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## Antiplatelet and antithrombotic therapy in diabetic patients recent updates

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### Abstract

Diabetes mellitus (DM) is a metabolic disorder associated with accelerated atherogenesis and an increased risk of atherothrombotic complications. Multiple mechanisms contribute to the pro-thrombotic status which characterizes DM patients underscoring the importance of antiplatelet therapies used for secondary prevention in these patients. For many years, dual antiplatelet therapy (DAPT) with aspirin and the P2Y12 inhibitor clopidogrel has represented the mainstay of treatment following an acute coronary syndrome (ACS) or in patients undergoing percutaneous coronary interventions (PCI). Although DAPT reduces the incidence of atherothrombotic recurrences, these rates remain high in DM patients underscoring the need for more efficacious therapies. The present manuscript provides an overview on the current status of knowledge on currently available antiplatelet agents, focusing on the benefits and limitations of these therapies in DM patients, and evaluating the potential role of new antithrombotic agents and treatment strategies currently under development to overcome these limitations.

**Keywords:** Diabetes mellitus, Antiplatelet and antithrombotic, updates

### Introduction

More than 17.3 million individuals die of cardiovascular disease (CVD) globally, and CV-related deaths are projected to account for 23.6 million deaths annually by 2030<sup>[1]</sup>. Coupled with the increase in diabetes prevalence, the impacts of CVD are exacerbated<sup>[2]</sup>. This is because diabetes and CVD are closely related; CVD is the leading cause of death in patients with diabetes, and in turn, diabetes is a significant risk factor for CVD development and can worsen outcomes in patients with established CVD<sup>[2]</sup>. Patients with type 2 diabetes are at high risk for adverse cardiovascular events, including myocardial infarction (MI) and other types of coronary artery disease (CAD), peripheral artery disease (PAD), and ischemic stroke<sup>[3]</sup>. Diabetes also worsens the prognosis of patients with existing CAD or PAD<sup>[4]</sup>. Patients with diabetes have a chronic prothrombotic state and are at a higher risk for cardiovascular events than individuals without diabetes<sup>[4]</sup>. The platelet function of individuals with diabetes is dysregulated at both the receptor and intracellular signaling levels, which leads to increased platelet activation and thrombin generation<sup>[30]</sup>. Patients with type 2 diabetes and stable CAD who have not had a stroke or MI event yet are considered at being a very high risk for these events. Studies show that standard antithrombotic therapy in this setting is not adequate, with adverse events occurring in these patients despite being on treatment<sup>[4, 6]</sup>.

### Oral antiplatelet therapies and diabetes mellitus

As such, more aggressive antithrombotic therapies may be necessary to prevent primary and secondary thrombotic events in these patients<sup>[4]</sup>. Aspirin inhibits cyclooxygenase 1 (COX-1) activity of platelet prostaglandin-endoperoxide synthase 1 by selectively and irreversibly acetylating the hydroxyl group of a serine residue at position 529 (Ser529). In turn, this prevents the conversion of arachidonic acid into multiple downstream bioactive prostanoids including thromboxane A2 (TXA2), prostaglandins and prostacyclin<sup>[4, 6]</sup>. Current guidelines recommend aspirin alone as the standard antiplatelet therapy for patients with type 2 diabetes with no prior CVD event who are at a high risk for future events<sup>[8, 9]</sup>. However, several studies have shown that this current strategy with aspirin is inadequate, and the clear benefit

of aspirin in the primary prevention of cardiovascular events remains unproven [8-10]. Additionally, there is conflicting evidence about the use and the appropriate antiplatelet strategies in patients with diabetes, given the hyperreactivity of platelets in this setting. Several clinical trials have been recently concluded or ongoing that have evaluated novel antithrombotic therapy in this setting and during CMHC west live online Dr. Mehran presented insights and evidence from the clinical trials that have been conducted so far to elucidate the optimized antiplatelet therapy for secondary prevention against myocardial infarction, stroke, and death in patients with diabetes. Many clinical trials have evaluated the net clinical benefit of dual-anti-platelets for secondary cardiovascular prevention in patients with diabetes. It has previously been shown that individuals with diabetes have a decreased response to the commonly used P2Y12 inhibitor clopidogrel than individuals without diabetes. Additionally, the current evidence indicates a low net clinical benefit in adding clopidogrel to aspirin in patients with diabetes and stable CAD [11-13].

### New therapeutic agents

New anti-platelets therapies are also being assessed in several clinical trials. The results of the PLATO and PEGASUS-TIMI 54 trials that used a potent agent – ticagrelor, showed a significant benefit attributed to patients with diabetes and treated with PCI or medical management [14, 15]. Especially PEGASUS-TIMI 54 trial, in a sub-set, patients with a prior MI and diabetes were randomized to two doses of ticagrelor versus placebo over a couple of years' periods of time with a background of aspirin. The results demonstrated an essential benefit of Ticagrelor in reducing ischemic events in the PEGASUS trial; however, the benefit was accompanied by the bleeding event. Therefore, it becomes imperative to figure out the correct and precise risk-benefit ratio, especially in patients with diabetes, while employing one or more than potent antiplatelet agents (Figure 2). In her talk, Dr. Mehran mentioned that "it's important to note that post-discharge bleeding increases mortality" However, ticagrelor's effect for primary prevention in patients with T2D and stable CAD was not confirmed in high-risk patients with diabetes until the recent results with the THEMIS and THEMIS-PCI trials. The THEMIS trial, the results of which were announced in 2019, compared the impact of the addition of ticagrelor to aspirin in clinical outcomes of patients with diabetes mellitus and stable coronary disease, without a prior myocardial infarction or stroke and on hyperglycemic medication for more than six months. Ticagrelor was deemed effective with the reduction of ischemic events of cardiovascular death, MI, and stroke. It came, however, with the increased incidence of Thrombolysis in Myocardial Infarction (TIMI) major bleeding and higher intracranial hemorrhage, and therefore, overall net clinical benefit was absent [16]. However, in one of their sub-analysis, which is known as THEMIS -PCI trial, as 11,154 patients with a history of previous PCI, diabetes, receiving anti-hyperglycemic drugs, with stable CAD were recruited. They were randomly assigned to either ticagrelor or placebo. The primary outcome is comprised of myocardial infarction or stroke and cardiovascular death. The results found that ticagrelor improved net clinical benefit, although with incidences of increased bleeding when compared to patients without PCI [16]. The investigators concluded that for

patients with a history of PCI, diabetes, and tolerance for antiplatelet therapy, with high ischemic and low bleeding risk, long-term therapy with ticagrelor with aspirin can be considered [16]. Based on the results of the THEMIS trial, recently, ticagrelor was FDA approved to reduce the risk of a first heart attack or stroke in high-risk patients with CAD, which includes those with type 2 diabetes [17]. Dr. Mehran said, "Therefore, when you add more risk factors in these stable coronary patients, you begin to see an especially important benefit of these patients that had prior PCI, and here more net benefit is exhibited." A Danish population-based study on 3.3 million people showed that 5 years cardiovascular mortality in DM patients without a history of CAD was the same as non-DM patients with a history of MI [18].

### Individual comparison of aspirin and P2Y12 inhibitors

A recent systematic review and meta-analysis of randomized trials looked at P2Y12 inhibitor monotherapy compared to aspirin monotherapy for secondary prevention in patients with established atherosclerosis, and showed a reduction of myocardial infarction, stroke, vascular or non-vascular death, as well as decreased gastrointestinal bleeding in patients who were treated with P2Y12 monotherapy [19]. Several mechanisms by which hyperglycemia may increase platelet reactivity have been proposed. These include glycation of platelet surface proteins resulting in a decrease in membrane fluidity and an increase in platelet adhesion [20, 21]; osmotic effect of glucose [22], and activation of protein kinase C, a mediator of platelet activation [23]. Early intensive glucose control with insulin in patients with ACS presenting with hyperglycemia was found to decrease platelet reactivity [24]. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial showed intensive glucose-lowering treatment to reduce mortality in DM patients presenting with an ACS after 3.4 years of follow-up [25].

### Some surgical studies

Yanamoto *et al.* in 2017 carried out a retrospective multicentric study on the risk factors of hemorrhage after dental extractions. In patients on dual antiplatelet therapy, according to the authors, they are more likely to have a hemorrhagic risk, so local hemostasis techniques are recommended, such as sutures, gauze, and compression [26], or other more complex techniques, such as membrane flaps or grafts, biomaterials, or socket preservation [27], especially in case of oral inflammation.

Pototski *et al.* in 2007, stated in their work that patients can be treated without risk if their INR is lower than 4.0 [28]. However, other studies assess that the risk of bleeding can be controlled by post-extraction hemostasis maneuvers [29]. Daniel *et al.*, in 2002, discuss the risk of bleeding patients in antiplatelet therapy in an excellent scientific article, highlighting that the decision is based on an understanding of the pharmacodynamics of these drugs and a thorough medical history of the patient [29].

### Conclusion

Patients with DM are at increased atherothrombotic risk and have elevated rates of ischemic recurrences. Abnormalities in platelet function profiles which characterize this patient population can contribute to these observations. While currently approved antiplatelet treatment strategies have

proven successful in improving outcomes in ACS, DM patients continue to experience high rates of adverse outcomes. Even though the use of more potent antiplatelet therapies, as well as prolonging intensified therapy, reduces ischemic events, the increase in bleeding complications represents a major concern. Therefore, strategies aimed at reducing ischemic events while minimizing the risk of bleeding complications represent an area on ongoing research. Ongoing trials are testing these strategies and will provide important understandings into optimizing outcomes in patients with DM.

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