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Dual antiplatelet therapy in coronary artery disease: A case-based approach

ABSTRACT

Current guidelines support dual antiplatelet therapy with aspirin and clopidogrel (Plavix) in a number of clinical scenarios, ie, in ST-segment-elevation myocardial infarction (MI), non-ST-elevation MI, and percutaneous coronary intervention. The guidelines are based on strong evidence from several large randomized clinical trials over the last 10 years. The authors present several cases to show how to put this evidence into day-to-day clinical practice.

KEY POINTS

Dual antiplatelet therapy is recommended after ST-elevation MI or non-ST-elevation acute coronary syndromes, with aspirin indefinitely and clopidogrel for up to 1 year.

Dual antiplatelet therapy is recommended for at least 1 month after placement of a bare-metal stent and for at least 1 year (or possibly indefinitely) after placement of a drug-eluting stent.

There is no compelling indication for clopidogrel in patients with chronic coronary artery disease.

Compared with clopidogrel, prasugrel (Effient) is associated with lower rates of MI, urgent target-vessel revascularization, and in-stent thrombosis, but at the cost of a higher risk of major bleeding.

PLAQUE RUPTURE AND THROMBOSIS play central roles in the genesis of acute coronary syndrome. Aspirin has long been the preventive agent of choice. But dual antiplatelet therapy with aspirin plus clopidogrel (Plavix) is warranted in many patients to further reduce their risk of future cardiovascular events.

Although dual antiplatelet therapy is usually started by a subspecialist, the primary care physician is often the one who ensures that the patient remains compliant with it in the long term. A review of the seminal published data is helpful in understanding the rationale behind dual antiplatelet therapy and its risks and benefits.

In the mid-1990s, the thienopyridine ticlopidine (Ticlid) was found to significantly decrease the number of deaths, target-lesion revascularizations, and myocardial infarctions (MIs) in the 30 days following stent placement.¹ However, 2% to 3% of patients experienced neutropenia² and thrombotic thrombocytopenic purpura with this drug,³ leading to the use of clopidogrel, another agent in the same class. Over the past decade, a large body of evidence has established the usefulness of clopidogrel in a number of clinical settings.

In this paper we review the current use of clopidogrel in ST-elevation MI, non-ST-elevation acute coronary syndromes, and percutaneous coronary intervention, and discuss the landmark trials that are the basis for the treatment guidelines published jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA).⁴⁻⁶ We also briefly discuss the use of prasugrel (Effient), the newest antiplatelet agent to gain

*Dr. Raymond has disclosed that he owns stock in Pfizer corporation.

doi:10.3949/ccjm.76a.09045

ROLE OF DUAL ANTIPLATELET THERAPY

TABLE 1

Major randomized clinical trials of clopidogrel

TRIAL	N	RESULTS
As a substitute for aspirin		
CAPRIE ⁸	19,185	9% lower incidence of ischemic stroke, myocardial infarction, or vascular death with clopidogrel (Plavix) vs aspirin in patients with recent ischemic stroke, MI, or symptomatic peripheral arterial disease
In acute ST-elevation MI		
CLARITY-TIMI 28 ⁹	3,491	31% lower incidence of death, occluded infarct artery, or recurrent MI with clopidogrel plus aspirin vs placebo plus aspirin
COMMIT ¹⁰	45,852	8% lower incidence of death, MI, or stroke with clopidogrel plus aspirin vs placebo plus aspirin
In non-ST-elevation acute coronary syndromes		
CURE ¹¹	12,562	18% lower incidence of death, MI, or stroke with clopidogrel plus aspirin vs placebo plus aspirin
After bare-metal stent placement		
CREDO ¹⁴	2,116	27% reduction in the combined risk of death, MI, or stroke with clopidogrel plus aspirin vs placebo plus aspirin
PCI-CURE ¹⁵	2,658	30% lower incidence of death, MI, or urgent target-vessel revascularization in 30 days with clopidogrel plus aspirin vs placebo plus aspirin
In stable coronary artery disease		
CHARISMA ²³	15,603	0.5% lower incidence of death, MI, or stroke (difference not statistically significant) with clopidogrel plus aspirin compared with placebo plus aspirin

CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CLARITY-TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CREDO = Clopidogrel for the Reduction of Events During Observation; PCI-CURE = Analysis of CURE patients who underwent a percutaneous coronary intervention; CHARISMA = Clopidogrel for High Atherothrombotic and Ischemic Stabilization, Management, and Avoidance

approval from the US Food and Drug Administration (FDA).

CLOPIDOGREL AS AN ALTERNATIVE TO ASPIRIN

Clopidogrel, a prodrug, is converted into its active form in the liver.⁷ It then irreversibly binds to the platelet P2Y12 receptor and inhibits adenosine diphosphate-induced platelet aggregation.

The CAPRIE trial⁸ (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) provided the data on the basis of which clopidogrel was approved by the FDA in 1998 (TABLE 1). In this trial, 19,185 patients with recent ischemic stroke, MI, or symptomatic peripheral arterial disease were randomized to receive

clopidogrel or aspirin and were followed for 1 to 3 years.

Those treated with clopidogrel had an annual risk of ischemic stroke, MI, or vascular death of 5.32%, compared with 5.83% in the aspirin group, for a statistically significant 8.7% relative risk reduction ($P = .043$). The observed frequency of neutropenia (neutrophils $< 1.2 \times 10^9/L$) was 0.10% with clopidogrel vs 0.17% with aspirin. This study showed clopidogrel to be an effective alternative in patients who cannot tolerate aspirin.

CASE 1: ST-ELEVATION MI

A 57-year-old farmer in rural Ohio with a history of hypertension and hyperlipidemia pre-

TABLE 2

ACC/AHA guidelines for dual antiplatelet therapy with aspirin and clopidogrel

ST-segment-elevation myocardial infarction (MI)⁴

Clopidogrel (Plavix) 75 mg per day orally should be added to aspirin in patients with ST-elevation MI regardless of whether or not they undergo reperfusion with a fibrinolytic (level of evidence: A)

Treatment with clopidogrel should continue for at least 14 days (level of evidence: B)

Long-term maintenance therapy (eg, 1 year) with clopidogrel 75 mg daily is reasonable in these patients, regardless of whether or not they undergo reperfusion with a fibrinolytic (level of evidence: C)

Non-ST-elevation acute coronary syndromes⁵

Aspirin 75 mg to 162 mg daily, indefinitely (level of evidence: A)

Clopidogrel 75 mg daily for at least 1 month (level of evidence: A) and ideally up to 1 year (level of evidence: B)

Percutaneous coronary intervention with placement of a bare-metal stent⁶

Aspirin 162 mg to 325 mg daily for at least 1 month, and then 75 to 162 mg indefinitely (level of evidence: B)

Clopidogrel 75 mg daily for at least 1 month and ideally up to 1 year However, if the patient is at increased risk of bleeding, then it should be given for a minimum of 2 weeks (level of evidence: B)

Percutaneous coronary intervention with placement of a drug-eluting stent⁶

Aspirin 162 to 325 mg daily for at least 3 months for a sirolimus-eluting stent, then 75 to 162 mg daily indefinitely

Aspirin 162 to 325 mg daily for at least 6 months for paclitaxel-eluting stent, then 75 to 162 mg daily indefinitely

Clopidogrel 75 mg daily for at least 12 months if patient is not at high risk of bleeding (level of evidence: B)

ACC = American College of Cardiology; AHA = American Heart Association

The value of clopidogrel in ST-elevation MI is well established

sents to the local emergency department 45 minutes after the onset, while he was chopping wood, of dull, aching, substernal chest pain that radiates to his jaw. Electrocardiography reveals 2-mm ST-segment elevation in leads V₁ through V₆. He is treated with aspirin 162 mg, low-molecular-weight heparin, and tenecteplase.

What would be the value of starting dual antiplatelet therapy with clopidogrel in this patient?

Clopidogrel, aspirin, and fibrinolysis in ST-elevation MI

The value of clopidogrel in ST-elevation MI is well established. The 2007 ACC/AHA guidelines include specific recommendations pertinent to this case (TABLE 2).⁴ These guide-

lines are supported by the results of two large randomized clinical trials.

The CLARITY-TIMI 28 trial (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction)⁹ included 3,491 patients (ages 18 to 75) from 319 international sites. All patients received a fibrinolytic agent, aspirin (162 mg to 325 mg on the first day and 75 mg to 162 mg thereafter), and heparin as part of standard care for acute ST-elevation MI (TABLE 1). Patients were randomized to receive a 300-mg loading dose of clopidogrel followed by 75 mg daily or placebo within 12 hours of onset of ST-elevation MI. The status of the infarct-related artery was ascertained by protocol-mandated coronary angiography 48 to 192 hours after starting the study medication. The primary end point was

the composite of an occluded infarct-related artery on angiography, death from any cause prior to angiography, or recurrent MI prior to angiography.

Significantly fewer patients had an end point event in the clopidogrel group than in the placebo group, 15% vs 21.7% ($P < .001$), for a relative risk reduction of 31%. There was no significant increase in major or minor bleeding events.

Of note, the CLARITY-TIMI 28 patients were relatively young (average age 57 years) and at low cardiovascular risk (30-day mortality risk < 5%).

The COMMIT trial (Clopidogrel and Metoprolol in Myocardial Infarction)¹⁰ consisted of 45,852 patients with suspected acute MI admitted to 1,250 hospitals in China. Each patient received aspirin 162 mg daily plus either clopidogrel 75 mg daily ($n = 22,961$) or placebo ($n = 22,891$) for the duration of hospitalization (average 16 days) or 28 days, whichever came first.

The incidence of the primary composite end point of death, reinfarction, or stroke was significantly lower with clopidogrel than with placebo (9.2% vs 10.1%, $P = .002$). This was regardless of age (the average age was 61, and 26% of patients were older than 70), sex, time to presentation (67% presented within 12 hours), or reperfusion strategy (49% underwent fibrinolysis). The clopidogrel group did not have a significantly higher incidence of bleeding, but patients in this trial did not receive a loading dose of clopidogrel.

Comment. In view of the results of these trials, our 57-year-old patient should start clopidogrel early.

CASE 2: NON-ST-ELEVATION ACUTE CORONARY SYNDROME

A 65-year-old woman living independently with no significant medical history presents to the emergency room with 2 hours of waxing and waning substernal chest pain. Her blood pressure is 145/90 mm Hg, her heart rate is 95 beats per minute, and the results of her physical examination are unremarkable. Resting electrocardiography reveals 1.5-mm ST-segment depression in the inferior leads, and her troponin T level on admission is two times the upper limit of normal. She is given aspirin and

is started on low-molecular-weight heparin and intravenous nitroglycerin.

What would be the value of starting clopidogrel in this patient?

Clopidogrel in non-ST-elevation acute coronary syndromes

The ACC/AHA guidelines strongly support starting clopidogrel in patients with non-ST-elevation acute coronary syndromes (TABLE 2).⁵

The CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events)¹¹ provided the evidence for this recommendation. In this trial, 12,562 patients from 482 centers in 28 countries who presented within 24 hours of coronary symptoms, without ST elevation, were randomized to receive either clopidogrel (a 300-mg loading dose, followed by 75 mg daily) or placebo for 3 to 12 months (mean 9 months).

Significantly fewer patients in the clopidogrel group reached one of the end points of the composite primary outcome (cardiovascular death, nonfatal MI, or stroke): 9.3% vs 11.4%, 95% confidence interval (CI) 0.72–0.90, $P < .001$. Significantly fewer of them also suffered one of the secondary outcomes, ie, severe ischemia, heart failure, or need for revascularization.

Of concern was a higher rate of major bleeding in the clopidogrel group (3.7%) than in the placebo group (2.7%) without an excess of fatal bleeding. For every 1,000 patients treated with clopidogrel, 6 required a blood transfusion. Nevertheless, CURE proved that patients with non-ST-elevation acute coronary syndromes benefited from clopidogrel, regardless of whether they underwent percutaneous coronary intervention.

Comment. Our patient should receive clopidogrel and, if she has no significant bleeding, she should continue to take it for at least 12 months after discharge. It is important for the primary care physician to ensure compliance with this agent and not discontinue it on routine clinical follow-up.

CASE 3: BARE-METAL STENT PLACEMENT

A 62-year-old man with a history of hypertension, diabetes, and hyperlipidemia presents to

The guidelines support starting clopidogrel in non-ST-elevation acute coronary syndromes

his primary care physician's office with stable-effort angina that is not responding to an excellent anti-ischemic regimen and is affecting his quality of life. He is referred for coronary angiography, which reveals 80% stenosis of the proximal left circumflex artery. He undergoes a percutaneous coronary intervention with placement of a bare-metal stent.

How long should he be on clopidogrel? And what if a drug-eluting stent had been placed instead of a bare-metal stent?

Dual therapy after bare-metal stent placement

Dual antiplatelet therapy with clopidogrel and aspirin is recommended in all patients receiving a stent (**TABLE 2**). The better safety and efficacy of clopidogrel compared with ticlopidine has been established in patients receiving a coronary artery stent,^{12,13} and clopidogrel's favorable safety profile soon made it the thienopyridine of choice.

The CREDO trial (Clopidogrel for the Reduction of Events During Observation)¹⁴ randomized 2,116 patients undergoing an elective percutaneous coronary intervention (bare-metal stent placement only) to receive a 300-mg loading dose of clopidogrel 3 to 24 hours before the procedure, or placebo. All patients received 325 mg of aspirin. After the intervention, all patients received clopidogrel 75 mg daily and aspirin 325 mg daily through day 28. For day 29 through 12 months, those who had received the 300-mg preprocedural loading dose of clopidogrel continued with 75 mg daily, and those who had not received clopidogrel before the procedure received placebo.

No significant difference was seen in the primary outcome for those who received pretreatment with clopidogrel; however, in a subgroup analysis, those who received clopidogrel at least 6 hours before the percutaneous coronary intervention had a 38.6% relative risk reduction (**TABLE 1**). Long-term use of clopidogrel (ie, for 12 months) was associated with an overall relative reduction of 26.9% in the combined risk of death, MI, or stroke.

PCI-CURE, an analysis of 2,658 patients in the CURE trial with non-ST-elevation acute coronary syndrome who underwent PCI,¹⁵ yielded results similar to those of CRE-

DO, with a 31% reduction in the rate of cardiovascular death or MI at 30 days and at 9 months. Of note, however, clopidogrel was given for a median of 6 days prior to the procedure.

Comment. The minimum suggested duration of clopidogrel treatment after placement of a bare-metal stent is 1 month. However, these trial results indicate that patients who are not at high risk of bleeding should take clopidogrel for at least 12 months.

Dual antiplatelet therapy with drug-eluting stents

Although rates of in-stent restenosis are clearly lower with drug-eluting stents than with bare-metal stents, the antiproliferative effect of drug-eluting stents may delay complete endothelialization of every strut. This may contribute to late (> 1 month after placement) or very late (> 1 year) thrombosis of the stent after clopidogrel is discontinued.^{16–18}

In 2006, the FDA indicated that dual antiplatelet therapy was needed for 6 months with paclitaxel-eluting (Taxus) stents and 3 months with sirolimus-eluting (Cyper) stents. As reports of very late stent thrombosis began to appear in 2007, concern arose over the need to extend the duration of clopidogrel treatment.

Bavry et al¹⁹ quantified the incidence of late and very late stent thrombosis in a meta-analysis of 14 clinical trials that randomized patients to receive either a drug-eluting stent (paclitaxel or sirolimus) or a bare-metal stent.¹⁹ The incidence of stent thrombosis within 30 days in this analysis was similar for both groups—4.4 per 1,000 patients vs 5 per 1,000 (relative risk 0.89; 95% CI 0.46–1.75; $P = .74$). However, the rate of very late stent thrombosis was significantly higher in those receiving a drug-eluting stent vs a bare-metal stent—5 per 1,000 patients treated (relative risk 5.02, 95% CI 1.29–19.52; $P = .02$).

The results of this and other studies led the ACC and AHA to revise their joint guidelines to recommend thienopyridine treatment for at least 1 year for patients who receive a drug-eluting stent.^{6,20–22} In fact, many cardiologists consider indefinite dual antiplatelet therapy in patients with a drug-eluting stent to avoid very late in-stent thrombosis, especially in

Patients with a drug-eluting stent need dual antiplatelet therapy for at least 1 year after stent placement

patients undergoing high-risk interventions such as placement of multiple stents, bifurcation lesions, and unprotected left main trunk interventions.

Thus, when faced with a patient with a recent coronary stent implantation, the primary care physician should be aware of the type of stent and the duration of therapy recommended by the interventional cardiologist. Also, in the absence of a pressing indication, elective surgery should be deferred for 1 year after placement of a drug-eluting stent, as this would necessitate stopping clopidogrel and would increase the risk of perioperative stent thrombosis, which is associated with high rates of morbidity and death.

CASE 4: HIGH-RISK CORONARY ARTERY DISEASE

A 67-year-old woman presents to your office to establish care. She has a history of diabetes and established coronary artery disease with two bare-metal stents placed 2 years ago. She is taking aspirin 81 mg.

What would be the value of adding clopidogrel to her regimen?

No indication for clopidogrel in chronic coronary artery disease

The CHARISMA trial (Clopidogrel for High Atherothrombotic and Ischemic Stabilization, Management, and Avoidance)²³ randomized 15,603 patients with stable cardiovascular disease or multiple risk factors to receive either clopidogrel plus low-dose aspirin or placebo plus low-dose aspirin and followed them for a median of 28 months (**TABLE 1**).

The primary end point (a composite of MI, stroke, or death) was 6.8% with clopidogrel plus aspirin and 7.3% with aspirin alone, indicating no significant benefit with clopidogrel plus aspirin compared with aspirin alone in reducing the rate of MI, stroke, or cardiovascular death in patients with high-risk but stable atherothrombotic disease. A marginal statistical benefit with dual antiplatelet therapy was noted in the subgroup of patients with previously documented coronary, cerebrovascular, or peripheral vascular disease—6.9% with aspirin plus clopidogrel vs 7.9% with aspirin alone (relative risk 0.88; 95% CI 0.77–0.998;

$P = .046$).

Consequently, there is no compelling reason to start clopidogrel in this patient.

PRASUGREL, THE NEWEST THIENOPYRIDINE

Prasugrel was recently approved by the FDA as antiplatelet treatment for patients with acute coronary syndromes planning to undergo a percutaneous coronary intervention.²⁴ It has been shown to inhibit adenosine-diphosphate-induced platelet activation in a more consistent and effective manner than clopidogrel.^{25,26}

Although both clopidogrel and prasugrel are prodrugs, 80% of absorbed clopidogrel is metabolized by esterases into inactive metabolites, and the availability of active metabolite can vary, as it is significantly influenced by polymorphisms in the cytochrome P450 system.²⁷ In contrast, prasugrel is not degraded by esterases, and its conversion to active metabolite by the cytochrome P450 system is not influenced by common genetic polymorphisms, particularly CYP2C19*2.

TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction) provided most of the evidence for the approval of prasugrel for clinical use.^{28,29} In this trial, a 60-mg loading dose of prasugrel followed by a daily maintenance dose of 10 mg was significantly superior to the current clopidogrel regimen in preventing death from cardiovascular causes, nonfatal MI, or nonfatal stroke during a study period of 15 months.²⁸ Also observed was a 24% lower rate of MI, a 34% lower rate of urgent target-vessel revascularization, and a 52% lower rate of stent thrombosis.

These benefits, however, came at the cost of a significantly higher risk of major bleeding, including the potential for three excess fatal bleeding events for every 1,000 patients treated. Patients at highest risk at the dosages evaluated included the elderly (age 75 and older), patients who weigh less than 60 kg, and patients with a history of stroke or transient ischemic attack. Based on these results, we recommend caution with the use of prasugrel in these patient subsets.

Clinical use of prasugrel is likely to be high-

**Metabolism
of clopidogrel
is affected by
polymorphisms
in the
cytochrome
P450 system**

est in patients presenting with ST-elevation MI who are undergoing a primary percutaneous coronary intervention. There is currently no evidence from any randomized clinical trial to support the safety of prasugrel given in the emergency room or "upstream" in the setting of non-ST-elevation acute coronary syndromes.

Of note, patients with non-ST-elevation

acute coronary syndromes in the TRITON trial were randomized only after angiographic definition. As a result, only 179 patients exposed to prasugrel were referred for coronary artery bypass surgery, but the rate of surgery-related major bleeding in this group was 13.4% (vs 3.2% in the clopidogrel group). Based on these data, prasugrel should be withheld for at least 1 week prior to any surgery. ■

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