Antiplatelet Therapy in Diabetes

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KEYWORDS

• Cardiovascular disease • Diabetes • Antiplatelet therapy • Thrombosis
• Antithrombotic therapy

KEY POINTS

- Patients with diabetes mellitus (DM) are higher risk for atherothrombotic events than patients without DM, in part due to increased platelet reactivity.
- Aspirin is effective for secondary prevention of cardiovascular events in DM.
- The role of aspirin for primary prevention in DM is uncertain.
- There is no role for dual antiplatelet therapy in DM patients without a history of cardiovascular disease.
- Using more potent antiplatelet therapy in DM patients with a history of myocardial infarction or acute coronary syndrome provides similar or greater risk reduction for ischemic events than in non-DM patients.

INTRODUCTION

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality among patients with diabetes mellitus (DM). Common cardiovascular comorbidities include coronary artery disease (CAD), stroke, and peripheral artery disease (PAD). The presence of DM alone is predictive of the risk of future cardiovascular events. Some older studies have suggested that patients with DM without a history of CAD have a future risk similar to non-DM patients with a history of myocardial infarction (MI).[1] In 2010, among those aged 20 years or older with DM, hospitalization for MI and stroke were 1.8 and 1.5 times higher, respectively, compared with those without DM. Among

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those with clinical CVD, DM status is also predictive of worse clinical outcomes. In 2003 to 2006, cardiovascular death rates were 1.7 times higher in patients diagnosed with DM that in those without DM.[2] An analysis of the Reduction of Atherothrombosis for Continued Health (REACH) registry of 45,227 patients at high risk of atherothrombosis or with established atherothrombosis suggested that DM was associated with an increased hazard for cardiovascular death, MI, or stroke, as well as an increase in both cardiovascular death and overall mortality.[3,4]

Although the mechanisms for predisposition to atherosclerosis in DM have not been entirely elucidated, the process is thought to be multifactorial and involve metabolic stress from hyperglycemia, increased oxidative stress, endothelial dysfunction, inflammation, and a hypercoagulable state with heightened platelet reactivity.[5] For these reasons, there has been tremendous interest in exploring the role of antiplatelet therapies in DM to reduce the frequency of cardiovascular events.[6]

PLATELET ACTIVATION AND AGGREGATION

Platelet activation and aggregation are integral to both normal hemostasis and pathologic atherothrombosis. Circulating platelets flow in the blood as smooth disks and are normally separated from the subendothelial connective tissue matrix by vascular endothelial cells. Healthy endothelium secretes nitric oxide and prostacyclin, which help keep platelets in an inactive state.[7] On the endothelial cell surface, adenosine diphosphate (ADP), a potent platelet activator, is normally converted to adenosine monophosphate (AMP) through the action of CD39, and AMP is further converted to adenosine through the action of CD79, additionally promoting platelet inactivity.[7]

If there is disruption in the integrity of the vascular endothelium, platelets are exposed to subendothelial collagen and von Willebrand factor. These subendothelial ligands interact with platelet membrane receptors glycoprotein (Gp)VI and GpIb/IX/V to promote platelet adhesion and subsequent activation.[8,9] These interactions induce conformational changes, allowing platelets to spread along collagen fibrils and promote the release of potent stimulants of platelet activation and aggregation, including thromboxane A2 (TXA2) and ADP, into the circulation. Activated platelets cross-link through the interaction of fibrinogen and the GpIIb/IIIa receptor. Platelet activation is further influenced by initiation of the coagulation cascade, which occurs when exposed tissue factor binds circulating factor VIIa, leading to the downstream production of thrombin, a highly potent platelet agonist, and fibrinogen.[8,9]

Antiplatelet therapies prevent thrombosis by disrupting platelet activation and aggregation at various steps along this pathway. Antiplatelet agents may interfere with activation of platelet membrane surface receptors, including the ADP (P2Y12) receptor, the GpIIb/IIIa receptor, and the thrombin (protease activated receptor [PAR]-1) receptor. Depending on the specific agent, this may occur through competitive or noncompetitive inhibition, reversibly or irreversibly, and with variable potency, influenced by drug metabolism pathways. Additional mechanisms for antiplatelet agents include disruption of prostaglandin synthesis and interference with cyclic AMP generation. The ultimate goal is to try to prevent the development of ischemic events (primary prevention of CAD, cerebrovascular disease, and PAD), or to prevent recurrent ischemic events (secondary prevention).

ASPIRIN

During the process of platelet activation, phospholipase A2 is stimulated by an increase in cytosolic calcium and releases arachidonic acid through enzymatic cleavage within the platelet. Through the action of cycloxygenase-1 (COX-1), arachidonic acid is