clopidogrel, but increases the risk of both gastrointestinal (GI) and intracranial bleeding³⁻⁷.

Antiplatelet therapy in secondary prevention of cardiovascular disease

The role of aspirin as an antiplatelet agent in the treatment of acute CVD events as well as for secondary prevention of future CVD events has been well established in multiple clinical trials, systematic reviews, and

Table 1. Randomized controlled trials (RCTs) that evaluated the efficacy and safety of short-term DAPT (3-6 months) versus long-term DAPT (12-24 months) after percutaneous coronary intervention (PCI) with a newer-generation drug-eluting stents (DESs).

RCT	Year	Trial design	Number of patients	Primary Study Endpoint	Outcome
EXCELLENT	2012	6-months vs. 12- months DAPT after EES or SES	1443	Cardiac death, MI, or ischemia-driven TVR	Non-inferiority confirmed
RESET	2012	3-months vs. 12- months DAPT after ZES	2117	Cardiac death, MI, ST, TVR, or bleeding	Non-inferiority confirmed
OPTIMIZE	2013	3-months vs. 12- months DAPT after ZES	3119	Death, MI, stroke, or major bleeding	Non-inferiority confirmed
SECURITY	2014	6-months vs. 12- months DAPT after ZES or biolimus A9-eluting stents	1399	Cardiac death, MI, ST, stroke or BARC type 3 or 5 bleeding	Non-inferiority confirmed
ITALIC	2015	6-months vs. 24- months DAPT after EES implantation	2031	Death, MI, urgent TVR, stroke, or major bleeding	Non-inferiority confirmed
ISAR-SAFE	2015	6-months vs. 12- months DAPT after SES, PES, ZES or EES	4005	Death, MI, ST, stroke, or TIMI major bleeding	Non-inferiority confirmed

DAPT - dual antiplatelet therapy; MI - myocardial infarction; TVR - target vessel revascularization; ST - stent thrombosis; SES - sirolimus-eluting stent; EES - everolimus-eluting stent; ZES - zotarolimus-eluting stent; PES - paclitaxel-eluting stent; BARC - Bleeding Academic Research Consortium.

meta-analyses (8-14). The Antithrombotic Trialists' Collaboration meta-analysis of 16 secondary prevention RCTs with more than 17,000 patients with previous MI, stroke or transient cerebral ischemia demonstrated that aspirin versus control therapy was associated with significant reduction in annual rates of any serious vascular events (OR, 0.81 [95% CI, 0.75-0.81]), non-fatal MI (OR, 0.80 [95% CI, 0.73-0.88]), total stroke (OR, 0.81 [95% CI, 0.71-0.92]) and CV death (OR, 0.83 [95% CI 0.78-0.87]) (13). In another meta-analysis of six RCTs with more than 9,000 patients comparing benefits and risks of low-dose aspirin treatment (50-325 mg daily) for secondary prevention in patients with stable CVD, aspirin was associated with a significant 21% reduction in total CV events (OR, 0.79 [95% CI, 0.72-0.88]), 26% reduction in non-fatal MI (OR, 0.74 [95% CI, 0.60-0.91]), 25% reduction in stroke (OR, 0.75 [95% CI, 0.65-0.87]), and 13% reduction in all-cause mortality (OR, 0.87 [95% CI, 0.76-0.98])⁴⁵. Although there was an increase risk of severe bleeding (especially major extracranial bleeding) in both meta-analyses, the net clinical benefit favored aspirin use in the secondary prevention of CVD events¹³⁻¹⁴.

The currently used ADP-P2Y₁₂ inhibitors, irreversible thienopyridines clopidogrel and prasugrel, and reversibly binding ticagrelor, have been administered as an adjunct to aspirin therapy in the management of ACS with or without ST-segment elevation, especially in patients undergoing PCI. Dual antiplatelet therapy given for a period of 12 months is a standard treatment in these patients, based on results from the CURE, PCI-CURE, CREDO, COMMIT, CLARITY-TIMI 28, CURRENT-OASIS-7, TRITON, and PLATO trials¹⁵⁻²³. Conversely, there are no clinical studies supporting the use of prasugrel and ticagrelor in patients with stable CAD¹⁵.

Clopidogrel is a prodrug which requires cytochrome P450 enzymes (including CYP2C19) in liver for its activation. It successfully replaces the first-generation ADP-P2Y₁₂ inhibitor ticlopidine which has several disadvantages such as bone-marrow depression (usually with

neutropenia), rash and diarrhea²⁴. Clopidogrel irreversibly inhibits ADP-induced platelet aggregation which is several times stronger than with ticlopidine²⁴. However, clopidogrel also has several limitations: 1) only 10-15% of the prodrug converts in the active drug, 2) the inhibition of platelet aggregation is dose-dependent, 3) delayed onset and offset of action, 4) there is a resistance to the drug because of CYP2C19 gene polymorphism in 15-46% of patients, and 5) the drug effect is decreased in interaction with other drugs such as proton-pump inhibitors (except pantoprazole) or non-steroidal anti-inflammatory drugs^{1,24}. Only one study compared the efficacy and safety of clopidogrel versus aspirin monotherapy for secondary prevention in patients with recent MI, ischemic stroke or symptomatic PAD²⁵. The CAPRIE trial demonstrated that clopidogrel was slightly superior than aspirin in reduction of major CV events (MI, ischemic stroke or CV death) in these patients, with relative-risk reduction of 8.7% in favour of clopidogrel²⁵. Aspirin was associated with more, but non-significant rate of major bleedings²⁵. Five RCTs showed that DAPT (loading dose of clopidogrel 300 mg, then 75 mg daily + low-dose aspirin 75-325 mg daily) versus aspirin alone significantly reduce the annual risk of total ischemic outcomes events (MI, ischemic stroke or CV death) in these patients¹⁶⁻²⁰. Among aforementioned RCTs, only the CURE study showed that DAPT was associated with a significant increase in the rate of TIMI-defined major bleeding (OR, 1.38 [95% CI, 1.13-1.67]), but without significant increase of life-threatening bleeding and/or hemorrhagic stroke (OR, 1.21 [95% CI, 0.95-1.56])¹⁶. In the CURRENT-OASIS 7 study, a strategy of double-dose clopidogrel (600 mg loading dose on day 1, followed by 150 mg for 6 days, and 75 mg daily thereafter) in addition to low or higher dose aspirin therapy did not further decrease the 30-days-rate of total CV events (MI, ischemic stroke or CV death) compared with standard dose of clopidogrel (300 mg loading dose on day 1 and 75 mg daily thereafter) in ACS patients (OR, 0.94 [95% CI, 0.83-1.06])²¹. However, in the subgroup of ACS patients

who underwent PCI, double-dose clopidogrel therapy was associated with a 32% reduction in the secondary outcome of definite stent thrombosis (OR, 0.68 [95% CI, 0.55-0.85]), with slightly increase in major bleeding (OR, 1.24 [95% CI, 1.05-1.46])²¹. Meta-analysis of 10 studies (7 RCTs, 3 non-randomized) with more than 1,500 patients referred for PCI, showed that high-loading dose of clopidogrel (>300 mg) before PCI reduces the 30-days risk of cardiac death or non-fatal MI compared with 300 mg dose of clopidogrel (OR, 0.54 [95% CI, 0.32-0.90]), without any significant increase in major or minor bleeding²⁶. Additionally, in the CURRENT-OASIS 7 study, there was no significant difference between higher-dose (300-325 mg daily) and lower-dose (75-100 mg daily) aspirin with respect to the total ischemic outcomes events (OR, 0.97 [95% CI, 0.86-1.09]) or major bleeding (OR, 0.99 [95% CI, 0.84-1.17])²¹.

Yet, previous data suggest that about 25% of patients on clopidogrel therapy are non-responders and the risks of recurrent major ischemic CV events in these patients are 3-fold greater compared with responders (OR, 3.52 [95% CI, 2.39-5.20])²⁷. Therefore, alternative strategies were proposed, such as increasing the loading and maintenance doses of clopidogrel,

aimed to achieve a greater, more rapid, and more consistent platelet inhibition. However, such strategies have failed to improve CV outcomes²⁸⁻²⁹. This led to the development of newer ADP-P2Y₁₂ antiplatelet agents that have more rapid and more consistent inhibition of platelet aggregation and improving CV outcomes²⁷.

Prasugrel is a third-generation thienopyridine that irreversibly inhibits ADP-induced platelet aggregation. It has several advantages over clopidogrel: 1) it has a more rapid onset of antiplatelet effect (within 30 minutes) since 80% of the prodrug converts into the active metabolite by gut enzymes CYP3A during its absorption, 2) it achieves more consistent and 10 times stronger inhibition of ADP-induced platelet aggregation than clopidogrel, 3) the drug metabolism is independent of the hepatic CYP450 enzyme complex which means that its effect does not depend on genetic polymorphism, and 4) the concomitant use of proton-pump inhibitors do not interfere with the drug metabolism^{1-2,24}. In the TRITON-TIMI 38 study, 13,608 patients with ACS scheduled for PCI were randomized to receive either clopidogrel 300 mg loading dose followed by 75 mg daily or prasugrel 60 mg loading dose followed by 10 mg daily, in addition to low-dose (75-162 mg daily) aspirin therapy³. Patients receiving prasugrel had a significant 19% reduction in total CV events (MI, stroke or CV death) during median follow-up of 14.5 months compared with clopidogrel (OR, 0.81 [95% CI, 0.73-0.90])³⁰. In the prasugrel group, there were also a significant 24% reduction in non-fatal MI (OR, 0.76 [95% CI, 0.67-0.85]), 34% reduction in urgent target-vessel revascularization (OR, 0.66 [95% CI, 0.73-0.90]) and 52% reduction in definite or probable stent thrombosis according to the Academic Research Consortium (ARC) definition (OR, 0.48 [95% CI, 0.36-0.64])³. The prasugrel efficacy was greater among patients with diabetes (OR, 0.70 [95% CI, 0.58-0.85]) than among patients without diabetes (OR, 0.86

[95% CI, 0.76-0.98])³. However, this beneficial effect was associated with an increased risk of non coronary artery bypass graft (CABG)-related TIMI major bleeding (OR, 1.32 [95% CI, 1.03-1.68]), including life-threatening (OR, 1.52 [95% CI, 1.08-2.13]) and fatal bleeding (OR, 4.19 [95% CI, 1.58-11.11])³. The study identified three subgroups of ACS patients that had less net clinical benefit or clinical harm with prasugrel: 1) patients with previous history of stroke or transient ischemic attack, 2) elderly ≥ 75 years, and 3) patients with a body weight of less than 60 kg³. After excluding these three groups of patients who were at higher risk for bleeding, there was a significant reduction in total CV events in prasugrel group of ACS patients compared with clopidogrel group (OR, 0.74 [95% CI, 0.66-0.84]), without a significant difference in the rate of non CABG-related TIMI major bleeding (OR, 1.24 [95% CI, 0.91-1.69])³. Therefore, the currently ACC/AHA and ESC guidelines do not recommend prasugrel therapy in ACS patients with: 1) active bleeding, 2) previous stroke or TIA, 3) 75 years or older, and 4) body weight less than 60 kg³⁰⁻³¹.

An additional subanalysis of the TRITON-TIMI 38 study also confirmed that ACS patients with diabetes had a greater net clinical benefit with prasugrel compared with clopidogrel (OR, 0.74 [95% CI, 0.62-0.89]), irrespective to diabetes treatment type (OR, 0.66 [95% CI, 0.47-0.92] for patients on insulin; OR, 0.78 [95% CI, 0.63-0.96] for patients on oral antidiabetic drugs)³². A significant 30% reduction in total CV events was seen in diabetics (OR, 0.70 [95% CI, 0.58-0.85]), mostly because of a significant 40% reduction in non-fatal MI (OR, 0.60 [95% CI, 0.48-0.76) and 48% reduction in stent thrombosis (OR, 0.52 [95% CI, 0.33-0.84])³². Among insulin-treated and non insulin-treated patients with diabetes, a significant reduction in total ischemic outcomes were observed (OR, 0.63 [95% CI, 0.44-0.89] for insulin-treated diabetics; OR, 0.74 [95% CI, 0.59-0.93] for non insulin-treated diabetics)³². Although a significant increase in non CABG-related TIMI major bleeding were observed among patients without diabetes (OR, 1.43 [95% CI, 1.07-1.91]), there was no difference in the rate of major bleeding among patients with diabetes (OR, 1.06 [95% CI, 0.66-1.69])³². According to this data, this study suggested that prasugrel in addition to aspirin therapy had a greater net clinical benefit for secondary prevention in ACS patients with diabetes (OR, 0.74 [95% CI, 0.62-0.89]) than in those without diabetes (OR, 0.92 [95% CI, 0.82-1.03])³².

Another subanalysis of the TRITON-TIMI 38 study was performed in 12,844 patients with ACS who received at least one coronary stent (5,743 drug-eluting stent, and 6,461 bare-metal stent)³³. This study showed that prasugrel compared with clopidogrel reduced the incidence of total ischemic outcomes for overall 19% (OR, 0.81 [95% CI, 0.72-0.90]), CV death for 16% (OR, 0.84 [95% CI, 0.66-1.08]), fatal or non-fatal MI for 24% (OR, 0.76 [95% CI, 0.67-0.86]), and urgent target-vessel revascularization for 32% (OR, 0.68 [95% CI, 0.55-0.84]), irrespective of stent type (OR, 0.80 [95% CI, 0.69-0.93] for bare-metal stent; OR, 0.82 [95% CI, 0.69-0.97] for drug-eluting stent)³³. Additionally, prasugrel significant-

ly reduced the incidence of stent thrombosis (OR, 0.48 [95% CI, 0.36-0.64]), irrespective of stent type, the ARC definition used, or clinical characteristics³³. Stent thrombosis was reduced both early (between 0 and 30 days) and late (> 30 days) after stent placement with prasugrel compared with clopidogrel (OR, 0.41 [95% CI, 0.29-0.59] for early stent thrombosis; OR, 0.60 [95% CI, 0.37-0.97] for late stent thrombosis)³³. In contrary, TRILOGY ACS study evaluated efficacy and safety of prasugrel (10 mg daily) versus clopidogrel (75 mg daily) in addition to aspirin (75-100 mg daily) therapy in patients with unstable angina or MI without ST-segment elevation who did not referred for PCI and who were under the age of 75 years, during median follow-up of 17 months⁴. This study failed to demonstrate the superiority of prasugrel over clopidogrel for reducing total ischemic events (MI, stroke or CV death) in these patients (OR, 0.91 [95% CI, 0.79-1.05]), with similar risks for severe and intracranial bleeding between the two groups⁴. The ACCOAST study compared efficacy and safety of prasugrel as pretreatment at the time of diagnosis or after the coronary angiography if PCI was indicated, in patients with non ST-elevation MI who were scheduled to undergo coronary angiography within 2-48 hours after randomization³⁴. Patients were treated with prasugrel (30 mg loading dose) before angiography (pretreatment group) or placebo (control group), and an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI, and 60 mg of prasugrel was given in the control group at the time of PCI³⁴. The rate of total CV events (MI, stroke, CV death and urgent revascularization) through day 7 did not differ significantly between the two groups (OR, 1.02 [95% CI, 0.84-1.25])³⁴. However, the rate of all TIMI major bleeding (CABG or non-CABG) through day 7 was increased in the pretreatment group (OR, 1.90 [95% CI, 1.19-3.02])³⁴. Bleeding events were predominantly associated with PCI or CABG and occurred early in patients who referred for PCI (OR, 2.69 [95% CI, 1.13-6.40])³⁴. The study found that pretreatment with prasugrel in patients with non ST-elevation MI who were scheduled to undergo cardiac catheterization within 48 hours after admission did not reduce the rate of major ischemic events up to 30 days, but increased the rate of major bleeding complications³⁴.

Ticagrelor is oral, reversible, direct-acting inhibitor of the ADP-P2Y12 platelet receptors that has several advantages over clopidogrel and prasugrel: 1) it does not require metabolic biotransformation for its antiplatelet activity, and 2) it is associated with a rapid onset of action, a greater level of AD-induced platelet inhibition and a more rapid offset of pharmacodynamic action^{1,24}. In the PLATO study, 18,624 patients admitted to the hospital within 24 hours after symptom onset, who suffered from ACS with or without ST-segment elevation and referred for cardiac catheterization, were randomized to receive either clopidogrel 300-600 mg loading dose followed by 75 mg daily or ticagrelor 180 mg loading dose followed by a dose of 90 mg twice daily, in addition to low-dose (75-100 mg daily) aspirin therapy⁵. Patients receiving ticagrelor had a significant 16% reduction in total CV events (MI, stroke or CV death) during

median follow-up of 12 months compared with clopidogrel (OR, 0.84 [95% CI, 0.77-0.92]). In the ticagrelor group, there were also a significant 16% reduction in non-fatal MI (OR, 0.84 [95% CI, 0.75-0.95]), and 21% reduction in death from vascular causes (OR, 0.79 [95% CI, 0.69-0.91]), but the rate of stroke did not differ significantly between the two treatment groups (OR, 1.17 [95% CI, 0.91-1.52])⁵. Among patients who received a stent during the study, the rate of definite, probable or possible stent thrombosis according to the ARC definition was significantly lower in the ticagrelor group than in the clopidogrel group (OR, 0.77 [95% CI, 0.62-0.95])⁵. There was no significant difference in the rates of TIMI major bleeding (OR, 1.03 [95% CI, 0.93-1.15]), including CABG-related TIMI major bleeding between the two groups (OR, 0.94 [95% CI, 0.82-1.07]), but ticagrelor was associated with a higher rate of non-CABG-related TIMI major bleeding (OR, 1.25 [95% CI, 1.03-1.53]), especially more instances of fatal intracranial and nonintracranial bleeding⁵. Because ticagrelor is structurally similar to adenosine, it may cause dyspnea and/or bradyarrhythmias (including ventricular pauses) that are usually resolved after first month of continued treatment^{5,35}. Several subanalyses of the PLATO study confirmed that ticagrelor versus clopidogrel significantly reduced the rates of total ischemic events in ACS patients scheduled either for early invasive strategy (PCI or CABG) (OR, 0.84 [95% CI, 0.75-0.94]) (36), or medical therapy only (OR 0.85 [95% CI, 0.73-1.00]) (37), in ACS patients with chronic kidney disease (OR, 0.77 [95% CI, 0.65-0.90])³⁸, or with diabetes (OR, 0.80 [95% CI, 0.70-0.91])³⁹, with similar rates of total major bleeding in all aforementioned substudies.

Meta-analysis of four RCTs with more than 31,000 patients who suffered from ACS without ST-Elevation MI (NSTEMI-ACS) showed that newer oral ADP-P2Y12 inhibitors (prasugrel or ticagrelor) significantly decreased major ischemic CV events (MI, stroke or CV death) by 13% compared with clopidogrel (OR, 0.87 [95% CI, 0.80-0.95])⁷. Newer oral ADP-P2Y12 inhibitor also significantly reduced MI (OR, 0.85 [95% CI, 0.75-0.96]) with a trend towards reduction of CV death (OR, 0.89 [95% CI, 0.71-1.01]) and without significant difference in the rate of stroke (OR, 0.96 [95% CI, 0.78-1.18])⁷. This results were similar when stratified by prasugrel versus ticagrelor for all primary and secondary end point ($p_{\text{interaction}} > 0.05$). Newer ADP-P2Y12 inhibitors showed a significant increase in non-CABG-related TIMI major bleeding (OR, 1.27 [95% CI, 1.07-1.5]) and in TIMI major or minor bleeding (OR, 1.20 [95% CI, 1.02-1.42]) compared with clopidogrel⁷. This results were similar when stratified by prasugrel versus ticagrelor for TIMI major bleeding ($p_{\text{interaction}} > 0.05$), but not for TIMI major and minor bleeding ($p_{\text{interaction}} < 0.05$) which was significantly increased with prasugrel⁷. Two additional meta-analyses demonstrated that newer ADP-P2Y12 inhibitors compared with clopidogrel had a stronger anti-ischemic effect in patients with ST-Elevation MI (STEMI) than in NSTEMI-ACS patients, with a 16-23% reduction in total CV events, 19-25% in non-fatal MI, 33-36% in stent thrombosis, 19% reduction in CV mortality, and 22-23% reduction in all-cause mor-

tality⁴⁰⁻⁴¹. Contrary to NSTEMI-ACS patients, both meta-analyses showed similar stroke and TIMI major bleeding rates between newer ADP-P2Y12 group and clopidogrel group among STEMI^{7,40-41}.

Prasugrel and ticagrelor in addition to low-dose aspirin therapy in secondary CVD prevention appear to be more effective for a reduction in major ischemic CV events compared with clopidogrel. The ESC guidelines support using ticagrelor and prasugrel over clopidogrel in NSTEMI-ACS and STEMI patients (Class of Recommendation I, Level of Evidence B)^{30,42-43}. The AHA/ACC guidelines provide a similar level of recommendation for all oral ADP-P2Y12 inhibitors (Class of Recommendation I, Level of Evidence B)^{31,44-45}. Clopidogrel is still the only ADP-P2Y12 inhibitor agent approved for patients with stable CAD undergoing PCI (Class of Recommendation I, Level of Evidence A)⁴⁶. Prasugrel and ticagrelor are not recommended in patients with stable CAD, unless in high-risk situations of elective stenting, such as documented stent thrombosis on clopidogrel or left main stenting (Class of Recommendation IIb, Level of Evidence C)⁴⁶.

Duration of dual antiplatelet therapy in patients with ischemic heart disease

According to previous RCTs^{3,5,16-18}, the currently ACC/AHA and ESC guidelines support the use of DAPT for up to 12 months in patients with ASC with or without ST-segment elevation, irrespective of revascularization strategy or stent type^{30-31,42-45}. In patients with stable CAD, DAPT is recommended only after elective PCI⁴⁶⁻⁴⁷. The CHARISMA trial did not show the superiority of DAPT over aspirin monotherapy in reduction of major CV events (MI, stroke, or CV death) among patients with previously documented CAD, PAD or CVD⁴⁸. This trial showed that DAPT (clopidogrel 75 mg/d in combination with low-dose aspirin 75-100 mg/d) was not significantly more effective than aspirin alone (75-100 mg/d) in reducing the rate of total CV events (MI, stroke, or CV death) among these patients (OR, 0.88 [95% CI, 0.77-0.998])⁴⁸. Contrary, this study suggested that DAPT was associated with a significant increase in the rate of GUSTO-defined moderate bleeding (OR, 1.62 [1.27-2.08]), especially in patients with documented CAD, PAD or CVD⁴⁸.

The recommendations for duration of DAPT in patients with stable CAD undergoing PCI are 1-12 months after bare-metal stents (BMS) and 6-12 months after first-generation drug-eluting stents (sirolimus-eluting stents [SES] and paclitaxel-eluting stents [PES])⁴⁶⁻⁴⁷. Both SIRIUS and TAXUS-IV trials demonstrated that PCI with first-generation drug-eluting stents (DES) compared to BMS has a significant reductions of in-stent restenosis, target-lesion revascularization (TLR) and target-vessel revascularization (TVR)⁴⁹⁻⁵⁰. However, observational BASKET-LATE trial suggested that the discontinuation of ADP-P2Y12 inhibitor 6 to 18 months after PCI leads to a 2- to 3-fold higher rates of delayed stent thrombosis and thrombosis-related events, such as MI or death, in DES-treated patients compared with BMS-treated patients⁵¹. This was explained by delayed endothelialization of DES. Therefore, the Food and Drug Administration (FDA) rec-

ommended a minimum duration of 12 months of DAPT after first-generation DES implantation (52).

Two recent RCTs, DAPT study and the PEGASUS-TIMI 54 trial, evaluated the efficacy and safety of DAPT therapy beyond 12 months⁵³⁻⁵⁴. In the DAPT study, 12 months after treatment with standard ADP-P2Y12 thienopyridine drugs (clopidogrel or prasugrel) and low-dose aspirin (75-162 mg daily), patients who had undergone PCI with a first- or new-generation DESs were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months in addition to aspirin⁵³. The longer-DAPT duration (beyond 12 months after DES placement) compared with standard-DAPT duration (up to 12 months) was associated with a significant reduction in the rates of definite or probable stent thrombosis according to ARC definitions (OR, 0.29 [95% CI, 0.17-0.48]), major CV events (MI, stroke or death) (OR, 0.71 [95% CI, 0.17-0.48]), and non-fatal MI alone (OR, 0.47 [95% CI, 0.37-0.61]), between 12 and 30 months after PCI, irrespective of the specific thienopyridine drugs used and stent type⁵³. The efficacy of longer-DAPT duration was even greater in patients presented with MI compared with those presented without MI (OR, 0.27 [95% CI, 0.13-0.57] for stent thrombosis; OR, 0.56 [95% CI, 0.42-0.76] for major CV events; OR, 0.42 [95% CI, 0.29-0.62] for non-fatal MI)⁵⁵. The rate of moderate or severe bleeding was significantly higher in the longer-DAPT duration group compared with standard-DAPT duration group (OR, 1.61 [95% CI, 1.21-2.16])⁵³. In addition, the rate of all-cause mortality was unexpectedly higher in the longer-DAPT duration group (OR, 1.36 [95% CI, 1.00-1.85]), mainly due to a higher rate of non-CV death (OR, 2.23 [95% CI, 1.32-3.78]), but the underlying reasons for this remains unclear⁵³. In the PEGASUS-TIMI 54 trial, patients with a history of MI in the previous 1 to 3 years, were randomly assigned to continue receiving ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo, for a median of 33 months, in addition to low-dose aspirin (75-150 mg daily)⁵⁴. The study found that the use of both ticagrelor dose compared with aspirin alone beyond 12 months significantly reduced the risk of major CV events (OR, 0.85 [95% CI, 0.75-0.96] for 90 mg of ticagrelor; OR, 0.84 [95% CI, 0.74-0.95] for 60 mg of ticagrelor), MI (OR, 0.81 [95% CI, 0.69-0.95] for 90 mg of ticagrelor; OR, 0.84 [95% CI, 0.72-0.98] for 60 mg of ticagrelor), and stroke (OR, 0.82 [95% CI, 0.63-1.07] for 90 mg of ticagrelor; OR, 0.75 [95% CI, 0.57-0.98] for 60 mg of ticagrelor)⁵⁴. The rate of TIMI-defined major bleeding was higher with the two ticagrelor doses than with placebo (OR, 2.69 [95% CI, 1.96-3.70] for 90 mg of ticagrelor; OR, 2.32 [95% CI, 1.68-3.21] for 60 mg of ticagrelor), with a significantly higher rates of bleeding leading to transfusion and bleeding leading to discontinuation of the drug⁵⁴. The PEGASUS-TIMI 54 trial did not demonstrate an increase in all-cause mortality in ticagrelor 90 mg twice daily group (OR, 1.00 [95% CI, 0.86-1.16] for 90 mg of ticagrelor), but rather a trend towards improved all-cause mortality in the ticagrelor 60 mg twice daily group (OR, 0.89 [95% CI, 0.76-1.04])⁵⁴. Thus, the results of DAPT study and PEGASUS-TIMI 54

trial suggest longer-DAPT duration with more potent ADP-P2Y₁₂ inhibitors without interruption in selected patients with high risk for ischemic CV events and lower risk for bleeding may be an option².

The PRODIGY trial investigated the efficacy of short-DAPT duration compared to longer-DAPT duration in patients with stable CAD or ACS after PCI⁵⁶. In this trial, patients were randomly assigned to receive up to 6 or 24 months of clopidogrel therapy (75mg daily) in addition to low-dose aspirin (80-325 mg daily) after PCI with BMS or DES (zotarolimus-eluting, paclitaxel-eluting or everolimus-eluting stents)⁵⁶. This study showed that the extended use of DAPT, for up to 24 months, was not significantly more effective than a 6-months DAPT duration in reducing the cumulative risk of major CV events (OR, 0.98 [95% CI, 0.74-1.29]), and the individual risk of all-cause mortality (OR, 1.00 [95% CI, 0.72-1.40]), MI (OR, 1.06 [95% CI, 0.69-1.63]), cerebrovascular accident (OR, 0.60, [95% CI, 0.29-1.23]) or delayed definite or probable stent thrombosis according to ARC definition (OR, 1.15 [95% CI, 0.55-2.41]) type⁵⁶. On the other hand, the prolonged use of DAPT was associated with a significant 62% greater risk of TIMI-defined major bleeding (OR, 0.38, [95% CI, 0.15-0.97]), including events that required medical or surgical treatment, red blood cell transfusion, and life-threatening events⁵⁶. An additional subanalysis of the PRODIGY trial demonstrated similar rate of ischemic CV events between 24-months and 6-months DAPT duration in both ACS (OR, 0.94 [95% CI, 0.69-1.27]) and stable CAD patients (OR, 1.59 [95% CI, 0.77-3.27]), while bleeding risk was significantly higher in the long-term DAPT arm in both groups⁵⁷. Long-term DAPT compared with short-term DAPT was associated with a 75% increase of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding in ACS patients (OR, 0.75 [95% CI, 1.11-2.74]), and a 5-fold increase in stable CAD patients (OR, 5.37 [95% CI 1.84-15.74])⁵⁷. The net adverse cardiac events (NACE), consisting of the death, MI, cerebrovascular accident, or BARC 2, 3, or 5 type of bleeding, was significantly increased in the 24-month DAPT duration in stable CAD patients (OR, 2.5 [95% CI 1.35-4.69]), but not in the ACS patients (OR, 1.15 [95% CI 0.88-1.50])⁵⁷. The study pointed out that prolonged use of DAPT after PCI may have a greater efficacy with a lower bleeding risk in ACS patients because of its higher platelet reactivity, while doubled the bleeding risk in patients with stable CAD⁵⁷. Three other RCTs (DES-LATE, ARCTIC-Interruption, and OPTIDUAL trial) confirmed that DAPT duration beyond 1 year after DES implantation in patients with ACS or stable CAD was not superior in the reduction of ischemic CV events, while the rate of major and minor bleeding was increased⁵⁸⁻⁶⁰.

Additionally, in a past few years, stent technology has improved and a new-generation DESs with a safety profile has been developed⁶¹. Six RCTs evaluated efficacy and safety of short-term DAPT (3-6 months) versus standard- and long-term DAPT (12-24 months) after PCI with newer-generation DESs. The EXCELLENT, RESET, OPTIMIZE, SECURITY, ITALIC, and ISAR-SAFE trials showed that the use of DAPT up to 6 months was safe and not inferior to the standard- and long-term DAPT for the

reduction in ischemic CV events (62-67). Several meta-analyses which included RCTs evaluating the short- (<6 months) and long-term DAPT (>12 months) after implantation of newer-generation DESs concluded that extension of DAPT beyond 6 months increased the risk of bleeding without reducing the risk of all-cause mortality, cardiac death, non-fatal MI, cerebrovascular accident, or stent thrombosis⁶⁸⁻⁷⁵. The meta-analysis by Giustino et al. found that short-term DAPT was associated with significantly higher rate of stent thrombosis (OR, 1.71 [95% CI, 1.26-2.32]), but its effect on stent thrombosis was attenuated with the use of newer-generation DESs (OR, 1.54 [95% CI, 0.96-2.47]) compared with the use of first-generation DESs (OR, 3.94 [95% CI, 2.20-7.05])⁷⁴. In contrast to this findings, a meta-analysis by Udell et al. evaluated the use of long-term DAPT in patients with prior MI and demonstrated a significant 22% reduction in ischemic CV events (OR, 0.78 [95% CI, 0.67-0.90]), 25% in cardiac death (OR, 0.85 [95% CI, 0.74-0.98]), 30% in non-fatal MI (OR, 0.70 [95% CI, 0.55-0.88]), 29% in stroke (OR, 0.81 [95% CI, 0.68-0.97]), and 50% in definite or probable stent thrombosis according to ARC definition (OR, 0.50 [95% CI, 0.28-0.89])⁷⁶. There was a significant increase in the risk of major bleeding (OR, 1.73 [95% CI, 1.19-2.50]), but not fatal bleeding (OR, 0.91 [95% CI, 0.53-1.58]), with no excess of non-CV causes of death (OR, 1.03 [95% CI, 0.86-1.23])⁷⁶. Previous trials and meta-analyses suggest that long-term DAPT is best used in patients who are at the highest risk of subsequent ischemic CV events, such as those with an ACS in the preceding 3 years and those who are at low risk for bleeding events⁷⁷. Furthermore, the long-term DAPT should be avoided in patients with stable CAD who are at lower risk for subsequent ischemic CV events, such as those with stable angina, elective PCI with a newer-generation DESs, no previous history of ACS, and high bleeding risk (elderly patients and those with diabetes or chronic kidney disease)⁷⁷. It should be pointed out that the use of DAPT beyond 1 year after PCI must be individualized; however, it remains difficult to predict which patients will have the greatest net clinical benefit from prolonged DAPT due to a lack of standardized risk-benefit algorithm⁷⁷. Regarding this issue, a new risk score (the „DAPT score“) has been developed (78-79). This score, which derived from the DAPT study, may be useful in assessing the benefit and risk of prolonged DAPT (>12 months) in patients treated with PCI (78-79). The score incorporates several factors with the respective weighting points (WP) for benefit/risk calculation of DAPT score: patient age (WP for <65 years = 0; WP for 65-74 years = 1; WP for ≥75 years = -2), cigarette smoking (WP = 1), diabetes (WP = 1), MI at presentation or earlier (WP = 1 for each), prior PCI (WP = 1), stent type (WP for paclitaxel-eluting stent = 1; WP for other DES or BMS = 0), stent diameter <3 mm (WP = 1), vein graft PCI (WP = 2), and congestive heart failure or left ventricular ejection fraction <30% (WP = 2) (78-79). The benefit/risk ratio of prolonged DAPT in patients with a high DAPT score (≥2) may be favorable because it reduces both ischemic and bleeding events when compared with short-term DAPT⁷⁸⁻⁷⁹. Conversely, in patients with a low

DAPT score (<2), benefit/risk ratio of prolonged DAPT is not favorable due to increased bleeding risk without a reduction in ischemic events⁷⁸⁻⁷⁹.

Taking into account the available data, the current 2016 ACC/AHA Guideline Focused Update addresses specific recommendations on duration of DAPT in patients with stable CAD or ACS after implantations of newer-generation DESs⁸⁰⁻⁸¹:

I Recommendations for DAPT duration in patients with stable CAD treated with PCI:

a. In patients with stable CAD treated with DAPT, ADP-P2Y12 inhibitor (clopidogrel) should be given for a minimum of 1 month after BMS implantation (Class of Recommendation I; Level of Evidence A), and for at least 6 months after DES implantation (Class of Recommendation I; Level of Evidence B-R),

b. In patients with stable CAD after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with ADP-P2Y12 inhibitor (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 of Recommendation IIb; Level of Evidence A),

c. In patients with stable CAD treated with DAPT after DES implantation who are at high risk of severe bleeding complication (eg, treatment with oral anticoagulant therapy), discontinuation of ADP-P2Y12 inhibitor therapy after 3 months may be reasonable (Class of Recommendation IIb; Level of Evidence C-LD),

d. In patients with stable CAD without prior history of ACS, PCI, or recent (within 12 months) coronary artery bypass grafting (CABG), DAPT treatment is not beneficial over aspirin monotherapy (Class of Recommendation III; Level of Evidence B-R).

II Recommendations for DAPT duration in patients with ACS treated with PCI or medical therapy alone:

a. In patients with ACS (NSTEMI-ACS or STEMI) after PCI with BMS or DES implantation, or medical therapy alone, DAPT with ADP-P2Y12 inhibitor should be given for at least 12 months (Class of Recommendation I; Level of Evidence B-R). The current 2016 ACC/AHA guideline support the use of ticagrelor over clopidogrel in patients with ACS, irrespective of the treatment type (Class of Recommendation IIa; Level of Evidence B-R). Prasugrel is recommended over clopidogrel in ACS patients only after PCI unless they are at high risk for bleeding complications, 75 years or older, who have body weight <60 kg and do not have a history of stroke or TIA (Class of Recommendation IIa; Level of Evidence B-R).

b. In patients with ACS (NSTEMI-ACS or STEMI) treated with PCI or with medical therapy alone, who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (Class of Recommendation IIb; Level of Evidence A),

c. In patients with ACS treated with DAPT after DES implantation who are at high risk of severe bleeding complication, or develop significant overt bleeding, discontinuation of ADP-P2Y12 inhibitor therapy after 6 months may be reasonable (Class of Recommendation IIb; Level of Evidence C-LD).

In patients after elective or primary PCI who subsequently undergo CABG, DAPT with ADP-P2Y12 inhibitor should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed (Class of Recommendation I; Level of Evidence C)⁸¹. In patients with stable CAD, DAPT with clopidogrel initiated early postoperatively for 12 months after CABG may be reasonable to improve vein graft patency (Class of Recommendation IIb; Level of Evidence B-NR)⁸¹.

Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation (Class of Recommendation I; Level of Evidence B-NR)⁸¹. It should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively (Class of Recommendation III; Level of Evidence B-NR)⁸¹. In patients after PCI who must undergo elective noncardiac surgery that mandate the discontinuation of DAPT, it is recommended that aspirin be continued if possible and the ADP-P2Y12 inhibitor be restarted as soon as possible after surgery (Class of Recommendation I; Level of Evidence C-EO).

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