CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will weigh the pros and cons of continuing dual antiplatelet therapy beyond 12 months in patients who receive drug-eluting stents after an acute coronary syndrome event

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Dual antiplatelet therapy for acute coronary syndromes: How long to continue?

ABSTRACT

For patients with an acute coronary syndrome event, current guidelines recommend dual antiplatelet therapy for at least 12 months after drug-eluting stent placement. However, several clinical trials have assessed whether continuing dual antiplatelet therapy beyond 12 months is beneficial. We review the pros and cons of extending dual antiplatelet therapy.

KEY POINTS

The outcomes of patients with acute coronary syndrome events have been improving as percutaneous coronary intervention and its accompanying medical therapy have evolved.

Newer, more potent antiplatelet agents are preferred over clopidogrel when possible.

Two earlier studies showed no advantage of extended dual antiplatelet therapy over the standard 12-month duration, but the recent Dual Antiplatelet Therapy trial did.

The protection against ischemia afforded by dual antiplatelet therapy comes at the price of increased risk of bleeding.

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Percutaneous coronary intervention for acute coronary syndromes has evolved, and so, hand in hand, has antiplatelet therapy. With the advent of clopidogrel and newer agents, several studies demonstrated the benefits of dual antiplatelet therapy in preventing major vascular ischemic complications. The findings culminated in a guideline recommendation for at least 12 months of dual antiplatelet therapy after placement of a drug-eluting stent, when feasible—a class I recommendation (treatment should be given), level of evidence B (limited populations evaluated).[1,2] But extending dual antiplatelet therapy beyond 12 months had no strong favorable evidence until the recent Dual Antiplatelet Therapy (DAPT) study[3] shed light on this topic.

Here, we review the evidence thus far on the optimal duration of dual antiplatelet therapy in the secondary prevention of coronary artery disease.

PLATELETS IN ACUTE CORONARY SYNDROMES AND STENT THROMBOSIS

Acute coronary syndromes begin with fissuring or ulceration of a vulnerable atherosclerotic plaque, followed by thrombosis and occlusion, mediated by platelet adhesion, activation, and aggregation (**Figure 1**). Transient occlusion results in unstable angina or non-ST-elevation myocardial infarction, while total occlusion usually results in ST-elevation myocardial infarction.

Platelet aggregation is prominent among the mechanisms leading to stent thrombosis and vaso-occlusive ischemic complications

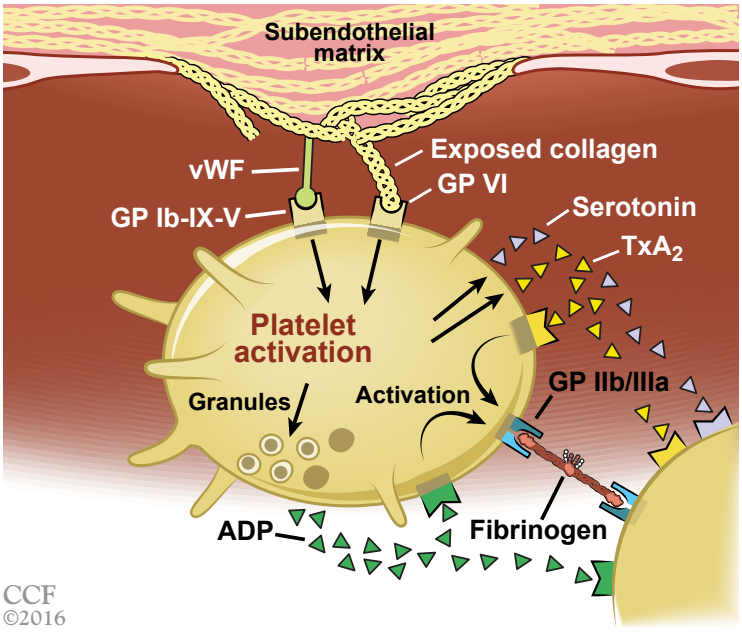

FIGURE 1. The platelet aggregation cascade. Exposure of subendothelial matrix leads to adhesion of platelets to the vessel wall, activation, and aggregation.

ADP = adenosine diphosphate; GP = glycoprotein; TxA_2 = thromboxane A_2; vWF = von Willebrand factor

Antiplatelet agents play a vital role in both primary and secondary prevention of cardiovascular events

after percutaneous coronary intervention. Thus, antiplatelet agents play a vital role in both primary and secondary prevention of cardiovascular events.[4–6]

Adhesion, activation, and aggregation

Adhesion. Disruption of the vascular endothelium as a result of vulnerable plaque fissuring or ulceration exposes subendothelial thrombogenic collagen and von Willebrand factor to blood. Collagen engages platelets through their glycoprotein (GP) Ia, IIa, and VI receptors, and von Willebrand factor binds platelets through the GP Ib-IX-V receptor.

Activation. Once platelets adhere to the subendothelium, they undergo a conformational change and become activated. Simultaneous release of various autocrine and paracrine mediators including adenosine diphosphate, serotonin, epinephrine, thromboxane, and various ligand-receptor interactions all contribute to the activation cascade. Adenosine diphosphate binds to the platelet receptor $P2Y_1$, leading to an increase in intracellular calcium, and it binds to $P2Y_{12}$, leading to a decrease in cyclic adenosine monophosphate, both of which cause GP IIb/IIIa receptor activation. Thromboxane A_2 released by platelets by cyclo-oxygenase 1 binds to alpha or beta variant receptors and contributes to GP IIb/IIIa activation through elevation of intracellular calcium levels.

Aggregation and thrombosis. Exposure of tissue factor to plasma following plaque rupture activates the coagulation cascade via the extrinsic pathway, which generates thrombin, a powerful platelet activator that causes thrombus formation via fibrin. Thrombin binds to protease-activated receptors PAR-1 and PAR-4 on platelets, causing an increase in intracellular calcium and a decrease in cyclic adenosine monophosphate with subsequent GP IIb/IIIa activation. GP IIb/IIIa facilitates platelet aggregation by binding to fibrinogen and forming a stable platelet thrombus.

In the early stages of thrombus formation, platelets predominate ("white" thrombi); further organization with fibrin results in older "red" thrombi. The stages of thrombi vary in non-ST-elevation and ST-elevation myocardial infarction and are prognostic markers of death.[4–8]

PERCUTANEOUS INTERVENTION, RESTENOSIS, AND STENT THROMBOSIS

Percutaneous coronary intervention, the preferred means of revascularization for many patients, is performed emergently in patients with ST-elevation myocardial infarction, urgently in those with acute coronary syndromes without ST elevation, and electively in those with stable ischemic symptoms.

Percutaneous revascularization techniques have evolved from balloon angioplasty to bare-metal stents to drug-eluting stents, but each of these procedures has been associated with a periprocedural and postprocedural risk of thrombosis.

Balloon angioplasty was associated with vascular intimal injury, inciting elastic vascular recoil and smooth muscle cell proliferation leading to restenosis.

Bare-metal stents reduced the restenosis rate by eliminating vascular recoil, although restenosis still occurred within the stent because of neointimal proliferation of vascular smooth muscle cells. This was an important

limitation, as both acute and subacute stent thrombosis were refractory to aggressive anticoagulation regimens that were associated with major bleeding complications and longer hospital length of stay. Stenting became mainstream practice only after the ISAR[9] and STARS[10] trials showed that dual antiplatelet therapy controlled stent thrombosis.

Drug-eluting stents coated with antiproliferative and anti-inflammatory polymers markedly reduced in-stent restenosis rates by suppressing the initial vascular smooth-muscle proliferative response. However, they were still associated with late and very late stent thrombosis with incomplete endothelialization, even up to 40 months after implantation. Proposed mechanisms include incomplete stent apposition and inflammatory hypersensitivity reactions to the polymer coating. Incomplete stent apposition associated with low-velocity blood flow at the junction of the stent strut and vessel wall, together with delayed endothelialization, promotes platelet adhesion and aggregation, followed by thrombus formation.[11]

Second-generation drug-eluting stents have thinner struts and more biocompatible polymers and are thought to favor more complete re-endothelialization, reducing the rates of stent thrombosis.[8,12,13]

Predictors of early stent thrombosis

The Dutch Stent Thrombosis Registry and other studies looked at risk factors for stent thrombosis.[14,15]

Procedure-related factors included:

- Stent undersizing
- Residual uncovered dissections after angioplasty
- Longer stents
- Low flow after angioplasty (< 3 on the 0–3 Thrombolysis in Myocardial Infarction [TIMI] scale).

Lesion-related factors included:

- Intermediate coronary artery disease both proximal and distal to the culprit lesions
- Bifurcation lesions.

Patient-related factors included:

- Low left ventricular ejection fraction
- Diabetes mellitus
- Peripheral arterial disease Premature discontinuation of clopidogrel.

Studies discussed in this article

ARCTIC-Interruption—Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation 1 Year After Stenting[46]

CAPRIE—Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events[25]

CHARISMA—Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance[36–38]

CLARITY-TIMI 28—Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction[33,34]

COMMIT/CCS 2—Clopidogrel and Metoprolol in Myocardial Infarction Trial[35]

CREDO—Clopidogrel for the Reduction of Events During Observation[20]

CURE—Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events[30–32]

DAPT—Dual Antiplatelet Therapy[3,48]

DES-LATE—Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event[47]

Dutch Stent Thrombosis Registry[14,15]

EXCELLENT—Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting[41]

ISAR—Intracoronary Stenting and Antithrombotic Regimen[9]

OPTIMIZE—Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice[42]

PEGASUS-TIMI 54—Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54[39]

PLATO—Study of Platelet Inhibition and Patient Outcomes[23]

PRODIGY—Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia[45]

RESET—Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation[43]

SECURITY—Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy[40]

STARS—Stent Anticoagulation Restenosis Study[10]

TRITON-TIMI 38—Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition With Prasugrel[22]

WOEST—What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting[49]

ANTIPLATELET AGENTS: MECHANISM OF ACTION

Various pathways play synergistic roles in platelet activation and aggregation and thrombus formation, and different antiplatelet agents inhibit these specific pathways, thus complementing

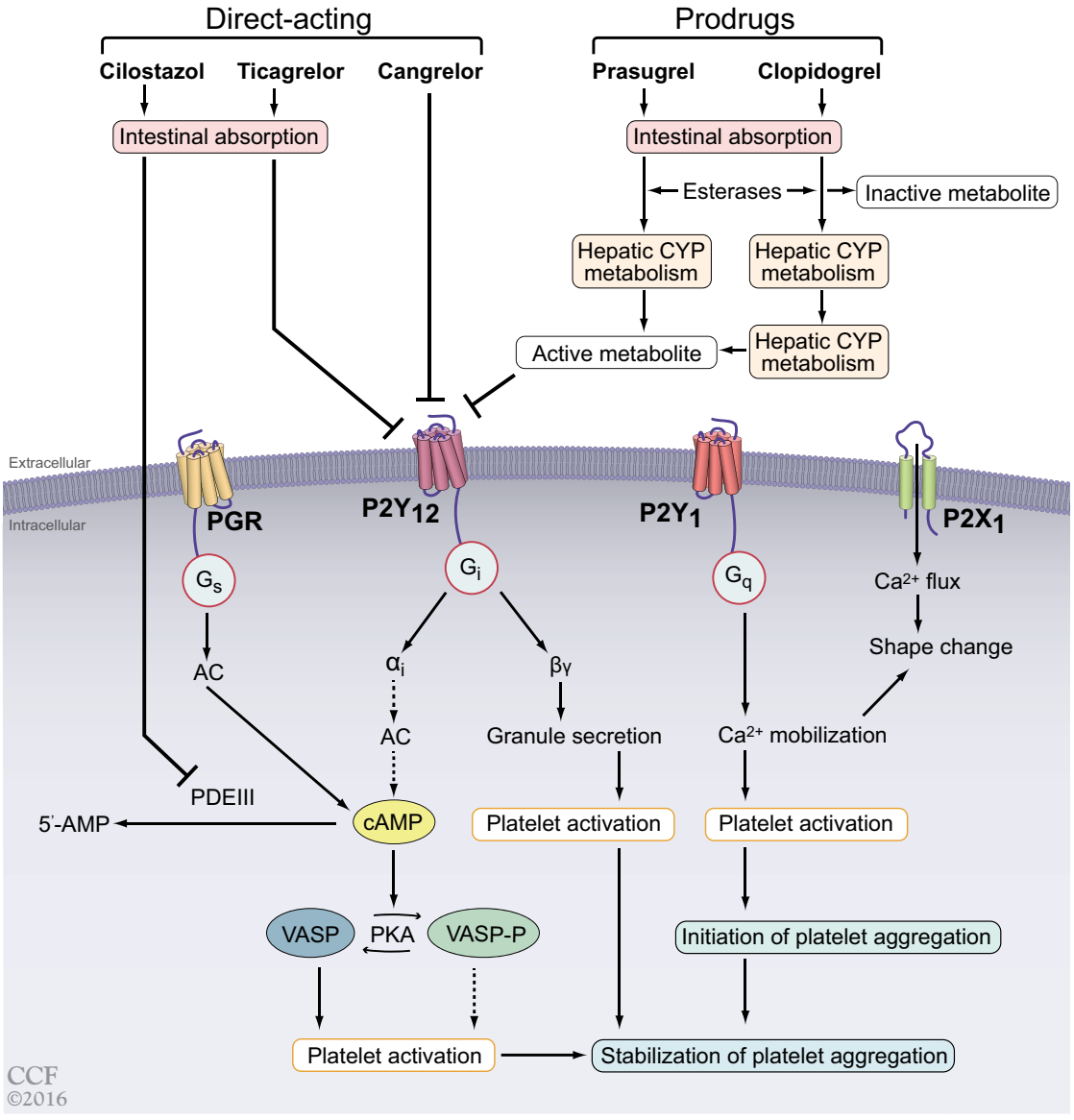

FIGURE 2. Mechanism of action of antiplatelet agents.

AC = adenyl cyclase; cAMP = cyclic adenosine monophosphate; Ca^{2+} = calcium; CYP = cytochrome P450; G_s, G_i, G_q = G proteins; PDEIII = phosphodiesterase III, PGR, $P2Y_{12}$, $P2Y_1$, $P2X_1$ = platelet receptors; PKA= protein kinase A; VASP = vasodilator-stimulated phosphoprotein; VASP-P = phosphorylated VASP

Techniques have evolved from balloon angioplasty to bare-metal stents to drug-eluting stents, but all pose a risk of thrombosis

each other and having additive effects (**Figure 2, Table 1**).[5,16–21]

Aspirin inhibits cyclo-oxygenase 1

Cyclo-oxygenase 1, found in platelets, endothelial cells, and other cells, catalyzes the conversion of arachidonic acid to thromboxane A_2. Aspirin irreversibly inhibits cyclo-oxygenase 1 by acetylating its serine residue, preventing formation of thromboxane A_2 and preventing platelet activation and aggregation.

$P2Y_{12}$ ADP receptor antagonists

Clopidogrel and prasugrel are thienopyridine agents that irreversibly inhibit the $P2Y_{12}$ receptor, thereby preventing binding of adenosine diphosphate and the subsequent platelet activation-aggregation cascade. They are both prodrugs and require conversion by cytochrome P450 enzymes to active metabolites. Prasugrel is 10 times more potent than clopidogrel due to more efficient formation of its

TABLE 1

Antiplatelet agents

Drug	Metabolic activation	Reversibility	Time to peak activity	Elimination half-life	Duration of effect	Elimination	Dosage
Aspirin	By esterases in gastrointestinal mucosa	No	1–2 hours	3 hours	7–10 days	Renal	162–325 mg loading dose, then 81–162 mg daily
Clopidogrel	By CYP450	No	2–6 hours	6 hours	5–7 days	Renal and gastrointestinal	300–600 mg loading dose, then 75 mg daily
Prasugrel	By CYP450	No	0.5–4 hours	2–15 hours	5–9 days	Renal and gastrointestinal	60 mg loading dose, then 10 mg daily
Ticagrelor	No	Yes	0.5–2 hours	7–9 hours	3–5 days	Gastrointestinal and renal	180 mg loading dose, then 90 mg twice a day
Cangrelor	No	Yes	2–30 minutes	3–5 minutes	0–30 minutes	Renal and gastrointestinal	4 µg/kg/min intravenous infusion

active metabolite, and it achieves a comparable effect on platelet inhibition 30 minutes faster than the peak effect of clopidogrel at 6 hours. The overall peak inhibitory effect of prasugrel is twice that of clopidogrel.[22]

Ticagrelor, a cyclopentyl-triazolo-pyrimidine, directly and reversibly inhibits the $P2Y_{12}$ ADP receptor. Unlike clopidogrel and prasugrel, it does not need to be converted to an active metabolite, and it noncompetitively inhibits $P2Y_{12}$ at a site different from the adenosine diphosphate binding site.[23] Like prasugrel, ticagrelor inhibits platelet function more rapidly and more completely than clopidogrel.

Cangrelor, an intravenously administered analogue of adenosine triphosphate, reversibly inhibits the $P2Y_{12}$ receptor. It has undergone phase 3 trials but is not yet approved for clinical use.[24]

WHY DUAL ANTIPLATELET THERAPY?

Aspirin is good, clopidogrel is better

Aspirin has a well-validated role in both primary and secondary prevention of coronary and noncoronary atherosclerotic vascular disease.

The CAPRIE trial found clopidogrel monotherapy to be superior to aspirin monotherapy in patients with established atherosclerotic vascular disease.[25]

After stenting, short-term dual therapy is better than short-term warfarin

Thrombotic complications in the early postprocedural period were a major limitation of stenting, and existing anticoagulation regimens were ineffective in preventing them.[26,27]

The ISAR trial studied the benefit of combined antiplatelet vs anticoagulant therapy after stent placement. Patients randomized to receive combined aspirin plus ticlopidine (an early $P2Y_{12}$ inhibitor) had significantly lower rates of primary cardiac, hemorrhagic, and vascular events at 30 days.[9] Two other trials confirmed this finding.[28,29]

STARS[10] also confirmed the benefit of aspirin and ticlopidine after stenting. Patients were randomly assigned to aspirin alone, aspirin plus warfarin, or aspirin plus ticlopidine after stent placement. The rate of stent thrombosis at 30 days was significantly lower in the dual antiplatelet group than in the other two groups. The dual antiplatelet group had a higher rate of bleeding than the aspirin-alone group, but the rate was similar to that of the aspirin-plus-warfarin group.

Prasugrel is 10 times more potent than clopidogrel due to more efficient formation of its active metabolite

Long-term dual antiplatelet therapy is beneficial in several situations

ISAR and STARS were landmark trials that showed stent thrombosis could be reduced by dual antiplatelet therapy for a 30-day period. However, the long-term role of dual antiplatelet therapy was still unknown.

The CURE trial[30–32] randomized patients presenting with acute coronary syndromes without ST elevation to receive clopidogrel plus aspirin or placebo plus aspirin for 3 to 12 months. The rate of the primary end point (cardiac death, nonfatal myocardial infarction, or stroke) was significantly lower in the clopidogrel-plus-aspirin group. A similar benefit of dual antiplatelet therapy was seen in the subgroup of patients who underwent percutaneous coronary intervention. Both pretreatment with clopidogrel plus aspirin for a median of 10 days prior to percutaneous intervention and continuing it for a mean of 9 months reduced major adverse cardiovascular events.

The CREDO trial[20] found that the combination of clopidogrel and aspirin significantly reduced the incidence of death, myocardial infarction, or stroke at 1 year after percutaneous coronary intervention. A subgroup of patients in this trial who had a longer pretreatment interval with a loading clopidogrel dose showed a benefit at 28 days, which was not as evident with a shorter loading dose interval.

Dual antiplatelet therapy improves outcomes with or without percutaneous coronary intervention

The CLARITY-TIMI 28 trial[33,34] showed the advantage of adding clopidogrel to aspirin in patients receiving fibrinolytic therapy for ST-elevation myocardial infarction. Adding clopidogrel both improved the patency of the infarct-related artery and reduced ischemic complications. In patients who subsequently underwent percutaneous coronary intervention and stenting, clopidogrel pretreatment was associated with a significant decrease in ischemic complications before and after the procedure. There was no significant increase in bleeding complications in either group.

COMMIT/CCS 2[35] also showed the benefit of dual antiplatelet therapy in patients with ST-elevation myocardial infarction. Clopidogrel added to aspirin during the short-term in-hospital or postdischarge treatment period significantly reduced a composite end point of reinfarction, death, or stroke as well as death from any cause.

The CHARISMA trial[36–38] aimed to determine if patients who were more stable (ie, no recent acute coronary syndrome event or percutaneous coronary intervention) would benefit. Overall, CHARISMA showed no benefit of adding clopidogrel to aspirin compared with aspirin alone in a broad population of patients with established vascular disease (secondary prevention) or risk factors for vascular disease (primary prevention).

But importantly, though no benefit was seen in the primary prevention group, the large subgroup of patients with established atherosclerotic vascular disease (12,153 of the 15,603 patients in the trial) did benefit from dual antiplatelet therapy.[36,37] This subgroup showed an overall reduction in absolute risk of 1.5% (relative risk 0.88, $P = .046$) over a median follow-up of 27.6 months. This benefit was even more apparent in the 9,478 patients with prior myocardial infarction, stroke, or peripheral artery disease, for whom the relative risk reduction was 17.1% ($P = .01$) and the reduction in absolute risk 1.5%.[38]

These results are comparable to the 2% absolute risk reduction in the CURE trial for similar end points over 9 months. In both studies, there was no significant increase in the risk of major bleeding or intracranial bleeding in the clopidogrel-plus-aspirin groups, although minor bleeding was increased by dual antiplatelet therapy.

The rate of severe bleeding, which was the primary safety end point in CHARISMA, was not significantly different in the clopidogrel-plus-aspirin group compared with the placebo-plus-aspirin group (relative risk 1.25, 95% CI 0.97–1.61, $P = .09$).

Thus, although the CHARISMA findings were negative overall, the positive finding observed in the predominant subgroup of patients with established vascular disease can therefore be considered supportive of the results of the subsequent trials discussed below.

The PEGASUS-TIMI 54 trial[39] studied the benefit of adding ticagrelor (60 or 90 mg) to low-dose aspirin in patients with stable coronary artery disease who had had a myocardial infarction 1 to 3 years earlier.

Confirming the results of the CHARISMA subgroup analysis, the incidence of the ischemic primary efficacy end point (a composite of car-

TABLE 2

ACC/AHA recommendations for initial antiplatelet therapy for patients with likely or definite non-ST-elevation myocardial infarction

Antiplatelet drug	Initial therapy (class of recommendation, level of evidence)[a]	Continued therapy (class of recommendation, level of evidence)[a]
General recommendations for non-ST-elevation myocardial infarction		
Aspirin	162–325 mg of nonenteric coated aspirin for all patients promptly after presentation (I, A)	81–162 mg/day indefinitely as maintenance dose (I, A)
$P2Y_{12}$ inhibitors	300–600 mg loading dose clopidogrel in patients with gastrointestinal intolerance or aspirin hypersensitivity (I, B) 300–600 mg loading dose of clopidogrel or 180 mg loading dose of ticagrelor in addition to aspirin in patients treated with an early invasive or ischemia-guided strategy (I, B) It is reasonable to use ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy (IIa, B)	Clopidogrel 75 mg/day as maintenance dose in patients with gastrointestinal intolerance or aspirin hypersensitivity (I, B) Clopidogrel 75 mg/day or ticagrelor 90 mg twice daily in addition to aspirin as maintenance dose for up to 12 months in patients treated with an early invasive or ischemia-guided strategy (I, B)
Recommendations for percutaneous coronary intervention (PCI)		
Aspirin	81–325 mg nonenteric coated aspirin before PCI in patients already taking aspirin (I, B) 325 mg nonenteric coated aspirin as soon as possible before PCI in patients not taking aspirin (I, B)	81–325 mg/day to be continued indefinitely after PCI (I, B) It is reasonable to use 81 mg/day in preference to a higher maintenance dose (IIa, B)
$P2Y_{12}$ inhibitors	A loading dose before PCI in patients undergoing stenting (I, A): Clopidogrel 300–60 mg (I, B) or Prasugrel 60 mg (I, B) or Ticagrelor 180 mg (I, B) It is reasonable to use ticagrelor in preference to clopidogrel for patients treated with an early invasive strategy or coronary stenting (IIa, B) It is reasonable to use prasugrel in preference to clopidogrel for patients who undergo PCI and are not at high risk of bleeding (IIa, B) Prasugrel should not be given to patients with a history of stroke or transient ischemic attack (III, B)	Maintenance dose to be continued for at least 12 months in patients receiving a bare-metal or drug-eluting stent. Options include: Clopidogrel 75 mg/day (I, B) or Prasugrel 10 mg/day (I B) or Ticagrelor 90 mg twice a day (I, B) If the morbidity of bleeding outweighs the anticipated benefit of duration of $P2Y_{12}$ inhibitor therapy after stent implantation, early discontinuation (ie, < 12 months) of $P2Y_{12}$ therapy is reasonable (IIa, C) Continuation of dual antiplatelet therapy beyond 12 months may be considered in patients undergoing stent implantation (IIb, C)

[a] Class of recommendation: I = treatment should be given, IIa = treatment is reasonable, IIb = treatment may be considered, III = treatment is not recommended or may harm. Level of evidence: A = multiple populations evaluated, B = limited populations evaluated, C = very limited populations evaluated.

Based on information in reference 2.

diovascular death, myocardial infarction, and stroke) was significantly lower in both groups receiving ticagrelor plus aspirin compared with those receiving placebo plus aspirin. The Kaplan-Meier rate at 3 years for the ticagrelor 90 mg-plus-aspirin group was 7.85% vs 9.04% for the placebo-plus-aspirin group (hazard ratio 0.85, 95% confidence interval [CI] 0.75–0.96, $P = .008$). The rate for the ticagrelor 60 mg-plus-aspirin group was 7.77% vs 9.04% for the placebo-plus-aspirin group (hazard ratio 0.84, 95% CI 0.74–0.95, $P = .004$).

The rates of all TIMI major and minor bleeding, as well as bleeding requiring transfu-

TABLE 3

ACC/AHA recommendations for antiplatelet therapy for patients with ST-elevation myocardial infarction (STEMI)

Antiplatelet drug	Initial therapy (class of recommendation, level of evidence)[a]	Continued therapy (class of recommendation, level of evidence)[a]
Antiplatelet therapy adjunctive to primary percutaneous coronary intervention (PCI)		
Aspirin	162–325 mg should be given to all patients before primary PCI (I, B)	81–325 mg maintenance dose indefinitely (I, A) 81 mg as preferred maintenance dose with ticagrelor (I, B)
$P2Y_{12}$ inhibitors	Loading dose should be given as early as possible or at the time of primary PCI in patients with STEMI. Options: Clopidogrel 300–600 mg (I, B) Prasugrel 60 mg (I, B) Ticagrelor 180 mg (I, B)	Maintenance dose should be continued for 1 year following a drug-eluting or bare metal stent placement. Options: Clopidogrel 75 mg daily (I, B) Prasugrel 10 mg daily (I, B) Ticagrelor 90 mg twice daily (I, B)
	Prasugrel should not be given to patients with a history of stroke or transient ischemic attack (III, B)	Continuation of $P2Y_{12}$ inhibitor beyond 1 year may be considered in patients with drug-eluting stent placement (IIb, C)
Antiplatelet therapy adjunctive to PCI after fibrinolytic therapy		
Aspirin	162–325 mg should be given to all patients who receive fibrinolytic therapy (I, A)	81–325 mg maintenance dose indefinitely (I, A) 81 mg is preferred maintenance dose (IIa, B)
$P2Y_{12}$ inhibitors	Clopidogrel loading dose based on age in all patients who receive fibrinolytic therapy (I, A) Age ≤ 75: 300 mg Age > 75: 75 mg	If drug-eluting stent placed: Continue $P2Y_{12}$ inhibitor for at least 1 year with either: Clopidogrel 75 mg daily (I, C) Prasugrel 10 mg daily (IIa, B)
	For patients who received loading dose during fibrinolytic therapy: clopidogrel 75 mg daily without an additional loading dose (I, C)	If bare-metal stent placed[b]: Continue therapy for at least 30 days and up to 1 year with either of the following: Clopidogrel 75 mg daily (I, C) Prasugrel 10 mg daily (IIa, B)
	For patients who did not receive loading dose during fibrinolytic therapy:	
	If PCI performed ≤ 24 hours after fibrinolytic therapy: clopidogrel 300 mg before or at the time of PCI (I, C)	
	If PCI performed > 24 hours after fibrinolytic therapy: clopidogrel 600 mg before or at the time of PCI (I, C)	
	If PCI performed > 24 hours after treatment with a fibrin-specific agent or > 48 hours after a non–fibrin-specific agent: prasugrel 60 mg at the time of PCI (IIa, B)	
	Prasugrel should not be given to patients with a history of stroke or transient ischemic attack (III, B)	

[a] Class of recommendation: I = treatment should be given, IIa = treatment is reasonable, IIb = treatment may be considered, III = treatment is not recommended or may harm. Level of evidence: A = multiple populations evaluated, B = limited populations evaluated, C = very limited populations evaluated.

[b] Balloon angioplasty without stent placement may be used in selected patients. It may be reasonable to provide P2Y12 inhibitor therapy to patients with ST-elevation myocardial infarction undergoing balloon angioplasty after fibrinolysis alone according to the recommendations listed for bare-metal stents (level of evidence C).

Based on information in reference 1.

TABLE 4

Randomized controlled trials of extended dual antiplatelet therapy after stent placement

Trial (No. of patients)	Design	Follow-up	Stent thrombosis (study vs control)	MACE (study vs control)	Bleeding events (study vs control	Conclusion
DAPT[3] (9,961)	DAPT vs aspirin alone beyond 12 months	18 months	0.4% vs 1.4% [a]	4.3% vs 5.9% [a]	2.5% vs 1.6% [a]	DAPT > 1 year decreased risk of stent thrombosis and MACE
ARCTIC–Interruption[46] (1,259)	DAPT vs aspirin alone beyond 12 months	17 months	0% vs 1%	4% vs 4%	1% vs < 0.5%	No benefit of DAPT beyond 12 months
DES-LATE[47] (5,045)	DAPT vs aspirin alone beyond 12 months	24 months	0.5% vs 0.3%	2.4 vs 2.6%	1.1% vs 1.4%	No benefit of DAPT for 24 more months at end of 1 year
CREDO[20] (2,116)	DAPT vs aspirin and placebo up to 12 months	12 months	Not reported	8.5% vs 11.5% [a]	8.8% vs 6.7% [a,b]	Significant benefit of DAPT vs placebo at 1 year
OPTIMIZE[42] (3,118)	DAPT for 3 vs 12 months	12 months	0.3% vs 0.1%	2.6% vs 2.6%	0.2% vs 0.4%	Noninferiority of 3 vs 12 months of DAPT
RESET[43] (2,117)	DAPT for 3 vs 12 months	12 months	0.2% vs 0.3%	4.7% vs 4.7%	0.5% vs 1%	Noninferiority of 3 vs 12 months DAPT
EXCELLENT[41] (1,493)	DAPT for 6 vs 12 months	12 months	0.9% vs 0.1%	8% vs 8.5%	0.3% vs 0.6%	Noninferiority of 6 vs 12 months of DAPT
PRODIGY[45] (1,970)	DAPT for 6 vs 12 months	12 months	3.9% vs 4.7%	10.1% vs 10%	1.6% vs 0.6% [a]	No significant benefit of 24 vs 6 months of DAPT with clopidogrel
SECURITY[40] (1,399)	DAPT for 6 vs 12 months	24 months	0.3% vs 0.4%	4.5% vs 3.7%	0.2% vs 0.3%	Noninferiority of 6 vs 12 months of DAPT

[a] $P < .05$.
DAPT = dual antiplatelet therapy; MACE = major adverse cardiac event

sion or discontinuation of the study drug, were significantly higher in both ticagrelor dosing groups than in the placebo group ($P < .01$ for both groups vs placebo). The rates of fatal bleeding and nonfatal intracranial hemorrhage were not significantly higher. Although there was an overall reduction in ischemic end points with the addition of ticagrelor, there was also a significantly higher incidence of bleeding in this group.

Comment. Thus, with or without percutaneous coronary intervention in acute coronary syndrome as well as in stable coronary artery disease, dual antiplatelet therapy was shown to improve outcomes and decrease ischemic complications compared with aspirin alone. It provided benefit in the setting of acute coronary syndrome (in the CURE trial) and percutaneous coronary intervention (in the CREDO trial) for up to 1 year.

Major questions remained to be addressed:

- Do the results of CREDO, which was performed before the current interventional era and the use of drug-eluting stents, reflect outcomes after current interventional practice?

- Could shorter periods of dual antiplatelet therapy be sufficient, especially with newer stents with less risk of late thrombosis?
- Does the benefit of dual antiplatelet therapy extend beyond the 1-year time period tested in those trials to date?

RECOMMENDATIONS FOR DOSING

The American College of Cardiology Foundation/American Heart Association guidelines for dosing of antiplatelet agents for non-ST-elevation myocardial infarction are summarized in **Table 2**, and those for ST-elevation myocardial infarction are summarized in **Table 3**.[1,2]

WOULD SHORTER THERAPY AFTER STENTING WORK AS WELL?

The American College of Cardiology Foundation/American Heart Association currently recommend dual antiplatelet therapy for at least 12 months after drug-eluting stent placement, with shorter courses appropriate for patients who develop excessive bleeding complications or who are at high risk of bleeding.

Four trials (**Table 4**) evaluated whether shorter durations of dual antiplatelet therapy would suffice: SECURITY,[40] EXCELLENT,[41] OPTIMIZE,[42] and RESET.[43] All of them showed that short-duration therapy was not inferior to standard-duration therapy.[44] These studies were comparable in that:

Studies were underpowered to make definitive conclusions about 6 vs 12 months of dual antiplatelet therapy

- Patients were randomized at the time of percutaneous coronary intervention or within 24 hours of it.
- Most patients received a second-generation drug-eluting stent, with the following exceptions: in EXCELLENT,[41] one-fourth of patients received a Cypher first-generation drug-eluting stent, and in RESET,[43] approximately one-fourth of the patients received a sirolimus-eluting stent in the standard-duration group for short lesions. Those patients with longer lesions in the RESET standard-duration group received an everolimus drug-eluting stent.
- The second antiplatelet added to aspirin in all studies was clopidogrel, with the exception of the SECURITY trial, in which fewer than 2% of patients received ticagrelor or prasugrel.[40]
- All the trials except RESET excluded patients who had had a myocardial infarction within 72 hours, and thus most patients studied had a lower risk profile.
- All of the trials sought to study noninferiority of short- vs standard-duration dual antiplatelet therapy, defined as the occurrence of a primary end point at 1 year (a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, target vessel failure or revascularization, or bleeding).

Their low-risk patient populations and infrequent end points rendered these studies underpowered to make definitive conclusions about the relative efficacy of 6-months vs 12-months of dual antiplatelet therapy.

WOULD LONGER THERAPY BE BETTER?

The PRODIGY trial[45] assessed durations of dual antiplatelet therapy both shorter and longer than the conventional 1 year, randomizing patients undergoing placement of a bare-metal stent, first-generation drug-eluting stent, or second-generation drug-eluting stent to receive aspirin and clopidogrel for either 6 months or 24 months. The study showed no significant difference in primary outcomes in the short- or long-duration groups.

Other trials that compared the standard 12 months of dual antiplatelet therapy with extended duration beyond 12 months were DAPT,[3] ARCTIC-Interruption,[46] and DES-LATE.[47] The trials were comparable in that:

- All patients were randomized after completing 12 months of dual antiplatelet therapy following drug-eluting stent placement.
- All patients who were included had been free of major cardiac ischemic events or bleeding during the 12 months following stent placement.
- The primary aim of all three studies was to compare primary end points in groups receiving aspirin alone vs extended dual antiplatelet therapy. The primary end point was a composite of death due to a cardiovascular cause, nonfatal myocardial infarction, stroke, or stent thrombosis.
- The principal safety end point was bleeding.

Although the two earlier studies (ARCTIC-Interruption and DES-LATE) did not

show any benefit of extended dual antiplatelet therapy compared with the standard 12-month duration, the recent DAPT study did.

The DAPT study

The DAPT study[3] was an international, multicenter, placebo-controlled, double-blind randomized trial designed to examine the benefit of dual antiplatelet therapy beyond 1 year in a patient population large enough to provide definitive assessment of benefit and risk.

A total of 9,961 patients who received drug-eluting stents were randomized after 12 months of dual antiplatelet therapy to receive either a thienopyridine (clopidogrel or prasugrel) plus aspirin or placebo plus aspirin. They were followed for an additional 18 months. The coprimary efficacy end points were stent thrombosis and a composite of death, myocardial infarction, or stroke, while the primary safety end point was moderate or severe bleeding. The patients were also observed from months 30 to 33 on aspirin alone after stopping the thienopyridine.

Results. Longer therapy substantially reduced the risks of stent thrombosis (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17–0.48) and the composite ischemic end point (HR 0.71, 95% CI 0.59–0.85). Follow-up during the 3-month thienopyridine discontinuation phase starting at 30 months revealed convergence of the ischemic event-rate curves in the two groups, which suggested that continuing dual antiplatelet therapy beyond 30 months might have been beneficial. Myocardial infarction unrelated to stent thrombosis accounted for 55% of the treatment benefit of dual antiplatelet therapy.

The risk of bleeding was higher in the thienopyridine group during the treatment period (2.5% vs 1.6%, $P = .001$). There was also a higher rate of noncardiovascular mortality in the thienopyridine group, although this difference may have been due to chance.[3,48]

Why were the results different?

All three trials included first- and second-generation drug-eluting stents, with different proportions in different trials. In ARCTIC-Interruption,[46] 43% of the patients in the continuation group had a first-generation stent, as did 64% of the patients in the dual antiplatelet group of DES-LATE.[47] In the DAPT trial,[3] 38% of the patients in the longer-duration arm had a first-generation stent, and in 26% of cases it was a paclitaxel-eluting stent.

Only clopidogrel was used as the second antiplatelet agent in DES-LATE, whereas prasugrel was used in 10% of patients in ARCTIC-Interruption and 35% in DAPT.

Yet none of these differences seem to explain the differences in outcome among the studies. ARCTIC-Interruption and DES-LATE did not show any benefit of continued dual antiplatelet therapy beyond 12 months. DAPT showed benefit of extended therapy with prasugrel or with clopidogrel, and with first-generation or second-generation drug-eluting stents. The most likely explanation for the different results was that DAPT was the only trial sufficiently powered to definitively assess the end points, including stent thrombosis.

A balance between ischemic efficacy and bleeding risk is the major consideration with any antithrombotic and antiplatelet therapy. In the three largest trials we discussed (the vascular disease subgroups of CHARISMA,[38] PEGASUS,[39] and DAPT[3]), comparison of the prespecified efficacy and safety end points of each trial suggests that dual antiplatelet therapy has a net benefit, particularly given the irreversible nature of ischemic end points.

In CHARISMA,[38] 60 cardiovascular deaths, myocardial infarctions, or strokes were prevented per year per 10,000 patients treated, at the cost of 28 excess moderate bleeding events.

In PEGASUS,[39] 42 cardiovascular deaths, myocardial infarctions, or strokes were prevented, at the cost of 79 excess bleeding events requiring transfusion.

In DAPT (a selected population who had tolerated dual antiplatelet therapy for 1 year), 106 deaths, myocardial infarctions, or stroke events were prevented, at the cost of 47 excess moderate bleeding events[3]

Indirect comparisons between trials are problematic, given different end point definitions, populations, and background therapies. But their results suggest that less-intensive inhibition with clopidogrel as the second antiplatelet long-term (as in CHARISMA) may provide the best balance of benefit vs risk.

Event curves continue to diverge, indicating the advantage of dual antiplatelet therapy may persist indefinitely

BALANCING RISK AND BENEFIT

The evidence is unequivocal that dual antiplatelet therapy suppresses coronary ischemic complications resulting from thrombosis at sites of spontaneous plaque rupture following acute coronary syndromes or mechanical plaque disruption and foreign body implantation associated with percutaneous coronary intervention.

Three large-scale trials (DAPT,[3] PEGASUS,[39] and the secondary prevention subgroup of CHARISMA[38]) showed that the protective effect of dual antiplatelet therapy continues with prolonged therapy in patients who have experienced an acute coronary syndrome event or have received a drug-eluting stent. That benefit seems to be due to the action of these therapies on the culprit vessel (the one that caused the acute coronary syndrome or the site of stenting), as well as nonculprit arteries, emphasizing that dual antiplatelet therapy protects against atherosclerosis progression and future plaque rupture events.

For the durations studied in the longest trials thus far, 30 months (DAPT[3]) and 36 months (PEGASUS[39]), event curves continue to diverge, indicating that the advantage of dual antiplatelet therapy may persist for an indefinite period of time. Thus, indefinite therapy with dual antiplatelet agents can be supported, particularly in patients with advanced coronary artery disease or those who have had multiple coronary events.

There has been little success in guiding dual antiplatelet therapy based on ischemic vs bleeding risk

We believe that the balance of evidence suggests that smaller studies that failed to show a benefit of longer-term therapy were underpowered to do so.

The ischemic protection is associated with the adverse effect of increased bleeding risk. Unfortunately, there has been little success in guiding dual antiplatelet therapy based on ischemic vs bleeding risk, in part because the same factors that predict risk of ischemic complications seem to predict increased susceptibility to bleeding. Nevertheless, indirect comparisons between studies suggest that for longer-term therapy clopidogrel may be superior to ticagrelor or prasugrel: the absolute excess bleeding risk with dual antiplatelet therapy vs aspirin in the CHARISMA secondary prevention subgroup was less than that in PEGASUS, with similar absolute reductions in ischemic events. So while the TRITON-TIMI 38[22] and PLATO[23] trials support the superiority of prasugrel or ticagrelor over clopidogrel for the first year after acute coronary syndrome, subsequent years of therapy may best be provided with clopidogrel.

Some patients may have identifiable factors that place them at very high risk of bleeding—need for surgical procedures, need for anticoagulation, or occurrence of bleeding complications or excessive "nuisance bleeding." In those patients, the data suggest that dual antiplatelet therapy could be discontinued after 6 months, or perhaps even 3 months in the highest bleeding risk circumstances after second-generation drug-eluting stent placement.

WOEST[49] was an open-label randomized controlled trial that studied the safety of antiplatelet regimens in patients on anticoagulation requiring percutaneous coronary interventions. Patients were randomized to double therapy with anticoagulant and clopidogrel vs triple therapy with additional aspirin following percutaneous coronary intervention. The primary end point was bleeding events within 1 year. Clopidogrel without aspirin was associated with significantly fewer bleeding events compared with triple therapy, with no increase in adverse ischemic events. The strategy tested in the WOEST trial seems reasonable in the specific group of patients who require ongoing anticoagulant therapy after drug-eluting stent placement, recognizing that the trial was somewhat underpowered to make definitive conclusions, particularly in patients at high risk for stent thrombosis.

Based on the results of PEGASUS and the CHARISMA subgroup with established ischemic burden, in which dual antiplatelet therapy was started after an interruption following the index coronary event, it is also reasonable to restart long-term dual antiplatelet therapy in patients who require interruption for short-term indications such as a surgical procedure. ■

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