Review Article

Diabetes and antiplatelet therapy: from bench to bedside

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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 $P2Y_{12}$ 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. Oral platelet $P2Y_{12}$ receptor inhibitors with enhanced potency, such as prasugrel and ticagrelor, as well as antiplatelet therapies such as vorapaxar inhibiting the thrombin-mediated platelet signaling pathway, constitute treatment opportunities for patients with DM and have shown to be associated with a greater reduction in ischemic recurrences, albeit at the cost of more bleeding. This article reviews currently available antiplatelet agents and delivers an update on the advances and drawbacks of these agents used for secondary prevention in DM patients experiencing an ACS or undergoing PCI.

Keywords: Coronary artery disease (CAD); diabetes mellitus (DM); antiplatelet therapy (APT); thrombosis; bleeding

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Introduction

Diabetes mellitus (DM) is a metabolic condition currently affecting over 150 million people worldwide, largely due to type 2 DM, representing a global pandemic (1). The prevalence of DM is in continuous increase and the global prevalence of DM among adults is estimated to be 7.7% (439 million individuals) by 2030 (2,3). In the United States, the costs related to DM have been projected at $172 billion in 2007, while they are anticipated to rise to $192 billion by 2020 (4).

Dysfunction in insulin secretion and insulin action at the target tissues leads to chronic hyperglycemia and multiple comorbidities affecting the cardiovascular and many other systems (5). Cardiovascular disease, predominantly coronary artery disease (CAD) deriving from accelerated atherosclerosis, is the primary cause of morbidity and mortality in DM patients (6). 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 myocardial infarction (MI) (6). In addition, DM is the main cause of accelerated atherogenesis and atherothrombosis detected in this patient cohort (7). Furthermore, the negative prognosis associated with DM status is maintained across the acute coronary syndrome (ACS) spectrum. This includes unstable angina, non-ST-segment elevation MI (NSTEMI) (8), ST-segment elevation MI (STEMI) treated

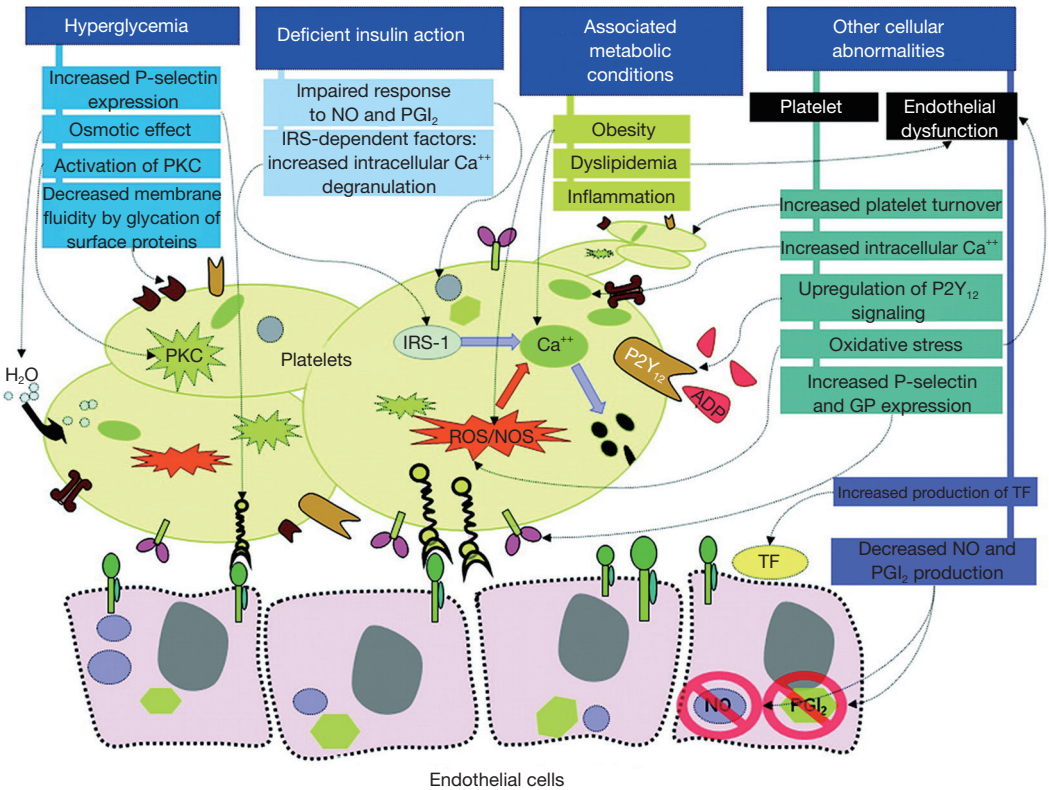

Figure 1 Mechanism involved in platelet dysfunction and prothrombotic status in diabetes mellitus patients. ADP, adenosine diphosphate; Ca^{++}, calcium; GP, glycoprotein, IRS, insulin receptor substrate; NO, nitric oxide; PGI2, prostacyclin; PKC, protein kinase C; ROS/NOS, reactive oxygen and nitrogen species; TF, tissue factor; H_2O, water. Reproduced with permission from Ferreiro and Angiolillo (12).

medically (9), and ACS undergoing percutaneous coronary intervention (PCI) (10,11).

These findings highlight the significance of antiplatelet therapy for secondary prevention of atherothrombotic recurrences in patients with DM. This is challenged by the fact that DM patients have heightened platelet reactivity, which may warrant the need for more potent therapies to reduce their ischemic risk (12). This article reviews currently available antiplatelet agents and provides an update on the advances and drawbacks of these agents used for secondary prevention in patients with DM experiencing an ACS or undergoing PCI.

Diabetes & atherothrombosis

Multiple mechanisms contribute to the accelerated atherogenesis and atherothrombotic risk in DM patients (12). Patients with DM have endothelial dysfunction and metabolic disorders, including obesity, hyperglycemia, dyslipidemia, insulin resistance, and increased oxidative stress (12). The prothrombotic and inflammatory state in patients with DM contribute to the accelerated progression of atherosclerosis as well as to the exacerbated risk of thrombosis in response to rupture of an atherosclerotic plaque (5,13,14). Platelets of DM patients are hyperreactive with intensified adhesion, activation, and aggregation (15,16). The prothrombotic status is the result of this increased platelet reactivity. However, other factors also contribute to this condition including: high levels of procoagulant agents (e.g., fibrinogen, tissue factor, von Willebrand factor, factor VII, platelet factor 4); impaired endogenous fibrinolysis (e.g., elevated levels of plasminogen activator inhibitor-1); and decreased concentrations of endogenous anticoagulants (e.g., antithrombin III and protein C) (*Figure 1*) (12).

Hyperglycemia and platelet reactivity

Several mechanisms can contribute to increased platelet reactivity in patients with DM (12). Hyperglycemia is one of

the most characteristic features for DM that may prompt the expression of the adhesion molecule P-selectin on the cell surface (17,18). Correlation between P-selectin expression and levels of fasting glucose has also been reported (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).

Insulin resistance and platelet reactivity

Type 2 DM is produced by the combination of resistance to insulin in the target tissues and an inadequate compensatory secretion of insulin leading to insulin deficiency (26). Reduced insulin secretion and tissue response is one of the factors contributing to platelet dysfunction in DM (27). Platelets express both insulin-like growth factor-1 receptors (IGF-1) and insulin receptors (28,29). When insulin binds to platelets, it increases the surface expression of adenylate cyclase-linked prostacyclin receptor (30). However, the expression of the insulin receptor has a tendency to be relatively low because the majority of its subunits heterodimerize with those of the IGF-1 receptor to conform an insulin/IGF-1 hybrid receptor, which avidly binds IGF-1 but not insulin (29). IGF-1 is present in the granules of platelets, and its receptor is expressed on the platelet surface, contributing to the amplification of platelet reactivity in DM patients leading to a prothrombotic status. Moreover, IGF-1 stimulates tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 and their subsequent binding to the p85 subunit of the phosphoinositide-3 kinase, leading to phosphorylation of protein kinase B, involving several cellular responses to insulin, IGF-1, and modulation of platelet reactivity (31).

Insulin resistance induces a rise in intracellular calcium, promoting enhanced platelet degranulation and aggregation (31). However, the exact mechanism by which calcium concentration is increased is not yet well-established (32,33). It has been suggested that IRS-1 mediates inhibition of Ca^{2+} mobilization by insulin via the inhibitory G-protein Gi (34). Type 2 DM patients who are carriers of the C allele of the rs956115 marker of the IRS-1 gene have a hyperreactive platelet phenotype and increased risk of ischemic events (35). IRS independent pathways are also involved in platelet hyperreactivity caused by insulin resistance, including impairment in platelet sensitivity to nitric oxide (NO) and prostacyclin (36,37). These mediators are released by the endothelium and reduce platelet activation. Consequently, impaired response to NO and prostacyclin is associated with increased platelet reactivity. The thiazolidinedione rosiglitazone is an insulin sensitizer associated with improved sensitivity to NO in platelets and reduced P-selectin expression in DM and non-DM patients, respectively (38,39). Clinical trials have also shown a benefit of insulin-sensitizer therapy over insulin-providing therapy on atherosclerosis progression and cardiovascular outcomes in DM patients (40,41). However, in DM patients treated with aspirin and clopidogrel therapy, the adjunctive use of pioglitazone was not associated with enhanced inhibition of platelet $P2Y_{12}$ mediated signaling (42).

Concomitant metabolic conditions and platelet reactivity

Multiple metabolic conditions like obesity, dyslipidemia, and systemic inflammation are commonly associated with type 2 DM. However, other factors present in obese individuals can contribute to platelet dysfunction such as high mean platelet volume and elevated platelet count (43), increase systolic calcium concentration (44), increase oxidative stress and high blood leptin concentrations (45) causing an enhanced effect for the platelet activation and adhesion. Abnormalities of the lipid profile are commonly found in DM subjects. Hypertriglyceridemia can lead to a higher platelet activation (46). It has been suggested that this effect is mediated by the apolipoprotein E content of the very-low-density lipoprotein particles, which are rich in triglycerides (47,48). Systemic inflammation may also contribute to increased platelet reactivity (49). Expression of platelet FcgammaRIIA receptor, which is heightened in DM patients and involved in platelet activation, has shown to be modulated by inflammation (50,51).

Other disorders associated with platelet reactivity

Dysregulation of calcium metabolism is a disorder present in DM platelets and the mechanisms involved in calcium

signaling abnormalities are not yet fully explained. Some of the suggested factors that may play a role are an augmented oxidative stress (52), insulin resistance, change in the activity of calcium ATPases and a disproportionate influx of calcium through the sodium/calcium exchanger (53). Oxidative stress is a disorder commonly associated with DM, especially the overproduction of reactive oxygen and nitrogen species with a reduction of platelet antioxidant levels that lead to impaired platelet function (54,55). The surge in reactive oxygen species enhances the production of advanced glycation end products, which has been proposed to play a role in atherosclerosis through the activation of the receptor for advanced glycation end products (56). In addition, the oxidative stress present in DM patients enhances endothelial dysfunction decreasing the production of NO and prostacyclin leading an increase in platelet reactivity and enhancing the prothrombotic state through increased production of tissue factor (*Figure 1*) (57,58).

Patients with DM have accelerated platelet turnover, which is represented by a greater number of reticulated platelets (59). These platelets are larger and more sensitive resulting in enhanced platelet reactivity with a reduced response to antiplatelet therapies like aspirin and clopidogrel (60). In addition to this mechanism, there is upregulation of platelet ADP $P2Y_{12}$ receptor signaling that suppresses cAMP leading to a reduced response to insulin, increasing the adhesion, aggregation and pro-coagulative state (61,62).

Oral antiplatelet therapies and diabetes mellitus

Aspirin and a $P2Y_{12}$ receptor antagonist, frequently used in combination and known as dual antiplatelet therapy (DAPT), represents the standard of care oral antiplatelet treatment for the prevention of recurrent ischemic events in patients with CAD, particularly those presenting with an ACS and undergoing PCI (63,64). In the section below, the efficacy and safety of these drugs, particularly for secondary prevention in DM patients, are described. The role of oral antiplatelet therapy (i.e., aspirin) for primary prevention in DM patients goes beyond the scope of this manuscript and described in details elsewhere (65).

Aspirin

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 A_2 (TXA_2), prostaglandins and prostacyclin (66).

Therefore, aspirin diminishes platelet activation mediated by the G protein-coupled thromboxane and prostaglandin endoperoxide (TP) receptor pathway leading to changes in platelet shape and enhancement of recruitment and aggregation of platelets. Due to the fact that platelets are enucleated this effect is irreversible and therefore they are unable to resynthesize COX-1 (67). Aspirin blocks TXA_2 induced platelet activation and prostacyclin-induced counter-regulation, which plays a central role in gastric mucosal protection. Prostacyclins derive from both COX-1 and more deeply from COX-2 especially with low-dose aspirin. This suggests that significant prostacyclin synthesis is preserved with low-dose aspirin therapy. With increasing doses of aspirin, COX-2 inhibition increases in a dose-dependent manner, which results in reduced prostacyclin generation resulting in a dose-dependent increase of bleeding, but with comparable reduction in ischemic risk (66).

The advantages of aspirin are well demonstrated in the collaborative meta-analysis (Antithrombotic Trialists' Collaboration) which comprised 43,000 person-years from 16 secondary prevention trials. In secondary prevention, aspirin significantly reduced major CV events (rate ratio 0.80, 95% CI, 0.73–0.88), including a 31% risk reduction (rate ratio 0.69, 95% CI, 0.60–0.80) in nonfatal MI (68-70). Aspirin was also effective in reducing the risk of ischemic stroke (rate ratio 0.78, 95% CI, 0.61–0.99), although it increased the risk of hemorrhagic stroke (rate ratio 1.67, 95% CI, 0.97–2.90) (67). Aspirin also increased major gastrointestinal and other extracranial bleeds [0·10% *vs.* 0·07% per year; RR 1.54 (1.30–1.82), P<0.0001]. However, the ischemic recurrences remains elevated (~20%) despite aspirin use. The persistence of this high percentage can be attributed to the increased platelet reactivity, enhanced platelet turnover, more reticular platelets, increased TXA_2 synthesis or early recovery of COX-1 activity characteristics present in patients with DM (12).

A number of studies have shown that twice-daily administration of aspirin enhance platelet inhibition to a greater extent than once-daily administration and a dose-dependent suppression of serum TXB2 levels in patients with DM (71,72) However, the clinical implications of a twice-daily dosing regimen are largely unknown and are being evaluated in the ongoing ANDAMAND

(Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome) trial (clinicaltrials.gov identifier NCT02520921). Higher aspirin doses (325 *vs.* 81 mg) have also been associated with greater platelet inhibition and decreased rates of aspirin resistance in DM patients (73). To a certain extent this was assessed in the CURRENT-OASIS 7 study (Clopidogrel and aspirin optimal dose usage to reduce recurrent events-7th organization to assess strategies in ischemic syndromes) which did not show significant differences in efficacy between high (300 to 325 mg daily) and low (75 to 100 mg daily) dose aspirin and observing a trend towards higher rates of gastrointestinal bleeds (74). Ultimately, studies are currently being conducted to identify aspirin formulations that are associated with more favorable pharmacodynamics effects (75,76).

P2Y$_{12}$ receptor antagonists

The platelet ADP signaling pathways play a key role in platelet activation and aggregation via the P2Y$_1$ and P2Y$_{12}$ receptors (77,78). While both receptors are required for aggregation, ADP-stimulated effects on platelets are mediated primarily by Gi-coupled P2Y$_{12}$ receptor activation, leading to persistent platelet aggregation and stabilization of the platelet aggregate, whereas P2Y$_1$ is responsible for an initial weak, transient phase of platelet aggregation (79). The importance of this signaling pathway is underscored by the clinical benefit associated with the use of oral P2Y$_{12}$ inhibitors. There are two main classes of oral P2Y$_{12}$ inhibitors: thienopyridines (ticlopidine, clopidogrel, and prasugrel) and non-thienopyridine (ticagrelor) agents. Thienopyridines are nondirect (requiring metabolism to generate an active metabolite), orally administered, irreversible P2Y$_{12}$ receptor inhibitors. Ticlopidine was a first-generation thienopyridine which is mostly no longer used due to safety concerns, in particular, bone marrow suppression (80). Clopidogrel and prasugrel are second and third generation thienopyridines, respectively (67). Ticagrelor, on the contrary, is a non-thienopyridine appertaining to a drug class called cyclopentyltriazolopyrimidine (CPTP) which is a direct (no metabolism required), orally administered agent, with reversible binding properties to the P2Y$_{12}$ receptor (67). With the exception of clopidogrel, which was studies in a head-to-head comparison with aspirin in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial (81), all other reported studies of P2Y$_{12}$ inhibitors in CAD patients were tested on a background of aspirin therapy.

Clopidogrel

Clopidogrel is a prodrug which, following intestinal absorption, is largely (~85%) hydrolyzed by human carboxylesterase-1 into an inactive acid metabolite, while the remaining 15% is metabolized by two-step oxidation processes using several hepatic cytochrome P-450 (CYP) isoenzymes to generate an active metabolite (67). The CYP2C19 isoenzyme is involved in both metabolic steps. Therefore, genetic polymorphisms associated with reduced enzymatic activity or drugs that interfere with enzyme activity (e.g., proton pump inhibitors), may impair clopidogrel's effects leading to potential complications (82-84).

In the CAPRIE study (n=19,185), composed of patients with recent MI, recent ischemic stroke or established peripheral artery disease (PAD), clopidogrel (75 mg daily) led to a significant 8.7% relative risk reduction of the composite endpoint (ischemic stroke, MI, or vascular death) compared with aspirin (325 mg daily) (*Table 1*) (81). In this study, DM patients (n=3,866) had more ischemic event rates than non-DM patients in both the clopidogrel and aspirin groups (15.6% *vs.* 11.8% in clopidogrel group; 17.7% *vs.* 12.7% in aspirin group). In this subgroup, clopidogrel was associated with a 21% risk reduction of the primary endpoint compared with aspirin (*Table 1*). Importantly, compared with aspirin, clopidogrel significantly reduced (37% relative risk reduction) any bleeding event, mainly driven by gastrointestinal bleeding.

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study was the first to assess the benefits of DAPT consisting of aspirin and clopidogrel compared with aspirin monotherapy in patients (n=12,562) with non-ST-segment elevation ACS (NSTE-ACS) (85,86). After a mean of 9-month treatment, DAPT was associated with a 20% relative risk reduction in the combined endpoint of cardiovascular death, nonfatal MI, and stroke in comparison with aspirin alone at the expense of 38% increased risk of major bleeding. However, life-threatening bleedings were not increased. DM was present in 22.6% of the study population (n=2,840) and there were consistent benefits of DAPT on the primary outcome with non-DM patients (*Table 1*) (85,86). DAPT with a aspirin and clopidogrel was subsequently tested in other studies of high-risk patients, including CREDO, CLARITY, and COMMIT, consistently showing superiority in terms of reducing ischemic events

Table 1 Outcomes in patients with DM in major secondary prevention with oral antithrombotic therapy

Trial	Patients (DM/overall)	Setting	Treatment arm	Primary efficacy endpoint	Outcomes in DM	Bleeding risk in DM
CURE	2,840/12,562	NSTE-ACS	Aspirin + clopidogrel *vs.* aspirin	CV death, nonfatal MI or ischemic stroke	14.2 % *vs.* 16.7% RR =0.84 (0.70–1.02), P<0.001	NA
CAPRIE	3,866/19,185	Recent MI, stroke, established PAD	Aspirin + clopidogrel *vs.* placebo	Vascular death, MI or ischemic stroke	15.6% *vs.* 17.7% RRR =21% (NA), P=0.0428*	1.8 % *vs.* 2.8 %, RRR =37% (3.8–58.7), P=0.31
CHARISMA	6,556/15,603	Multiple risk factors, documented CAD, CVD or symptomatic PAD	Aspirin + clopidogrel *vs.* aspirin + placebo	CV death, MI or stroke	Not provided but no interaction with the overall results	3.0% *vs.* 4.1% not provided with statistical analysis
TRITON-TIMI38	3,146/13,608	ACS patient undergoing PCI	Aspirin + prasugrel *vs.* aspirin + clopidogrel	CV death, nonfatal MI or nonfatal stroke	12.2% *vs.* 17.0% HR =0.70 (0.58–0.85), P_{int}=0.09	2.6% *vs.* 2.5% HR =1.06 (0.66–1.69), P_{int}=0.29
PLATO	4,662/18,624	ACS	Aspirin + ticagrelor *vs.* aspirin + clopidogrel	Vascular death, MI or stroke	14.1% *vs.* 16.2% HR =0.88 (0.76–1.03), P_{int}=0.49	14.1% *vs.* 14.8% HR =0.95 (0.81–1.12), P_{int}=0.21
TRAP 2P-TIMI trial	6,724/26,449	History of MI, ischemic stroke or PAD	Standard APT + vorapaxar *vs.* standard APT + placebo	CV death, MI or stroke	4.6% *vs.* 16.3% HR =0.89 (0.78–1.02), P_{int}=0.62	4.4% *vs.* 0.2% HR =1.60 (1.07–2.40), P_{int}=0.02

*, composite of vascular death, MI, stroke, or rehospitalization for ischemia or bleeding. APT, antiplatelet therapy; NSTE-ACS, non-ST segment elevation acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; HR, hazard ratio; NA, not applicable; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; P_{int}, P for interaction *vs.* non-DM; RR, relative risk; RRR, relative risk reduction.

compared with aspirin monotherapy, albeit at the expense of bleeding complications (87-89). However, the net benefit was in favor of the use of DAPT making this a standard of care approach in high-risk patients with CAD, such as those with ACS and undergoing PCI. The outcomes were consistent according to DM status. On the contrary, in a study of lower-risk patients called the CHARISMA trial, there was no ischemic benefit of DAPT, which was also associated with harm over aspirin therapy due to the increased risk of bleeding (90).

While the role of maintaining DAPT for up to 12 months in patients undergoing PCI was supported by clinical trial evidence, there has been much debate surrounding the need to prolong DAPT beyond 12 months (91). This was largely attributed to stent thrombosis, particularly with first generation drug-eluting stents, that were still occurring after 12 months (92,93). The benefit of 12 *vs.* 30 months of DAPT, most consisting of aspirin and clopidogrel, was tested in the DAPT trials (94). The study included patients (n=9,961) who had not experienced ischemic and bleeding events at 1 year after PCI. Prolonging DAPT by 18 months significantly reduced the composite outcome of all-cause mortality, MI, or stroke (4.3% *vs.* 5.9%; HR, 0.71; 95% CI, 0.59–0.85; P<0.001) and in-stent thrombosis (0.4% *vs.* 1.4%; HR, 0.29; 95% CI, 0.17–0.48; P<0.001). Notably, 55% of the ischemic benefit from DAPT prolongation derived from MI not related to the stent. However, this occurred at the expense of increased moderate or severe bleeding (2.5% *vs.* 1.6%; HR, 1.61; 95% CI, 1.21–2.16; P=0.001) (94). In patients with DM (n=3,037), there was a trend in reduced stent thrombosis (0.5% *vs.* 1.1%; HR, 0.47; 95% CI, 0.21–1.05; P=0.06) with prolonged DAPT, but this strategy was not effective in reducing the composite outcome (6.6% *vs.* 7.0%; HR, 0.92; 95% CI, 0.71–1.20; P=0.55) (95). Nevertheless, in a post hoc analysis to develop a risk prediction model, known as the DAPT score, DM was a predictor of stent thrombosis or MI (94,96).

Although in the studies mentioned above DAPT with aspirin and clopidogrel showed consistent benefits irrespective of DM status, DM patients had more ischemic recurrences than non-DM patients. These have led to investigations to define why DM patients continued to have high atherothrombotic events despite clopidogrel therapy. Pharmacodynamic investigations have consistently shown patients with DM to persists with high levels of platelet reactivity compared with non-DM patients (97-100). There are multiple mechanisms contributing to poor clopidogrel-induced antiplatelet effects. However, this appears to be most significantly due to impaired generation of the active metabolite (97). These observations have led to studies aimed to optimize platelet inhibition in DM patients. In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study, while doubling the clopidogrel maintenance dose (MD) enhanced platelet inhibition in DM patients, 60% of patients persisted as poor responders, highlighting the need for alternate therapies (101).

Prasugrel

Similarly to clopidogrel, prasugrel also needs to be converted into an active metabolite through an oxidation process by hepatic CYP isoenzymes to exert its effects of irreversible inhibition of the $P2Y_{12}$ receptor (67). However, prasugrel has more effective bioactivation leading to >5-fold higher active metabolite levels compared with clopidogrel leading to greater platelet inhibition and less interindividual response variability making it an attractive agent in DM patients (102). The OPTIMUS-3 study showed that standard- dose prasugrel [60 mg of loading dose (LD) plus 10 mg of maintenance dose (MD)] achieved enhanced platelet inhibition than double-dose clopidogrel (600 mg of LD plus 150 mg of MD) in DM patients (103). Nevertheless, patients with DM have reduced generation of active metabolites and platelet inhibition in comparison with non-DM patients even with prasugrel therapy (104).

Nevertheless, its ischemic benefits are supported by the results of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) study. This trial included ACS patients undergoing PCI (n=13,608) (105). At 15-months, prasugrel significantly reduced (19% relative risk reduction) ischemic events (cardiovascular death, non-fatal MI or non-fatal stroke). Notably, prasugrel was associated with a 52% relative risk reduction of stent thrombosis. However, this occurred at the expense of a 32% risk increase of TIMI major bleeding, including a significant increase in fatal and life-threatening bleeding, than clopidogrel (105). Subgroup analysis showed a neutral effect of prasugrel in certain patient cohorts, including those ≥75 year of age or weighing <60 kg, because the ischemic benefit was outweighed by the higher risk of bleeding complications compared with clopidogrel in these subjects (105). Importantly, in patients with a previous history of stroke or transient ischemic attack (TIA), there was harm, including more ischemic and bleeding events (including intracranial hemorrhage) with the use of prasugrel (105).

In a prespecified subgroup analysis, a greater magnitude of reduction in ischemic events was observed in DM (n=3,146) compared with non-DM patients (12.2% *vs.* 17.0%; HR, 0.70; P<0.001 in DM patients, and 9.2% *vs.* 10.6%; HR, 0.86; P=0.02 in non-DM patients, P for interaction=0.09) (*Table 1*) (106). There were no significant differences in TIMI major bleeding in DM patients (106). The magnitude of the net clinical benefit with prasugrel was enhanced in DM patients (14.6% *vs.* 19.2%; HR, 0.74; P=0.001) compared with non-DM patients (11.5% *vs.* 12.3%; HR, 0.92; P=0.16, P for interaction=0.05) (88). DM patients ≥75 year of age also attained a significant 36% risk reduction in the primary endpoint with prasugrel use (106).

The TRITON TIMI 38 trial specifically studied ACS patients undergoing PCI and did not include medically managed patients, which were selectively studied in the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial (107). In this study, although the bleeding end points of non-CABG-related severe or life-threatening events occurred with similar frequency among patients under the age of 75 years in the two study groups (clopidogrel *vs.* prasugrel), prasugrel use was not associated with a reduction in the primary endpoint (a composite of CV death, nonfatal MI and nonfatal stroke) among NSTE-ACS patients who were medically managed (n=7,243) (107). Event rates were higher in DM patients irrespective of treatment group (17.8% in prasugrel group *vs.* 20.4% in clopidogrel group) than non-DM patients (11.5% in prasugrel group *vs.* 13.2% in clopidogrel group) and the clinical effect of prasugrel was consistent irrespective of DM status (P for interaction=0.71) (107).

In light of these observations, prasugrel (60 mg LD and 10 mg MD) is only indicated for ACS patients after PCI; it not recommended for those undergoing non-invasive treatment or being medically managed (108,109). Prasugrel is contraindicated in patients with a prior history of stroke/TIA, at high risk of bleeding or hypersensitivity. In elderly patients (≥75 years old), prasugrel at standard dosing can be cautiously used only in high-risk patients with a history of DM or prior MI according to the United States Food and Drug Administration (FDA); according to the European Medical Agency (EMEA), prasugrel should be used at a reduced dose (5 mg MD) in the elderly. In low weight patients (<60 kg), both the FDA and EMEA recommend that prasugrel be used at a reduced dose (5 mg MD) (108,109).

Ticagrelor

Ticagrelor is a CPTP that reversibly blocks ADP-induced conformational changes of the $P2Y_{12}$ receptor and downstream signal transduction through the G-coupled protein (67). It is an active drug (i.e., not requiring an activation process) that undergoes a rapid absorption accompanied by degradation to its main active metabolite (AR-C124910XX) and inactive metabolite AR-C133913XX via CYP3A4 and 3A5 (67). Ticagrelor also inhibits adenosine uptake through the adenosine transporter ENT1 (type 1 equilibrated nucleoside transporter) providing adenosine-related effects (110). In addition to favoring platelet inhibition, the adenosine-related effects can contribute the anti-inflammatory effects, coronary vasodilation, inhibition of atrioventricular conduction and the sensation of dyspnea associated with ticagrelor therapy (110). Ticagrelor provides faster and more potent antiplatelet effects compared with clopidogrel, including in patients with DM (111-113). Furthermore, ticagrelor achieves comparable or higher platelet inhibition than prasugrel, a finding that was also shown in DM patients (114-116).

In the PLATO (Platelet Inhibition and Patient Outcomes) trial, compared with clopidogrel, ticagrelor significantly reduced the rate of the primary end point (composite of death from vascular causes, MI or stroke at 12 months; 10.2% *vs.* 12.3 %; HR, 0.84; P=0.0001) in ACS patients (n=18,624) treated either medically or undergoing revascularization (117). The trial also showed a reduction in the rate of cardiovascular death (4.0% *vs.* 5.1%; HR, 50.79; P=0.001) and the occurrence of definitive/probable stent thrombosis (2.2% *vs.* 2.9%; HR, 0.75; P=0.02) in the subgroup of patients undergoing PCI. Ticagrelor was not associated with an increase in protocol-defined major bleeding (11.6% *vs.* 11.2%; HR =0.03), although a higher rate of major bleeding not related to CABG occurred (4.5% *vs.* 3.8%; HR, 1.19; P=0.030) (117). DM patients (n=4,662) had significantly higher risks of both ischemic and bleeding events than non-DM patients (n=13,951) (*Table 1*) (118). The rates of primary endpoint and all-cause death among DM patients were respectively 66% and 84% higher compared with non-DM patients (118). DM patients had a 41% higher risk of major bleeding than non-DM patients (118). The benefits of ticagrelor in DM patients were consistent with the overall cohort and there was no heterogeneity in relation to DM status (14.1% *vs.* 16.2%; HR, 0.88; 95% CI, 0.76–1.03 in DM patients;

8.4% *vs.* 10.2%; HR, 0.83; 95% CI, 0.74–0.93 in non-DM patients; P for interaction=0.49) (118). Notably, compared with clopidogrel, ticagrelor reduced the primary endpoint by 20%, all-cause death by 22%, and stent thrombosis by 48% in patients with poor metabolic control (HbA1c ≥6%) without increasing major bleeding (8.4% *vs.* 8.2%).

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial evaluated the clinical efficacy of prolonged ticagrelor use in patients >50 years old with a history of MI 1–3 years prior to enrollment. Patients also needed to have at least 1 additional risk factor, among which DM requiring pharmacological treatment was included (119). Patients were randomized to either one of 2 doses of ticagrelor (90 or 60 mg b.i.d.) or placebo in addition to aspirin. At 3 years, a similar reduction of the primary efficacy endpoint (CV death, MI, and stroke) was observed in patients treated with either dose of ticagrelor (7.85% in 90 mg b.i.d. *vs.* 7.77% in 60 mg b.i.d. *vs.* 9.04% in placebo; P=0.004 for 90 mg b.i.d. *vs.* placebo and P=0.008 for 60 mg b.i.d. *vs.* placebo) (119). However, both ticagrelor doses were associated with increased major bleeding (but not fatal or intracranial bleeding) compared with placebo, albeit a numerically lower rate was shown with the 60 mg dose than with the 90 mg dose (2.60% in 90 mg b.i.d. *vs.* 2.30% in 60 mg b.i.d. *vs.* 1.06% in placebo; P<0.001 both for 90 mg b.i.d. *vs.* placebo and 60 mg b.i.d. *vs.* placebo) (119). A dose-dependent increase in dyspnea resulted in a higher treatment discontinuation rate in ticagrelor users (6.5% in 90 mg b.i.d. *vs.* 4.55% in 60 mg b.i.d. *vs.* 0.79% in placebo; P<0.001 for each ticagrelor dose *vs.* placebo (119). There was a higher rate of the primary efficacy endpoint in DM patients (n=6,806, 32%) (10.1% in 90 mg b.i.d. *vs.* 10.0% in 60 mg b.i.d. *vs.* 11.60% in placebo) compared to non-DM patients (6.77% in 90 mg b.i.d. *vs.* 6.68% in 60 mg b.i.d. *vs.* 7.83% in placebo) (120). Nevertheless, the relative risk reduction in MACE with ticagrelor was consistent for the pooled doses versus placebo in DM patients (HR, 0.84; 95% CI, 0.72 to 0.99; P=0.035) and non-DM patients (HR, 0.84; 95% CI, 0.74 to 0.96; P=0.013; P interaction=0.99). Because DM patients have higher event rates, their absolute risk reduction was greater than in non-DM patients (1.5% *vs.* 1.1%, with corresponding 3-year number needed to treat of 67 *vs.* 91). Additionally, in DM patients, ticagrelor reduced cardiovascular death by 22% and coronary heart disease death by 34%. Similar to non-DM patients, there was increased TIMI major bleeding in DM patients (HR, 2.56; 95% CI, 1.52 to 4.33; P=0.0004) (119,120). A pharmacodynamic substudy of the trial showed consistently high level of platelet inhibition with ticagrelor irrespective of DM status, even in insulin-treated patients. Patients with diabetes did not have an increased incidence of high platelet reactivity in either ticagrelor group (121,122). Platelet reactivity was comparable in DM patients treated with ticagrelor 60 *vs.* 90 mg bid. Pharmacokinetics of ticagrelor were not affected by DM status (121,122). The ongoing THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study NCT01991795) study is currently testing the clinical impact of ticagrelor in patients with type 2 DM and CAD but without prior MI.

Based on these results, ticagrelor (180 mg LD and 90 mg b.i.d. MD) is recommended for the management of ACS patients irrespective of planned treatment approach (invasive or non-invasive). After 1 year from an ACS, ticagrelor is recommended for secondary prevention at a lower dosing regimen (60 mg b.i.d.). Ticagrelor is contraindicated in patients with a history of intracranial bleeding, active pathological bleeding, severe hepatic dysfunction or hypersensitivity to the drug (123,124).

New therapeutic agents

Although DAPT has significantly reduced the risk of ischemic events in high-risk CAD patients, recurrences still occur particularly in patients with DM. This has underscored the need to define alternative strategies or newer antiplatelet therapies to reduce the risk of ischemic recurrences. Cilostazol is a phosphodiesterase III inhibitor clinically approved for the reduction of claudication symptoms in patients with peripheral arterial disease (125). However, cilostazol also has antiplatelet properties and has been tested in adjunct to DAPT, also known as triple antiplatelet therapy. The benefits of adding cilostazol to aspirin and clopidogrel in reducing ischemic events has been demonstrated particularly in patients with DM (125,126). This is also supported by pharmacodynamic studies specifically conducted in DM patients (127,128). However, this approach is not largely utilized following the introduction of the newer generation $P2Y_{12}$ receptor inhibitors. A number of other antiplatelet agents that inhibit other pathways of platelet activation have been under development, including thromboxane receptor inhibitors and thrombin receptor inhibitors, among others

(129-131). However, of these only vorapaxar, a PAR-1 receptor inhibitor, has been approved for clinical use.

Vorapaxar

Vorapaxar is a PAR-1 inhibitor which blocks thrombin-mediated platelet activation without affecting fibrinogen cleavage in the coagulation cascade (67,132-134). A combination of thrombin and $P2Y_{12}$ receptor inhibitors has a synergistic effect in the inhibition of thrombin-induced platelet activation. Vorapaxar was studied in 2 large-scale phase 3 clinical trials. In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial (n=12,944) conducted in NSTE-ACS patients, compared with placebo, vorapaxar (40 mg LD and 2.5 mg daily MD) utilized on top of standard DAPT, did not reduce the primary efficacy outcome (CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) at 2 years (135,136). Vorapaxar was associated with a significant increase in major bleeding and intracranial hemorrhage, and patients with previous stroke had a higher risk for intracranial hemorrhage (135).

The TRA 2P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis) study, including patients (n=26,449) with a history of atherosclerosis (defined as MI or ischemic stroke within the previous 2 weeks to 12 months or PAD), showed that, compared with placebo, vorapaxar (2.5 mg daily MD without LD) added on top of aspirin and/or a thienopyridine was associated with a significant 13% relative risk reduction of the primary endpoint (a composite of CV death, MI, stroke)after a median of 30 months' follow-up (136). In a subgroup analysis of the TRA 2P-TIMI 50 study including 16,896 patients with a history of MI, 3,623 (21%) had DM (137). The occurrence of the primary endpoint was more frequent in DM patients than in non-DM patients (14.3% *vs.* 7.6%; HR, 1.47; P<0.001) (136). Vorapaxar reduced the primary endpoint in both DM- and non- DM patients (*Table 1*) but increased the incidences of moderate or severe bleeding in both DM patients (4.4% *vs.* 2.6%; HR, 1.60; 95% CI, 1.07–2.40; P=0.02), and non- DM patients (2.9% *vs.* 1.9%; HR, 1.56; 95% CI, 1.22–2.00; P<0.001) (P for interaction=0.93) (137). Despite the increased risk of bleeding, vorapaxar enhanced the net clinical benefit (combined outcome of CV death, MI, stroke, recurrent ischemia leading to revascularization, and moderate or severe bleeding) in DM patients (16.4% *vs.* 19.6%; HR, 0.79; 95% CI, 0.67–0.93; P=0.005), whereas the net clinical benefit of vorapaxar was not significant in non-DM patients (10.4% *vs.* 10.9%; HR, 0.95; 95% CI, 0.85–1.06; P=0.32) (137).

Future perspectives and conclusions

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. Emerging strategies include dropping aspirin and maintaining therapy with a potent $P2Y_{12}$ receptor inhibitor as well as the use of low-dose oral anticoagulant therapy in adjunct to aspirin (138). Ongoing trials are testing these strategies and will provide important understandings into optimizing outcomes in patients with DM.

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Footnote

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