Diabetes, Platelet Dysfunction and Cardiovascular Events

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The global prevalence of diabetes mellitus has been estimated at 170 million individuals and is rapidly increasing with projections of > 350 million by 2030. The presence of elevated blood glucose levels, diabetes mellitus, or both contribute to more than 3 million cardiovascular deaths worldwide each year. Coronary heart disease is common in people with diabetes mellitus. In people with diabetes, coronary heart disease causes almost 60% of their deaths. In people with diabetes, coronary heart disease occurs at a younger age and women are affected as often as men.

In people with type 1 diabetes degree of glycemic control is not related with cardiovascular events whereas a relationship appears to exist in patient of type 2 diabetes. In people with type 1 diabetes, the Pittsburg Epidemiology of Diabetes Complications Study reported no association with HBA1C and the four year incidence of coronary heart disease. In contrast the incidence of CHD mortality and events increased with each tertile of HBA1C in elderly men with type 2 DM in Kuopio, Finland.

More than 30 years ago, the Framingham Heart Study followed 239 patients with diabetes and observed a 3-fold increase in age adjusted cardiovascular mortality. Diabetes is now considered to be a risk equivalent of CAD for future MI and cardiovascular deaths. With the increase in obesity, insulin resistance and the metabolic syndrome the world wide prevalence of diabetes is expected to double by the year 2030. This burgeoning diabetes epidemic will increase cardiovascular events attributable to diabetes. In addition to being a risk factor for cardiovascular events, diabetes influences outcomes following Acute Coronary Syndrome (ACS). Among patients with ACS, those with DM are at higher risk for subsequent events including death, independent of other comorbidities. Indeed patients with DM but without known cardiovascular disease are at a risk of morbidity and mortality after ACS similar to that of patients without DM but with known cardiovascular disease.

Subgroup analysis of patients with diabetes with ST-elevation myocardial infarction (STEMI) in GUSTO-1 trial demonstrated significantly higher all causes mortality at 30 days compared with patients without diabetes (10.5% vs. 6.2%). Similarly the OASIS registry of patients with UA/NSTEMI observed an increased rate of post-MI complications and mortality among patients with diabetes compared with patients without diabetes (odds ratio 1.57) during two years follow-up. Moreover, a large prospective multinational registry GRACE revealed that hospital case fatality rate for patients with diabetes and ACS were almost twice as high as those of patients without diabetes.

Numerous mechanism may explain this increased risk. Diabetes patients are more likely to have other comorbidities such as renal insufficiency, hypertension that lead to worse outcomes. Diabetic subjects often have early signs of heart failure, particularly diastolic heart failure which can lead to increasing morbidity and mortality. Several other mechanisms may play roles in the increased risk of events in patients with DM including greater frequency of other cardiac risk factors, a greater burden of atherosclerotic disease, hyperglycemia, inflammation and a greater
tendency toward thrombosis\textsuperscript{10}. Perhaps the most important difference is that type 2 diabetes mellitus is associated with a proinflammatory and prothrombotic state. Of interest, is the insulin resistant state, which perhaps through glycospoylation causes an upregulation of platelet membrane protein such as the P\textsubscript{Y\textsubscript{12}} receptor pathway which is the target of the active metabolite of clopidogrel. Patients with DM are at high risk for recurrent cardiovascular events after ACS, in part because of increased platelet reactivity. The trial to Assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with Prasugrel - TIMI 38 (TRITON-TIMI 38) showed a more impressive decrease in ischaemic events with more intensive antiplatelet therapy with prasugrel than with clopidogrel in diabetic subjects compared to non-diabetic subjects.

**PLATELET HYPERACTIVITY IN TYPE 2 DIABETES**

Platelet in individuals with diabetes show increased activity at baseline and in response to agonists, ultimately leading to increased aggregation, increased expression of platelet surface adhesion molecules and receptors, enhanced production of thromboxane and thrombin and disturbances in platelet calcium homeostasis\textsuperscript{11}. As intra-arterial thrombi are initiated by platelets, strategies to limit acute thrombotic events have largely focused on antiplatelet agents. Platelet activation and aggregation are key factor in the development of ACS and its complications. It has been known far decades that platelets from patients with DM are characterized by increased reactivity\textsuperscript{12}. An increased sensitivity of platelets to aggregation from ADP and epinephrine is described in diabetes. This sensitivity correlates with elevated levels of VWF, which, in turn appears to be influenced by growth hormone. Platelets from diabetic subjects are more sensitive than platelets from normal subjects to arachidonic acid induced aggregation. This sensitivity is abolished by aspirin. Platelet from diabetic subjects synthesize increased amounts of PGE\textsubscript{2} like material (iPGE) in response to ADP, epinephrine, collagen and arachidonic acid. The later finding suggests that a fundamental mechanism for increased platelet aggregation in diabetes is increased prostaglandin synthetase activity. More recent study have demonstrated heightened shear - induced platelet adhesion and aggregation ex vivo in blood from diabetes\textsuperscript{13}. A significant correlation between glucose levels and platelet dependent thrombosis even among non-diabetic patients with fasting blood glucose in normal range has also been reported\textsuperscript{14}.

The biochemical and molecular links between diabetes and altered platelet activation have been explored by several groups (Table I). Increased levels of cell surface adhesion molecules, including P-selectin and the GP Ib/IIa receptor have been reported in platelet from diabetes\textsuperscript{15}. Davi and colleagues demonstrated enhanced thromboxane biosynthesis in diabetic patients and its reduction in response to tight metabolic control. More recently this group has also demonstrated that diabetic patients have elevated levels of isoprostanes which are recently characterized eicasanoids derived from arachidonic acid via non-enzymatic lipid peroxidation\textsuperscript{16}. These investigators hypothesized that the increased oxidant stress in diabetics might lead to enhanced generation of certain isoprostanes, especially 8-i0 PGF2\textalpha, which induces vasoconstriction and platelet activation.

**PLATELET DYSFUNCTION IN TYPE 2 DM**

Insulin resistance is a uniform finding in type 2 DM as are abnormalities in the microvascular and macrovascular circulations. These complications are associated with dysfunction of platelets and the neurovascular unit. Platelet are essential for hemostasis and knowledge of their function is basic to understanding the pathophysiology of vascular disease in diabetes. Intact healthy vascular endothelium is central to the normal functioning of smooth interaction with platelets. What is not clear is the role of hyperglycaemia in the functional and organic microvascular deficiencies and platelet hyperactivity in individuals with diabetes. The entire coagulation cascade is dysfunctional in diabetes. Increased levels of fibrinogen and PAI-1 favour both thrombosis and defective dissolution of clots once formed. Platelets in type 2 DM adhere to vascular endothelium and aggregate more readily than those in healthy people. Loss of sensitivity to the normal restraints exercised by PGI\textsubscript{2}, and NO generated by the vascular endothelium persists as the major defect in platelet function. Insulin is a natural antagonist of platelet
hyperactivity. It sensitizes the platelet to PGI₂, and enhance endothelial generation of PGI₂ and NO which are vasodilators and inhibits platelet aggregation. This explains the platelet dysfunction in diabetes.

DISCUSSION
A number of important observations can be made. First the diabetic sub-study of TRITON goes beyond the notion that diabetes is just a higher risk group. The exaggerated response to prasugrel validates the concept that for diabetic patients the degree of platelet inhibition may be an important marker of outcome.

Second, patients treated with insulin represent those who have had a longer duration of the disease and have had difficulty reaching a target level of HbA1C on oral therapy alone. The trial demonstrated an ≈ 8% absolute reduction in ischaemic events for those treated with insulin, suggesting that prasugrel has durable effects across the spectrum of DM; this appears to be another unique finding of study. Prasugrel is a third generation thienopyridine antiplatelet agent that like clopidogrel, exerts its antiplatelet effect by P₂Y₁₂ receptor blockade. Treatment with prasugrel results in higher and more consistent levels of platelet inhibition than standard or higher dose of clopidogrel. In TRITON-TIMI 38, treatment with prasugrel compared with clopigogrel resulted in 19% lower incidence in cardiovascular deaths, non fatal MI or non fatal stroke but with more bleeding among patients with ACS in whom PCI was planned. Third, for those with DM, the difference in ischaemic events was driven largely by a reduction in myocardial infarction; this finding is consistent with our understanding of the mechanism of cardiovascular events after ACS.

Fourth, the overall TRITON - TIMI 38 finding raised concerns about excess of TIMI major bleeding in the prasugrel arm. The diabetic subgroup did experience a higher rate of TIMI major bleeding (2.6% vs. 2%) compared with the non-diabetic cohort, but, regardless of the possible explanations, no differences was found in excess bleeding between clopidogrel (usual care) and prasugrel.

ANTIPLATELET THERAPY IN DIABETES
There are 3 different classes of platelet inhibiting drugs : Cox-1 inhibitors (aspirin), ADP-P₂Y₁₂ receptor antagonists (Thienopyridines) and platelet GP IIb/IIIa inhibitors which are mostly used for the prevention and treatment of atherothrombotic disorders. The limitations of currently available anti-platelet agents that are used for prevention of atherothrombotic events and that have been shown to be of greater magnitude among diabetic patients underscore the need for more specific antiplatelet regimens particularly in these patients.

In 2007, American Diabetes Association (ADA) and American Heart Associations (AHA) jointly recommended that aspirin therapy (75-162 mg/day) be used as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are over 40 years of age or who have additional risk factors (family history of CV, hypertension, smoking, dyslipidaemia or albuminuria). These recommendations were derived from several older trials that included relatively small number of patients with diabetes. Results of two recent randomized controlled trials of aspirin performed specifically in patients with diabetes raised questions about the efficacy of aspirin for primary prevention in diabetes and adverse effect, especially risk of gastrointestinal bleeding, has been highlighted. Consequently, use of aspirin in diabetes without history of previous vascular disease but 10 year risk of CVD events over 10% now have ACCF/AHA Class IIa indication (Level of evidence B) if there is no increased risk of bleeding. Use of aspirin in diabetes with intermediate CVD risk (10-year CVD risk of 5-10%) has ACCF/AHA Class IIb indication. Use of aspirin in diabetes with low CVD risk is contraindicated. A post-hoc analysis of the diabetic patients randomized in the CAPRIE (Clopidogrel versus Aspirin in patients at Risk of Ischaemic Events) study found that clopidogrel therapy reduced the relative risk of death, MI, stroke or repeat hospital stay compared with aspirin therapy. However, specific randomized trials to determine whether clopidogrel alone or clopidogrel plus aspirin is superior to aspirin alone in prevention of cardiovascular events in diabetic patients with established CVD have not been carried out;

The development of newer antiplatelet agents that can effectively and safely inhibit platelet activation and aggregation processes appears to be the most promising strategy in view of a hypothetical future in which antiplatelet drug regimens will be used according to individual need. There are several P₂Y₁₂ receptor antagonists under advanced clinical investigation. These include Prasugrel, ticagrelor (AZD 6140), Cangrelor and elinogrel (PRT128). Prasugrel and Ticagrelor are administered orally, cangrelor is for (iv) use and elinogrel can be administered via both routes. Prasugrel is an irreversible agent whereas other are reversible. All agents have increased potency and are associated with less response variability compared with clopidogrel.
Prasugrel has a more favorable pharmacokinetic profile because compared with clopidogrel, it is more efficiently transformed into its active metabolic, which leads to more prompt, potent and predictable degree of platelet inhibition as shown in numerous pharmacodynamic studies even when compared with platelet inhibition associated with both high and maintenance dosing of clopidogrel\textsuperscript{21}. The clinical implication of these more favorable pharmacological properties were evaluated in the TRITON-TIMI 38\textsuperscript{22} comparing prasugrel with clopidogrel in patients (n=13,608) with moderate to high risk ACS who underwent PCI. After a median duration of 14.5 months, the primary end point (composite of cardiovascular death, non fatal MI or, non-fatal stroke) occurred in 12.1 % vs. 9.9% of clopidogrel and prasugrel treated patients respectively (p<0.001). In pre-specified subgroup analyses, treatment with prasugrel seemed to be particularly effective in subjects with diabetes mellitus. In the diabetic sub-group\textsuperscript{23}, prasugrel as compared with clopidogrel led to significant reduction in ischaemic events and in contrast to entire study population this was achieved without an accompanying increase in the rate of major bleeding complications (Fig.1).

**Diabetic Subgroup**

![Fig. 1](image)

A meta-analysis of glycoprotein IIb/IIIa inhibitors in diabetic patients with non-ST segment elevation acute coronary syndrome undergoing PCI demonstrated a 30-day mortality\textsuperscript{24} reduction. The NHLBT Dynamic Registry\textsuperscript{25} indicated planned glycoprotein IIb/IIIa inhibitor therapy in diabetes might reduce the incidence of in-hospital death and death or non-fatal MI at 1 year after PCI. Another meta-analysis demonstrated a survival advantage conferred by abciximab in DM\textsuperscript{26}. The ISAR-SWEET trial prospectively tested the effect of abciximab in diabetic PCI patients who had been pretreated with 600 mg of clopidogrel\textsuperscript{27}. Although the combined primary end point rates of death and MI at 1 year were similar in abciximab and placebo-treated patients (8.3% vs. 8.6%, p = 0.91), TVR was reduced by abciximab. Adjunctive glycoprotein IIb/IIIa inhibitor therapy represents an advance for diabetic patients, particularly those undergoing complex PCI.

The most recent and specific trial of antiplatelet therapy in diabetes mellitus has been OPTIMUS-3 which was presented at American Heart Association meeting in 2009. Primary objective of the trial was to compare the pharmacodynamic effects of a 60 mg loading dose (LD) of Prasugrel vs. Clopidogrel 600 mg LD in subjects with diabetes mellitus and CAD using inhibition of platelet aggregation (IPA), as measured by the Verify Now P2Y12 assay at 4-hours post-LD. Significantly higher levels of IPA was observed with Prasugrel 60 mg LD within one hour of the LD compared to clopidogrel 600 mg LD and this higher IPA was maintained over subsequent 24 hours (Fig.2). Maintenance dose of Prasugrel 10 mg demonstrated higher IPA after one week of therapy compared to Clopidogrel 150 mg.

**CONCLUSION**

Platelets play a key role in vascular thrombus formation, and abnormalities in their function may enhance the progression of atherosclerosis. Patients with diabetes exhibit increased platelet reactivity compared with subjects without diabetes. This phenomenon has been described even in patients on combined aspirin and clopidogrel treatment. Newer agents like Prasugrel have demonstrated superior anti-platelet activity in diabetes both with respect to clinical parameters and in terms of inhibition of platelet aggregation.