

Cardiometabolic

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The Role of Antiplatelet Therapy in Chronic and Acute Coronary Disease in Patients with Diabetes

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Diabetes mellitus (DM) is a potent risk factor for the development of premature cardiovascular disease (CVD) and its complications. The prevalence of coronary artery disease (CAD) is approximately 2-4 times higher in individuals with DM. Among patients with CAD, those with DM have significantly higher mortality than nondiabetic individuals with both stable CAD and following an acute coronary syndrome (ACS). Despite this higher risk, patients with DM receive less than optimal guideline-recommended treatment, both for vascular protection and for management of acute coronary events. The higher incidence and severity of CAD reflect the multifaceted pathophysiological actions of hyperglycemia and insulin resistance (IR) on the arteries, endothelium, and blood constituents (particularly platelets), as well as the myocardium. Platelet activity is abnormally elevated in DM and in acute hyperglycemic states. Furthermore, the response to conventional antiplatelet therapy is reduced in these patients. Antiplatelet therapy is a cornerstone of both primary and secondary prevention in CAD although, in primary prevention, there is limited evidence for benefit. This issue of *Cardiometabolic Rounds* reviews the pathophysiological basis for platelet dysfunction in patients with DM and the evidence for antiplatelet therapy in both the acute and chronic setting. Finally, information about a newer antiplatelet agent and an upcoming study in this field are presented.

The World Health Organization predicts that the prevalence of DM will increase by 39% between 2000 and 2030.¹ In Canada, however, the prevalence of DM increased by 69% between 1995 and 2005, with the greatest increase in younger age groups.² Diabetes confers a 2- to 4-fold increased incidence of CAD in comparison with individuals without diabetes.^{3,4} There has been recent awareness of the undertreatment of CV risk factors and the increased contribution of DM to the global burden of CAD.^{5,6}

The increased CV risk associated with DM results from an accumulation of atherosclerotic risk factors, in association with IR, especially in patients with type 2 DM (T2DM). IR comprises a continuum that ranges from dysglycemia (impaired glucose tolerance and fasting glucose) through to frank T2DM. T1DM is characterized by a lack of insulin and hyperglycemia, with IR becoming apparent only in the later stages of the disease. IR by itself has wide-ranging effects on cellular function, including a prothrombotic state that contributes to the increased risk for atherothrombosis.⁷

Endothelial dysfunction: The vascular endothelium plays an important regulatory role in vascular homeostasis. It interacts with circulating cells and proteins to influence both platelet and leukocyte adhesion and the coagulation pathway.⁸ Paracrine secretion of mediators such as nitric oxide (NO) and prostacyclin help regulate vascular tone. Impairment of endothelial function is pivotal in the development of atherosclerosis. Endothelial dysfunction is found in individuals with IR, T2DM, and in first-degree relatives of patients with T2DM.

Altered hemostasis: DM is associated with a range of hemostatic abnormalities that promote prothrombotic risk, including increased levels of coagulation factors such as factor VII and fibrinogen, as well as impaired fibrinolysis due to elevated levels of the endogenous fibrinolysis inhibitor, plasminogen activator inhibitor-1 (PAI-1).⁹ There is a familial relationship between IR and prothrombosis, with similar abnormalities in nondiabetic first-degree relatives of patients with T2DM.^{10,11} Acute hyperglycemia and new-onset DM is associated with increased thrombotic risk in patients with an ACS. Undas et al¹² recently demonstrated lower



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clot permeability and prolonged clot lysis time in hyperglycemic patients with ACS, with and without a prior history of DM.

Platelet function: The regulation of platelet function is achieved by a balance between pro- and anti-aggregatory factors. Inhibitors of platelet aggregation, including prostacyclin (PGI₂) and NO, are produced by the intact vascular endothelium and contribute to normal blood flow in healthy arteries.¹³ As insulin attenuates the effect of certain pro-aggregatory agents, including collagen and adenosine diphosphate (ADP),¹⁴ hyperinsulinemia would be expected to have a beneficial effect on thrombosis. However, IR is associated with a loss of this benefit, as well as a reduced response of platelets to NO and PGI₂.^{15,16} Vinik et al demonstrated that platelets adhere to the vascular endothelium more in individuals with DM than in nondiabetic controls, a finding consistent with endothelial dysfunction in diabetes.¹⁷ Hyperglycemia *per se* is also known to exert deleterious effects on platelet function. In 1988, Oswald et al demonstrated that hyperglycemia, independent of a prior diagnosis of DM, was associated with excess platelet activation in patients presenting with acute myocardial infarction (MI).¹⁸ The inflammatory milieu of acute MI could be responsible for platelet activation. However, acute hyperglycemia also results in increased platelet aggregation in patients with stable CAD.¹⁹ In this study, the degree of platelet activation correlated with the level of hyperglycemia. Platelet activation increased in individuals with and without DM, although larger increases were seen in the patients with DM.

Antiplatelet therapy in patients with DM – with and without CAD

Acetylsalicylic acid (ASA): The prognostic benefit of ASA in individuals without DM and stable CAD is well-established. The Physicians Health Study²⁰ included data from >22,000 male physicians randomly allocated to either ASA 325 mg on alternate days or placebo. ASA use was associated with a 44% relative risk reduction (RRR) in the incidence of MI ($P<0.00001$) in all patients and a 70% RRR in the incidence of first MI in the subgroup with chronic stable angina (but without previous MI, stroke, or transient ischemic attack [TIA]), ($P=0.003$). After controlling for other CV risk factors, the RRR in the stable angina subgroup was 87% ($P=0.006$).

Patients with DM, with or without CAD, may have less benefit from ASA than individuals without DM. In the Physicians Health Study, there was no statistically significant reduction in events in the 533 subjects with DM (11/275 in the ASA group versus 26/258 in the placebo group, $P=0.22$). The Anti-Thrombotic Trialists²¹ performed a meta-analysis of 195 randomized trials of antiplatelet therapy up to 1997 that revealed a 22% reduction in the risk of major CV events among all high-risk subjects. In contrast, in the 9 trials that included 5000 individuals with DM, there was no benefit from ASA

A more recent review of ASA use in patients with or without known CAD, analyzed 4 studies – 3 clinical trials and 1 observational study – totaling >4700 patients.²² In the randomized trials, there was a range of findings from “no benefit” (The Early Treatment Diabetic Retinopathy

Study²³), a reduction in the incidence of stroke and death (the European Stroke Prevention Study²⁴), to a significant reduction in CV death, stroke, and MI (the Primary Prevention Project²⁵). When subgroup analysis was performed for individuals with DM, the benefits disappeared or became nonsignificant, a finding attributed either to more advanced vascular disease in the subjects with DM or to the small numbers in the subgroup analyses.

In contrast, an open-label registry evaluated long-term registry data from individuals screened for the Bezafibrate Infarction Prevention Study (BIP) and suggested ASA usage was associated with a significant reduction in both cardiac mortality (10.9% vs 15.9%, $P<0.001$) and all-cause mortality (18.4% vs 26.2%, $P<0.001$).²⁶

Belch et al²⁷ recently published a randomized trial comparing the effects of ASA and antioxidants as vascular primary prevention in subjects with DM, but without overt CAD. They found no difference between the ASA and placebo groups (hazard ratio [HR] 0.98, 95% confidence interval [CI], 0.76-1.26), although the study was likely underpowered due to small sample size (about 640 patients). The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study was presented at the American Heart Association Scientific Meeting (Late-Breaking Clinical Trials session, November 9, 2007). This study, in 2539 subjects with T2DM and no evidence of vascular disease, showed no reduction in the primary combined CV primary endpoint after treatment with ASA 80-100 mg daily for 4.4 years. ASA reduced fatal coronary and cerebrovascular events and appeared to have a benefit in subjects aged >65 years. Although gastrointestinal bleeding was more frequent with ASA, there was no increase in intracerebral hemorrhage.

To summarize the evidence, patients with DM, with or without CAD, have a smaller benefit from ASA therapy than nondiabetic individuals. This is reflected in the recent downgrading of the level of evidence for the recommendation for ASA use for vascular protection by the Canadian Diabetes Association from Grade A in 2003 to Grade D, consensus in 2008.²⁸

Clopidogrel: Clopidogrel irreversibly binds to the platelet ADP P2Y₁₂ receptor. Activation of the P2Y₁₂ receptor promotes platelet activation and aggregation with fibrin cross-linkage between glycoprotein IIb/IIIa receptors. The Clopidogrel versus Aspirin in Patients with Risk of Ischemic Events (CAPRIE) trial²⁹ compared clopidogrel with ASA for the prevention of recurrent ischemic events in patients with established vascular disease (recent stroke, MI, or established peripheral vascular disease). In the 3866 subjects with DM, there was a 12% RRR in the composite primary endpoint of vascular death, all-cause stroke, MI, or rehospitalization for ischemia or bleeding ($P=0.042$), which is similar to the benefit observed in the overall group. However, the absolute benefit of clopidogrel compared to ASA was amplified due to the increased event rates in the subjects with DM. Consequently, only 48 patients required treatment to prevent 1 event, which is almost twice the benefit seen in the overall study group.

In contrast, the addition of clopidogrel to ASA in individuals with DM, with or without vascular disease, was not shown to be beneficial in the Clopidogrel and

Table 1: Mechanisms for prothrombotic risk in patients with diabetes

Vascular endothelial dysfunction

- Promotes atherosclerosis
- Decreased prostacyclin/NO production
- Promotes thrombosis, inflammation

Abnormal hemostasis

- Impaired fibrinolysis

Abnormal coagulation

- Elevated factor VII coagulant activity
- Elevated von Willebrand factor levels

Abnormal platelet function

- Resistant to antithrombotic actions of insulin, prostacyclin and NO
- Increased platelet activation/aggregation
- Resistant to conventional antiplatelet agents

NO = nitric oxide

Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial.³⁰

ASA use in patients with DM should probably be confined to individuals with CAD or CVD. Clopidogrel can be used as an alternative in patients unable to tolerate ASA or who have vascular events while receiving ASA. There is no evidence to support long-term dual antiplatelet therapy in patients with DM in the absence of recent ACS or intracoronary stent.

Acute coronary syndromes

People with DM have their first MI an average of 15 years earlier than those without DM.³¹ DM is an independent predictor of an adverse outcome following an ACS, with a 50% greater early and late mortality than for those without DM.^{32,33} Heart failure, cardiogenic shock, and recurrent MI are all more common in individuals with DM.

As the diabetic milieu is pro-atherosclerotic and prothrombotic (Table 1), antiplatelet and antithrombotic drugs play an important role in the management of patients with ACS. However, there are no prospective trials examining ACS therapies only in patients with DM. Hence, current practice is guided by the results of subgroup analyses of diabetic cohorts from large, multicentre trials. The benefit of ASA therapy in the management of patients with ACS was established >20 years ago. The ISIS-2 study,³⁴ which involved 17 600 patients with MI, demonstrated that ASA therapy for 1 month resulted in a significant 23% RRR in mortality and a 50% RRR in re-infarction. The Anti-Thrombotic Trialists' Collaboration meta-analysis, demonstrated that ASA therapy reduced mortality by 30% in patients with MI.³⁵ Earlier studies had demonstrated that ASA halves event rates in patients with unstable angina.^{36,37}

Clopidogrel has been shown to reduce ischemic cardiac events in patients with non-ST-segment elevation (NSTEMI)-ACS and in those with STE-ACS when given prior to thrombolysis. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial³⁸ evaluated the addition of clopidogrel to ASA in patients presenting with NSTEMI-ACS. Clopidogrel resulted in a 20% reduction in the primary endpoint (a composite of death, MI, or stroke),

driven largely by a 23% reduction in the incidence of MI, with a trend toward a reduction in CV mortality. A similar benefit was observed in the subgroup with DM. For patients with STE-ACS, 2 trials – Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) and Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI-28)^{39,40} – indicated a benefit from the addition of clopidogrel to ASA in patients undergoing thrombolysis; however, there has been no sub-group analysis of the patients with DM.

As a result of these pivotal trials, dual oral antiplatelet therapy with ASA and clopidogrel is now standard treatment for almost all patients (including those with DM) presenting with ACS and is supported by evidence-based guideline recommendations in Europe and North America.

Platelet glycoprotein receptor inhibitors: The platelet glycoprotein (GP) IIb/IIIa inhibitors abciximab, tirofiban, and eptifibatid have been studied in randomized trials of patients with ACS and in those undergoing percutaneous coronary intervention (PCI). Roffi et al⁴¹ performed a meta-analysis of 6 large-scale trials of platelet GP IIb/IIIa inhibitors in ACS, with a special focus on their use in patients with DM. Among 6458 patients with DM, GP IIb/IIIa inhibitor use resulted in a reduction in 30-day mortality, from 6.2% to 4.6% (OR 0.74; 95% CI, 0.59-0.92; $P=0.007$). It is notable that no benefit was observed in the nondiabetic population. The greatest benefit was in the 1279 diabetic patients with ACS who underwent PCI during the index hospitalization. In this group (20% of the diabetic population), GP IIb/IIIa inhibitor use was associated with a reduction in mortality from 4.0% to 1.2% (OR 0.30; 95% CI, 0.14-0.69; $P=0.002$). These analyses have led to the widespread use of GP IIb/IIIa inhibitors in patients with DM and recent ACS undergoing early PCI.

Antiplatelet drug resistance

Resistance to an antiplatelet drug can be defined as “laboratory” or “clinical.” Laboratory resistance is defined as the failure of the agent to inhibit *in vitro* tests of platelet function (eg, aggregation), whereas clinical resistance is the failure of the agent to prevent atherothrombotic episodes in patients prescribed the drug. Laboratory resistance to the effects of antiplatelet drugs has recently been shown to be associated with an increase in atherothrombotic events.⁴² Diabetes is associated with ASA resistance, and this effect is more pronounced in T2DM.^{43,44} The mechanism of ASA resistance may be due to ASA-insensitive thromboxane synthesis that is catalysed by free radicals and augmented by smoking, diabetes, and hyperlipidemia. Another mechanism in the patient with DM may be due to the glycation of platelet receptors that reduces receptor susceptibility to acetylation by ASA.

The incidence of ASA resistance varies widely and, depending on the definition of resistance, ranges from 1.7% to 35%.⁴⁵⁻⁴⁸ A recent meta-analysis on ASA resistance found rates of 28% and, interestingly, suggested that there was no increased rate among patients with DM.⁴⁹ Yet, with the huge range in the incidence of ASA resistance and the lack of good comparative studies, it is difficult to interpret this meta-analysis.

A reduced response to clopidogrel is observed in patients with DM.^{50,51} Furthermore, insulin-treated patients with DM have greater ADP-induced platelet aggregation than those not receiving insulin.^{52,53} Resistance to clopidogrel was studied in the Optimizing Anti-platelet Therapy in Diabetes Mellitus (OPTIMUS) trial⁵⁴ in patients with DM and CAD, on stable doses of ASA and clopidogrel. The study assessed the effect of clopidogrel on *in vitro* platelet aggregation to 20 mol/L ADP. Resistance to clopidogrel was observed in 63.1% of patients, a rate that was reduced to 52.3% by doubling the clopidogrel dose to 150 mg/day ($P=0.002$). In a series of patients undergoing cerebrovascular stent procedures, ASA resistance was noted in only 3%, yet clopidogrel resistance was detected in 52%. Older age and DM inversely correlated with the degree of platelet inhibition.⁵⁵

Antiplatelet drug resistance is not without consequence. Eikelboom et al⁵⁶ measured urinary 11-dehydro thromboxane B2 levels (a marker of platelet activity) in patients in the Heart Outcomes Prevention (HOPE) study who were taking ASA. Compared with patients in the lowest quartile, patients in the highest quartile of 11-dehydro thromboxane B2 levels had 1.8 times the risk of MI, stroke, or CV death ($P=0.009$). Chen et al⁵⁷ assessed ASA resistance as a risk factor for myonecrosis in elective patients undergoing PCI. ASA resistance was found in 29% patients and was associated with increased rates of periprocedural elevation of serum troponin levels (51.7% versus 24.6%, $P=0.006$).

Matetzky et al⁴² enrolled 60 patients who received clopidogrel at the time of primary PCI for ST elevation MI (STEMI). The highest quartile of response to clopidogrel (as measured by inhibition of ADP-induced platelet aggregation) was compared with the lowest quartile. Patients with the least response to clopidogrel were 25% more likely to suffer a CV event in the subsequent 6 months as compared with those in the other 3 quartiles ($P=0.007$). Similarly, in elective patients undergoing PCI for stable angina, Muller et al⁵⁸ described rates of clopidogrel resistance of 5%-11%. In this study of 105 patients, 2 out of 5 patients who were described as non-responders suffered sub-acute stent thrombosis. The relatively small numbers of patients included in these studies preclude any analysis of the impact of DM.

The optimal management of antiplatelet resistance is as yet undefined. Currently, routine measurement of platelet aggregation and determination of the response to antiplatelet agents is not recommended. However, increased doses of medications and starting treatment earlier may overcome some of the resistance to treatment. Duzenli et al⁵⁹ demonstrated that increasing the dose of ASA from 100 mg to 300 mg per day decreased ADP-induced platelet aggregation in patients previously labeled as non-responders. Yet, the Anti-Thrombotic Trialists Collaboration^{21,35} suggested that an increased ASA dose was not associated with better outcomes and two other studies have suggested that there are higher rates of bleeding using this strategy.^{38,60}

Higher than currently used doses of clopidogrel have been shown to have a clinical benefit in patients previously naïve to clopidogrel. The Anti-Platelet Therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2)⁶¹ study revealed that there were less adverse outcomes with the 600 mg clopidogrel dose compared with the usual 300 mg loading dose. This finding has been confirmed in the Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis (ALBION) and the Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE) trials.^{62,62} These trials also revealed a more rapid onset and achievement of maximal platelet inhibition with a higher (900 mg) clopidogrel loading dose.

The concept of antiplatelet resistance and its sequelae is relatively recent. As physicians become increasingly aware of the problem, interest will focus on identifying those who have, or who *will* develop antiplatelet resistance, and adjusting treatment accordingly. Patients with DM may have special benefit from this tailored approach to antiplatelet therapy.

New antiplatelet agents

Dual antiplatelet therapy with clopidogrel and ASA is the current standard of antiplatelet therapy for most patients with recent ACS, and after receiving intracoronary stents. However, resistance to clopidogrel is common and maximal antiplatelet inhibition takes many hours to achieve. New antiplatelet agents are about to become available that will overcome some of these limitations.

Prasugrel is a third-generation thienopyridine platelet ADP P2Y₁₂ receptor inhibitor that is readily absorbed and requires fewer metabolic steps to generate the active metabolite as compared to clopidogrel. Consequently, platelet inhibition occurs more rapidly, is greater, and incurs less interpatient variability than clopidogrel.⁶⁴ In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel – TIMI (TRITON-TIMI) 38,⁶⁵ either prasugrel or clopidogrel was administered to patients in the cardiac catheter laboratory immediately prior to coronary stenting. Prasugrel treatment resulted in a 19% lower incidence in CV death, nonfatal MI, or nonfatal stroke (Table 2); however, serious bleeding was more common in the prasugrel-treated patients. In the diabetic subgroup of the TRITON-TIMI 38 study (3146 patients, with 776 receiving insulin), prasugrel was associated with a 30% reduction in the primary endpoint (a composite of death, nonfatal MI, nonfatal stroke, and nonfatal TIMI major bleeding) from 17.0% to 12.2% (HR, 0.70; $P<0.001$). The benefit was even more pronounced in the cohort receiving insulin (14.3% versus 22.2%, HR, 0.63). In patients with DM, the amplified benefit was achieved without any increase in hemorrhage.

Table 2: Hazard ratios for primary and other endpoints for patients with and without diabetes in the TRITON-TIMI 38 study⁶⁵

Endpoint	No diabetes HR (95% CI)	Diabetes HR (95% CI)	P value
CV death, nonfatal MI, or stroke*	0.86 (0.76–0.98)	0.70 (0.58–0.85)	0.09
MI	0.82 (0.72–0.95)	0.60 (0.48–0.76)	0.02
Major hemorrhage	1.43 (1.07–1.91)	1.06 (0.66–1.69)	0.29
Major or minor hemorrhage	1.32 (1.08–1.61)	1.30 (0.92–1.82)	0.93
All-cause death or nonfatal MI, stroke, or major hemorrhage	0.92 (0.82–1.03)	0.74 (0.62–0.89)	0.05

* composite primary endpoint

HR = hazard ratio; MI = myocardial infarction;
CI = confidence interval; CV = cardiovascular

The analysis of the diabetic cohort of the TRITON study has helped raise awareness that DM is more than just an additional risk factor for thrombotic complications and less successful PCI; it is a condition that requires specific management strategies that include more aggressive platelet inhibition.⁶⁶

Prospective trial of interest

ASCEND (A Study of Cardiovascular Events in Diabetes) is a prospective, randomized, multicentre, placebo-controlled trial comparing ASA (and omega 3 fatty acids) versus placebo in patients with DM (either T1 or T2) without established arterial disease. Enrollment commenced in 2004 and it is anticipated that 10 000 patients will ultimately be enrolled. Hopefully this study will provide a definitive answer to the role of ASA in patients with DM with no known vascular disease.

Summary

Patients with DM have poor outcomes after acute coronary events and do not fare as well after coronary revascularization as patients without DM. DM is associated with a pro-thrombotic state, yet the routine use of antiplatelet therapy for primary prevention of vascular events in patients with DM and no established vascular disease has limited support. In contrast, antiplatelet therapy has major benefits in patients with DM and a recent acute coronary event. For these patients, aggressive treatment with multiple antiplatelet drugs, especially when associated with an early invasive strategy, results in important reductions in morbidity and mortality.

The recent interest in antiplatelet drug resistance, particularly in patients with DM, has helped recognize the need to adjust treatment to match the risk. This attention may lead to long-term benefits in these high-risk patients by ensuring they receive appropriate, timely, and suitably aggressive treatment.

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