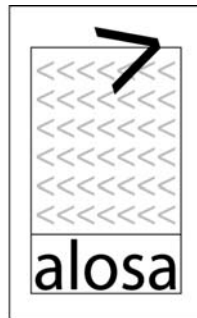


Antiplatelet therapy update

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The Alosa Foundation



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Several recent studies have added to our knowledge of antiplatelet therapy:

- (1) The [Prevention Regimen for Effectively Avoiding Second Strokes \(PROFESS\)](#) study¹ compared aspirin-dipyridamole with clopidogrel for secondary prevention in patients with a recent ischemic stroke;
- (2) The [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial \(TRITON-TIMI 38\)](#) study² compared prasugrel (a new antiplatelet agent) to clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI);
- (3) Two studies, [The Prevention of Progression of Arterial Disease and Diabetes \(POPADAD\)](#)³ and [Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes \(JPAD\)](#)⁴, add to the uncertainty about the efficacy of aspirin for the primary prevention of cardiovascular events in type 2 diabetes.

In addition, evidence continues to emerge regarding the genetic determinants and clinical significance of resistance to clopidogrel therapy. In this clinical update we highlight key findings of these trials and issues.

The PRoFESS study

Background

Two large randomized clinical trials have examined dipyridamole and aspirin for the secondary prevention of stroke or TIA. The [European Stroke Prevention Study 2 \(ESPS2\)](#)⁵ found that both aspirin and dipyridamole as monotherapy were significantly better than placebo in preventing recurrent stroke, and aspirin-dipyridamole in combination was significantly better than either agent alone. More recently, the [European/Australasian Stroke Prevention in Reversible Ischemia Trial \(ESPRIT\)](#)⁶ found that aspirin-dipyridamole in combination was significantly better than aspirin alone in preventing serious vascular events in patients with a recent transient ischemic attack (TIA) or ischemic stroke.

Indirect comparisons from a recent meta-analysis suggest that aspirin-dipyridamole in combination is more effective than clopidogrel in the secondary prevention of serious vascular events after TIA or stroke.⁷

PRoFESS

The [PRoFESS](#) study¹ was the first trial to directly compare clopidogrel with aspirin-dipyridamole in combination for patients with a recent ischemic stroke (within 90 days prior to randomization). Patients received either 25 mg of aspirin plus 200 mg of extended-release dipyridamole (ASA-ERDP) twice daily or 75 mg of clopidogrel daily.

The primary outcome was first recurrence of stroke. The secondary outcome was a composite of stroke, myocardial infarct (MI), or death from vascular causes. A total of 20,332 patients were followed for a mean of 2.5 years. Study results are shown below.

Table 1. PRoFESS outcomes

	ASA-ERDP Group	Clopidogrel Group	Hazard Ratio
Stroke	9.0%	8.8%	Not significantly different between groups
Composite of stroke, MI, or death from vascular causes	13.1%	13.1%	Not significantly different between groups
Major hemorrhagic events	4.1%	3.6%	Not significantly different between groups
Intracranial hemorrhage	1.4%	1.0%	1.42; 95% CI, 1.11 to 1.83
Recurrent stroke or major hemorrhagic event	11.7%	11.4%	Not significantly different between groups

The trial showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There was no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.

What we already know

- Aspirin-dipyridamole is more effective than aspirin alone in reducing recurrent stroke and other serious vascular events in patients with recent stroke.
- There is no clear benefit of clopidogrel over aspirin in the secondary prevention of stroke. Consider clopidogrel if patient has a stroke while on aspirin therapy, or has an aspirin allergy.
- The comparative benefit of aspirin-dipyridamole and clopidogrel is unclear.

What PROFESS adds

- Clopidogrel may offer similar efficacy to aspirin-dipyridamole in the prevention of recurrent stroke in patients with a recent ischemic stroke.

Bottom line

- The PROFESS study does not alter current recommendations for the use of aspirin-dipyridamole for the secondary prevention of ischemic stroke in patients who have had a stroke within the previous 6 months.
- In patients who have had an ischemic stroke more than 6 months ago:
 - Clopidogrel is recommended in high risk patients (history of coronary artery disease, stroke, or TIA, **and** any of the following: bypass surgery, events involving multiple vascular beds, two or more ischemic events, diabetes, or high cholesterol). Also, consider clopidogrel if a patient has had a stroke while on aspirin therapy, or in cases of aspirin allergy.
 - Aspirin is recommended for all other patients.

Prasugrel – a new antiplatelet drug

TRITON-TIMI 38

The **TRITON-TIMI 38** study² randomized 13,608 patients with acute coronary syndrome and scheduled for PCI to receive:

- prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose); **or**
- clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose)

The primary efficacy end point was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The primary safety end point was major bleeding, and treatment follow-up was for between 6 and 15 months. Most (94%) patients had received PCI with an intracoronary stent before randomization. Study results are shown below.

In this trial of patients with acute coronary syndromes scheduled for PCI, prasugrel was associated with significant reductions in ischemic events, including stent thrombosis, but also with an increased risk of major bleeding and fatal bleeding. Overall mortality did not differ significantly between treatment groups.

Table 2. TRITON-TIMI 38 outcomes

	Prasugrel	Clopidogrel	Hazard ratio
Death from CV causes, nonfatal MI, or nonfatal stroke (primary end point)	9.9%	12.1%	0.81; 95% CI, 0.73 to 0.90; P < 0.001
Death from any cause	3.0%	3.2%	No significant difference between groups
Rate of non-fatal MI	7.3%	9.5%	0.76; 95% CI, 0.67 to 0.85; P < 0.001
Urgent target-vessel revascularization rate	2.5%	3.7%	0.66; 95% CI, 0.54 to 0.81; P < 0.001
Stent thrombosis rate	1.1%	2.4%	0.48, 95% CI, 0.36 to 0.64; P < 0.001
Major bleeding rate	2.4%	1.8%	1.32; 95% CI, 1.03 to 1.68; P = 0.03
Fatal bleeding	0.4%	0.1%	4.19; 95% CI, 1.58–11.11 P = 0.002

The FDA Cardiovascular and Renal Drugs Advisory Committee met in February 2009 to discuss a new drug application for the use of prasugrel, based largely on the **TRITON-TIMI 38** study.² It has been reported that the advisory committee voted unanimously to recommend approval of prasugrel for the treatment of acute coronary syndromes, with a further recommendation that prasugrel be contraindicated in patients with a prior stroke or transient ischemic attack (see <http://www.theheart.org/article/939227.do>). At the time of writing, the FDA had not made a decision regarding prasugrel.

There are several issues and questions arising from the TRITON-TIMI 38 study for clinicians treating patients with ACS:

- The 300 mg loading dose of clopidogrel in this trial does not reflect the routine clinical practice of a 600 mg loading dose. Loading with prasugrel 60 mg is approximately 3 times more potent an antiplatelet regimen than a 300 mg loading dose of clopidogrel.⁸
- Non-fatal MI as a clinical efficacy outcome may be the only difference between the prasugrel and clopidogrel groups.⁸

If prasugrel is approved by the FDA, clinicians will need to carefully consider the factors listed above when deciding which medications to choose for patients with ACS.

Aspirin therapy in type 2 diabetes

Aspirin has been a mainstay of cardiac prevention, with clear evidence from randomized controlled trials that it can reduce the incidence of MI in patients with existing cardiac disease. Diabetes is generally thought to be coronary artery disease “risk equivalent” and thus aspirin has generally been recommended for most patients with diabetes, including those without known vascular disease. However, two recent large trials have raised new questions about the role of aspirin in primary prevention. Their findings and an overview of current recommendations are summarized below.

The POPADAD study

The **POPADAD** study³ evaluated whether 100 mg of aspirin daily is effective in preventing cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease. It enrolled 1,276 adults (mean age 60) with type 1 or type 2 diabetes but no symptomatic cardiovascular disease. Approximately 10% of participants were using insulin. About a third of study subjects were current smokers and another third were previous smokers. Time since diagnosis of diabetes was approximately 6 years, median BMI was 29, systolic BP was approximately 145 mm Hg, mean HbA1c was 8%, and median LDL was 121 mg/dL.

Median follow-up was almost seven years, and the 2 primary outcome measures were (1) death from coronary heart disease or stroke; and (2) any of death from coronary heart disease or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia.

In this trial, aspirin conferred no significant benefit in terms of either outcome measure. The rate of death from any cause was 14.7% in patients randomized to aspirin and 15.8% in controls; the difference was not statistically significant. The rate of gastrointestinal bleeding was 4.4% with aspirin and 4.9% in controls, also non-significant. The study also randomized patients to receive an anti-oxidant (α-tocopherol 200 mg, ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, zinc sulphate 10 mg, nicotinamide 10 mg, lecithin 9.4 mg, and sodium selenite 0.8 mg) or placebo. That, too, had no effect on cardiovascular outcomes.

The JPAD study

Like **POPADAD**, the **JPAD** study⁴ examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes. It randomized 2,539 patients with type 2 diabetes and no history of atherosclerotic disease to receive either 81 or 100 mg aspirin per day or placebo.

The primary outcome measure was any atherosclerotic event.* Secondary endpoints studied included each primary endpoint and combinations of primary endpoints, as well as death from any cause. Median follow-up was 4 years.

* death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis)

In this primary prevention study of patients with type 2 diabetes, low-dose aspirin did not reduce the incidence of total atherosclerotic events, (coronary, cerebrovascular, and peripheral vascular) compared to placebo. However, deaths from MI or stroke were significantly reduced in the low-dose aspirin group (1 death vs. 10 deaths, $p = 0.0037$), though all-cause mortality was not significantly reduced. Gastrointestinal bleeding occurred in 12 patients in the aspirin group and 4 patients in the placebo group (p value not stated). There was no significant difference in the composite outcome of hemorrhagic stroke and severe gastrointestinal bleeding.

What we already know

- The benefit of aspirin for patients with diabetes who have known cardiovascular disease is well established. Patients with established CV disease should be treated with aspirin unless there is a compelling contraindication.
- The benefit of aspirin for diabetic patients without known cardiovascular disease is less well established.
- Aspirin can cause important gastrointestinal morbidity.

What POPADAD and JPAD add

- These studies add to the uncertainty about the efficacy of aspirin for the primary prevention of cardiovascular events in type 2 diabetes, but do not diminish its established usefulness in secondary prevention.

Bottom line

- The benefit of aspirin for the primary prevention of cardiovascular events in patients with diabetes is unclear. An individual clinical decision must be made weighing the degree of cardiovascular risk and the risk of bleeding.

Clopidogrel resistance, a fast-changing story

Definition

Platelet-dependent thrombosis can occur despite treatment with clopidogrel.⁹ This phenomenon has been termed “clopidogrel resistance,” but a concise definition of resistance to clopidogrel therapy based on pathophysiology does not exist.¹⁰ Treatment failure in patients taking clopidogrel has been ascribed to variety of causes including poor adherence, inadequate dosage, and coexisting medical conditions. It is also apparent that genetic factors play a major role in resistance.¹¹

Platelet activity assays

A number of platelet function assays have been used to evaluate platelet activity and response to clopidogrel. However, these tests are expensive, have significant limitations, and are not routinely available in primary care.^{9, 12} Also, definitions of clopidogrel resistance differ, depending on which test is used.¹³ There is no evidence that changes to clopidogrel therapy based on platelet activity tests translate into a reduction of adverse cardiovascular outcomes.

Genetics of resistance

The responsible genetic variant for clopidogrel resistance occurs in an enzyme responsible for the metabolism of the drug. Clopidogrel is a pro-drug that requires activation by specific hepatic cytochrome P-450 (CYP) enzymes. Studies have shown that carriers of the specific alleles of CYP2C19 and CYP3A4 have a diminished response to the effects of clopidogrel.^{11, 14-19} A reduced response to clopidogrel has been specifically associated with the CYP2C19*2 allele, which causes loss of function, in patients after coronary-stent placement and after non ST-elevated MI.¹¹

PPIs and clopidogrel

There is some evidence that the concomitant use of a proton-pump inhibitor decreases the platelet inhibitory effect of clopidogrel, because both drugs are metabolized by CYP2C19.¹¹ A recent retrospective study assessed outcomes of patients taking clopidogrel with or without a PPI after hospitalization for acute coronary syndrome (ACS).²⁰ The study included 8205 patients and the main outcome measure was all-cause mortality or re-hospitalization for ACS. Use of clopidogrel with a PPI compared to clopidogrel alone was associated with an increased risk of death or re-hospitalization for ACS (odds ratio 1.25; 95% CI, 1.11-1.41); an increased risk of hospitalization for recurrent ACS (odds ratio 1.86; 95% CI, 1.57-2.20); and an increased risk of revascularization procedures (odds ratio 1.49; 95% CI, 1.30-1.71). All cause mortality rates were not significantly different between the 2 groups.

It is important to note that the patients in the clopidogrel + PPI group had significantly higher incidences of diabetes, COPD, prior MI, heart failure, cerebrovascular disease, peripheral vascular disease, renal disease, liver disease, cancer, and dementia than the clopidogrel only group. Despite adjusting for confounders, it is possible that residual confounding remained. The use of a PPI in patients not taking clopidogrel after hospital discharge (n = 6450) was not associated with an increased risk of death or re-hospitalization for ACS.

Another recent retrospective study assessed the recurrence of MI within 90 days in patients aged 66 years or older who commenced clopidogrel following hospital discharge after treatment of acute MI. Among 13636 patients prescribed clopidogrel following acute MI, current use of PPIs was associated with an increased risk of re-infarction (adjusted odds ratio 1.27, 95% CI 1.03–1.57). Current use of PPIs was defined as use within 30 days of re-infarction. Pantoprazole, which does not inhibit CYP 2C19 was not associated with readmission for MI.²¹

One prospective study showed that PPIs did not affect clinical response to clopidogrel.¹⁸ The clinical significance of a PPI-clopidogrel interaction remains unclear. To date, no prospective randomized controlled trial has shown that a PPI used in conjunction with clopidogrel causes an increased risk of adverse CV outcomes.

Summary

Loss-of-function CYP2C19 alleles are common in the general population and are associated with an increased risk of acute cardiovascular events, particularly among patients undergoing PCI. Further studies are needed to answer a number of important clinical questions:

- Can clopidogrel resistance be overcome?

- Can patients with a loss-of-function CYP variant have improved platelet function and clinical outcomes (thrombosis and hemorrhage) with an alternative platelet inhibitor such as prasugrel that does not require hepatic activation?
- Would genetic testing and adjustments in therapeutic dose or type enhance efficacy?
- Do drug interactions that inhibit clopidogrel metabolism by CYP2C19 have clinically meaningful effects?

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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