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Cardiovascular disease, particularly coronary artery disease resulting from accelerated atherosclerosis, is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM).[1] Of note, DM patients without a history of coronary artery disease have overall the same cardiac risk as non-DM patients with a history of myocardial infarction (MI).[2] Furthermore, patients with DM also have a higher risk of cardiovascular complications and recurrent atherothrombotic events than non-DM patients.[3] In fact, in the setting of acute coronary syndromes (ACS), the presence of DM is a strong independent predictor of short-term and long-term recurrent ischemic events, including mortality.[4,5] The concomitant presence of cardiovascular risk factors and comorbidities that negatively affect the outcomes of ACS is higher in DM patients.[6] The negative impact of DM on outcomes is maintained across the ACS spectrum, including unstable angina and non–ST-elevation MI (NSTEMI),[7] ST-elevation MI (STEMI) treated medically,[8] and ACS undergoing percutaneous coronary intervention (PCI).[9,10]

Platelets of DM patients are characterized by dysregulation of several signaling pathways, both receptor (eg, increased expression) and intracellular downstream signaling abnormalities, which leads to increased platelet reactivity.[11–15] This may play a role not only in the higher risk of developing ACS and the worse outcomes observed in DM, but also in the larger proportion of DM patients with inadequate response to antiplatelet agents compared with non-DM subjects,[13,16–18] which may also contribute to the impaired outcomes observed in DM patients despite compliance with recommended antiplatelet treatment regimens.

The aim of this article is to provide an overview of the current status of knowledge on platelet abnormalities that characterize DM patients, to analyze the benefits and limitations of currently available antiplatelet agents used in ACS, focusing on drawbacks of these therapies in DM patients, and to describe potential future directions to overcome these limitations, which include new agents and treatment strategies.

Platelet Dysfunction in DM: The "Diabetic" Platelet

Platelets play a pivotal role in atherogenesis and its thrombotic complications such as those occurring in patients with ACS,[19–22] which is a platelet-driven process. Platelets of DM patients have been proven to be hyperreactive with intensified adhesion, activation, and aggregation.[11–15] Multiple mechanisms have been proposed to contribute to increased platelet reactivity. Although many of them are closely interrelated, these mechanisms are caused by metabolic and cellular abnormalities that occur in DM patients, which can be grouped together into the following categories: hyperglycemia, insulin resistance, associated metabolic conditions, and other cellular abnormalities (Figure 1).

Hyperglycemia

Hyperglycemia, one of the most characteristic features of DM, may play an independent role in the abnormalities found in platelets of DM patients.[23] Induction of hyperglycemia has been shown to increase platelet P-selectin expression (a surface adhesion molecule) in patients with DM.[24] Correlation between levels of fasting glucose and P-selectin expression has also been reported.[25] Proposed mechanisms by which hyperglycemia may increase platelet reactivity are glycation of platelet surface proteins that decreases membrane fluidity, which may increase platelet adhesion[26,27]; osmotic effect of glucose,[28] and activation of protein kinase C, a mediator of platelet activation.[29]

In line with the laboratory findings, there are some clinical data supporting the idea that glucose-lowering therapy is beneficial in DM patients with ACS. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, which randomized patients with DM and acute MI to intensive glucose-lowering treatment (standard treatment plus insulin-glucose infusion for 24 hours followed by multidose insulin therapy) or standard treatment, observed a reduction in mortality in the intensive treatment group after 3.4 years of follow-up.[30] In the DIGAMI-2 trial, no differences in mortality or morbidity were observed among 3 different glucose-lowering strategies.[31] In this trial, the glucose-lowering levels were similar among the 3 groups, suggesting that the benefit of decreasing glucose levels is independent of the way this is achieved. However, the optimal blood glucose levels remain unknown. In fact, an excessive glucose lowering (targeting a glycohemoglobin level $<6.0\%$) was proven to be harmful in the Action to

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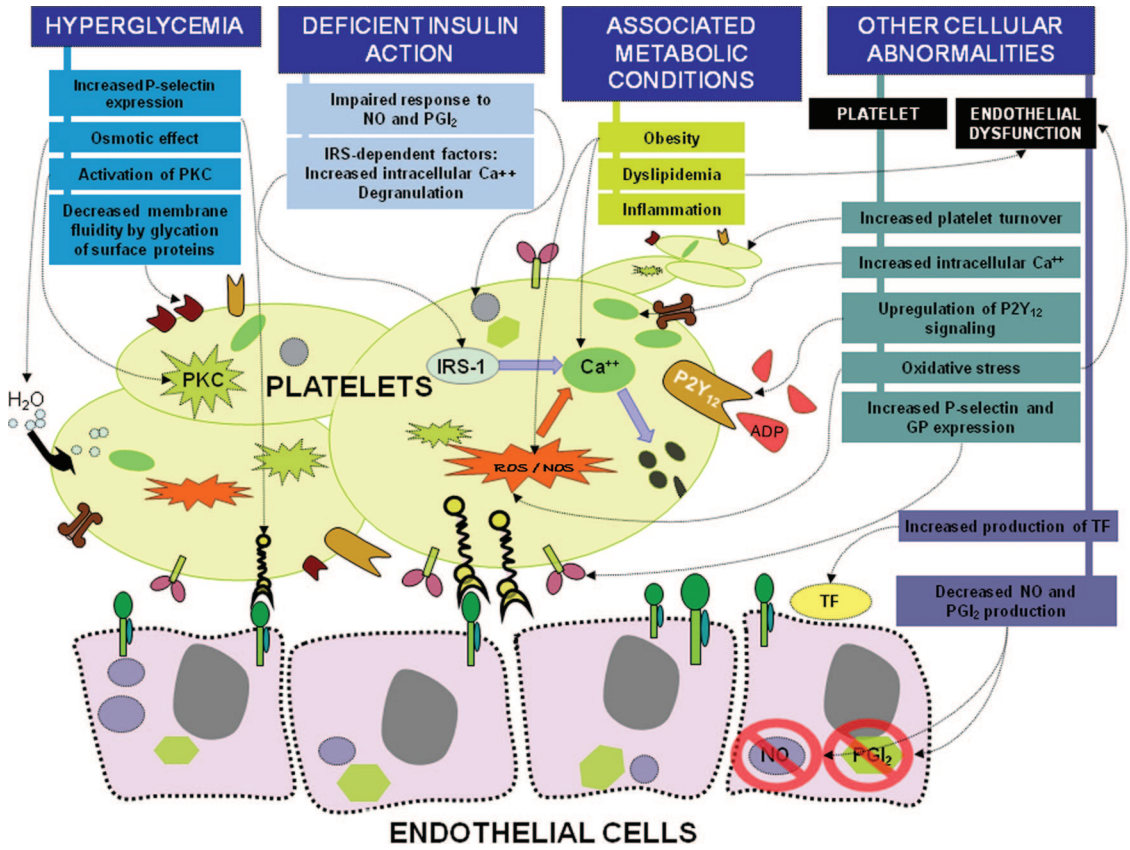

Figure 1. Mechanisms involved in platelet dysfunction in patients with DM. Several mechanisms contribute to platelet dysfunction in diabetes mellitus (DM) patients, including hyperglycemia, insulin deficiency, associated metabolic conditions, and other cellular abnormalities. Hyperglycemia may increase platelet reactivity by inducing P-selectin (a surface adhesion protein) expression, glycating platelet surface proteins (decreasing membrane fluidity and, thus, increasing platelet adhesion), and activating protein kinase C (PKC; a mediator of platelet activation) and as a result of the osmotic effect of glucose. Insulin deficiency also contributes to platelet dysfunction by different mechanisms. Some have been suggested to be IRS dependent such as the increase in intracellular calcium concentration, which leads to enhanced platelet degranulation and aggregation. Other factors associated with insulin resistance are not dependent on IRS, eg, the impaired response to NO and PGI_2, which enhances platelet reactivity. Some metabolic conditions frequently associated with DM may play a role in platelet hyperreactivity, including obesity, dyslipidemia, and enhanced systemic inflammation. In addition to being associated with insulin resistance, obesity contributes to platelet dysfunction, mainly in terms of adhesion and activation, with factors like augmented cytosolic calcium concentration and increased oxidative stress. Abnormalities of the lipid profile, especially hypertriglyceridemia, also affect platelet reactivity by different mechanisms, which include inducing endothelial dysfunction. The presence of endothelial dysfunction is another characteristic feature associated with DM, which enhances platelet reactivity by decreasing the production of NO and PGI_2 and contributes to a prothrombotic state through increased production of tissue factor (TF). Other platelet abnormalities present in DM patients can enhance platelet adhesion and activation, including increased expression of surface proteins (P-selectin and GP IIb/IIIa), augmented cytosolic calcium concentration, upregulation of certain pathways like $P2Y_{12}$ signaling, increased platelet turnover, and oxidative stress, which causes an impairment in platelet function as a result of overproduction of reactive oxygen (ROS) and nitrogen species (NOS).

Control Cardiovascular Risk in Diabetes (ACCORD) study, which randomized DM patients (n=10 251) to receive an intensive glucose-lowering regimen or a standard regimen, because the trial was interrupted after 3.5 years of follow-up as a result of an increased mortality in the intensive therapy group.[32]

Insulin Deficiency and Resistance

The majority of cases of DM fall into 2 etiopathogenetic categories. In type 1 DM, the underlying cause is an autoimmune destruction of the β cells of the pancreas, leading to an absolute deficiency of insulin secretion. In type 2 DM, which accounts for ≈90% to 95% of DM, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, usually having relative (rather than absolute) insulin deficiency.[33] Deficient insulin action resulting from inadequate insulin secretion and/or diminished tissue responses is the cardinal factor for the development of DM and contributes to platelet dysfunction.[34] Platelets express both insulin receptors and insulin-like growth factor-1 (IGF-1) receptors.[35,36] Among other effects, the binding of insulin to platelets increases surface expression of adenylate cyclase–linked prostacyclin receptor.[37] However, insulin receptor expression is relatively low because the majority of its subunits heterodimerize with those of the IGF-1 receptor to form an insulin/IGF-1 hybrid receptor, which avidly binds IGF-1 but not insulin.[36] However, IGF-1 is present in the α granules of platelets, and its receptor is expressed on the platelet surface, which may contribute to the amplification of platelet responses and the pathogenesis of cardiovascular disease. The functional and signaling pathways involved in IGF-1 modulation of platelet function, however, are currently

not fully elucidated. IGF-1 stimulation of platelets results in dose-dependent phosphorylation of the IGF receptor. Furthermore, IGF-1 stimulates tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 and their subsequent binding with the p85 subunit of phosphoinositide-3 kinase, leading to phosphorylation of protein kinase B, which is involved in several cellular responses to insulin and IGF-1, including modulation of platelet reactivity.[38]

Various abnormalities in insulin-mediated signaling have been proposed to be involved in the hampered or abolished platelet-inhibitory effect observed in patients with insulin resistance.[39] Among IRS-dependent factors, insulin resistance provokes an increase in intracellular calcium concentration, leading to enhanced platelet degranulation and aggregation.[40] However, the precise mechanism by which calcium concentration is increased is not yet fully elucidated.[41,42] IRS-independent pathways are also involved in platelet hyperreactivity caused by insulin resistance such as impairment in platelet sensitivity to nitric oxide (NO) and prostacyclin.[43,44] Both mediators are released by the endothelium and retard platelet activation. Therefore, impaired response to NO and prostacyclin is associated with enhanced platelet reactivity.

The importance of insulin resistance in platelet dysfunction among DM patients is underscored by recent studies with thiazolidinediones that have shown a beneficial effect of this group of insulin sensitizers on platelet function. Rosiglitazone improved sensitivity to NO in platelets and reduced P-selectin expression in DM and non-DM patients, respectively.[45,46] Clinical trials have also shown a benefit of insulin-sensitizer therapy over insulin-providing therapy in terms of atherosclerosis progression and cardiovascular outcomes.[47,48] The results of these studies emphasize the important role of insulin resistance in the development of atherothrombotic disease in DM patients.

Associated Metabolic Conditions

Type 2 DM is commonly associated with a number of metabolic conditions that may have an impact on platelet function, including obesity, dyslipidemia, and enhanced systemic inflammation.

Obesity is frequently associated with an insulin-resistant status. However, other factors present in obese subjects may contribute to platelet dysfunction: elevated platelet count and high mean platelet volume,[49] high blood leptin concentration,[50] increased cytosolic calcium concentration,[51] and increased oxidative stress.[52] These abnormalities result mostly in enhanced platelet adhesion and activation.[53,54] Likewise, response to antiplatelet drugs such as clopidogrel is also impaired in subjects with elevated body mass index.[55,56]

Abnormalities of the lipid profile commonly accompany DM. Hypertriglyceridemia, which induces higher platelet activation, is a typical manifestation.[57] This effect has been suggested to be mediated by the apolipoprotein E content of the very-low-density lipoprotein particles, which are rich in triglycerides.[58,59] Low levels of high-density lipoprotein have been associated with endothelial dysfunction, which may increase the atherothrombotic risk in DM patients.[60] Recently, Calkin et al[61] observed that administration of reconstituted high-density lipoprotein reduced platelet aggregation in DM subjects by promoting cholesterol efflux from platelets.

DM is also associated with systemic inflammation. In fact, DM patients show high levels of inflammatory and platelet activation markers.[62] In particular, an in vitro study showed that the platelet-activating factor released by leukocytes increased platelet activity. In addition, expression of platelet FcgammaRIIA receptor, which is enhanced in DM patients and involved in platelet activation, has been reported to be modulated by inflammation.[63,64] Therefore, systemic inflammation may contribute to increased platelet reactivity of DM subjects.

Other Cellular Abnormalities

Dysregulation of calcium metabolism is a major feature in DM platelets. To date, the exact mechanisms involved in calcium signaling abnormalities are not fully elucidated. Some of the proposed factors that may play a role are excessive influx of calcium through the sodium/calcium exchanger,[65] changes in the activity of calcium ATPases,[66] insulin resistance,[51] and augmented oxidative stress.[67] The result of this calcium dysregulation is an increase in cytosolic calcium concentration, which leads to enhanced platelet reactivity.[68]

DM is also associated with oxidative stress, in particular with an overproduction of reactive oxygen and nitrogen species, as well as reduced platelet antioxidant levels.[69,70] Alterations in the redox state of platelets may impair platelet function. The excessive generation of potent oxidants such as superoxide anions and hydrogen peroxide increases platelet activation.[69] An increase in reactive oxygen species enhances the production of advanced glycation end products.[71] These glycated proteins have been suggested to play a role in atherosclerosis by activation of the receptor for advanced glycation end products.[72] Furthermore, oxidative stress accompanying DM impairs endothelial function, which leads to increased platelet reactivity by decreasing the production of NO and prostacyclin.[73] In addition, platelets of DM patients have diminished sensitivity to the actions of NO and prostacyclin.[43,44] Endothelial dysfunction is another characteristic feature in DM patients that may result in a prothrombotic state through an increased production of tissue factor.[74]

An upregulation of platelet ADP $P2Y_{12}$ receptor signaling, which suppresses cAMP levels, and a lower responsiveness to insulin have been suggested in patients with type 2 DM, leading to increased adhesion, aggregation, and procoagulant activity.[75,75a] Another platelet abnormality observed in DM is an increased expression of surface proteins like P-selectin and glycoproteins (GPs) Ib and IIb/IIIa, which are integrins that mediate platelet adhesion.[53,76]

In addition to the above-mentioned mechanisms, DM patients have accelerated platelet turnover.[77] Platelet turnover is represented by the presence of a higher number of reticulated platelets, which are larger and more sensitive and thus result in platelet hyperreactivity and lower response to antiplatelet therapies like aspirin.[78] In line with these findings, Guthikonda et al[79] recently reported an association between a higher percentage of circulating reticulated platelets and a lower response to both aspirin and clopidogrel,

although only a small number of DM patients were included in this study.

Antiplatelet Therapies

Currently, 3 different classes of antiplatelet agents are approved for the treatment and/or prevention of recurrent events in the setting of ACS: cyclooxygenase-1 (COX-1) inhibitors (aspirin), ADP $P2Y_{12}$ receptor antagonists (thienopyridines), and GP IIb/IIIa inhibitors.[80,81] The following section provides an overview of the benefits and limitations of these drugs in DM patients.

Aspirin

Aspirin selectively acetylates the hydroxyl group of a serine residue at position 529 (Ser529) of the COX-1 enzyme, thereby blocking platelet formation of thromboxane A_2 (TXA_2) and thus diminishing platelet aggregation mediated by thromboxane and prostaglandin endoperoxide (TP) receptors pathway.[82] This effect is irreversible because platelets are enucleate and therefore unable to resynthesize COX-1. TXA_2 binds to TP receptors, which results in changes in platelet shape and enhancement of recruitment and aggregation of platelets. Although expert consensus statements recommend the use of aspirin for primary prevention in DM patients, its use in this setting has been controversial, and its description goes beyond the scope of this review, which focuses primarily on secondary prevention in the ACS setting.[83–89] Ongoing studies will provide further insights into the role of aspirin as a primary prevention measure in DM patients, including A Study of Cardiovascular Events in Diabetes (ASCEND; NCT00135226) and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; ISRCTN48110081).

Aspirin is still the antiplatelet drug of choice for secondary prevention of recurrent ischemic events in patients with atherothrombotic disease, including those with DM.[80–82,90,91] The benefit of aspirin therapy in the early management of ACS patients has been demonstrated repeatedly and consistently in earlier trials, including those evaluating unstable angina/NSTEMI[92–94] and STEMI.[95,96] Aspirin should be given as promptly as possible at an initial dose of 162 to 325 mg followed by a daily dose of 75 to 162 mg.[80,81] The recommended dose of aspirin for secondary prevention in DM patients with atherosclerotic disease is 75 to 162 mg daily.[90] The use of low-dose aspirin is supported mainly by 2 large meta-analyses of secondary prevention trials performed by the Antithrombotic Trialists' Collaboration that include 287 studies and involve 212 000 high-risk patients (with acute or previous vascular disease or some other predisposing condition implying an increased risk of occlusive vascular disease).[97,98] The results of these meta-analyses showed oral antiplatelet agents, mainly aspirin, to be protective for suffering vascular events in high-risk patients. In particular, the incidence of vascular events was reduced from 22.3% to 18.5% in the cohort of DM patients ($P<0.002$) and from 16.4% to 12.8% ($P<0.00001$) in non-DM patients. Although the overall incidence of vascular events was much higher in DM patients, the benefit of antiplatelet therapy was consistent regardless of DM status.[97] In these trials, aspirin was the most frequently evaluated antiplatelet agent at doses ranging from 75 to 325 mg daily. A low dose of aspirin (75 to 150 mg/d) was found to be at least as effective as higher daily doses, and importantly, bleeding complications were reduced with lower doses.[97,98]

The first large-scale prospective randomized study to compare high- and low-dose aspirin was the recently reported Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT/OASIS-7) trial, which randomized ACS patients scheduled to undergo angiography within 72 hours of hospital arrival.[99,99a] The study had a 2×2 factorial design, and patients were randomized in a double-blind fashion to high- or standard-dose clopidogrel for a month and in an open-label way to high-dose (300 to 325 mg daily) or low-dose (75 to 100 mg daily) aspirin. The trial did not show significant differences in efficacy between high- and low-dose aspirin. A trend toward a higher rate of gastrointestinal bleeds in the high-dose group (0.38% versus 0.24%; $P=0.051$) was observed.[99] No data regarding the DM subgroup of this study have been reported yet.

$P2Y_{12}$ receptor antagonists

Platelet ADP signaling pathways mediated by the $P2Y_1$ and $P2Y_{12}$ receptors play a central role in platelet activation and aggregation.[100,101] Although both receptors are needed for aggregation,[102] ADP-stimulated effects on platelets are mediated mainly by G_i-coupled $P2Y_{12}$ receptor activation, which leads to sustained platelet aggregation and stabilization of the platelet aggregate, whereas $P2Y_1$ is responsible for an initial weak, transient phase of platelet aggregation. Several families of $P2Y_{12}$ inhibitors have been developed. However, only thienopyridines (ticlopidine, clopidogrel, and prasugrel), which are nondirect, orally administered, irreversible $P2Y_{12}$ receptor inhibitors, are currently approved for clinical use. Ticlopidine was the first thienopyridine to be developed and was approved for clinical use in 1991. It showed its superiority in combination with aspirin compared with aspirin alone or anticoagulation in combination with aspirin in a number of trials for the prevention of recurrent ischemic events in patients undergoing PCI.[103–106] However, as a result of safety concerns (mainly high rates of neutropenia), ticlopidine has been largely replaced by clopidogrel (a second-generation thienopyridine) because of its better safety profile.[107]

Clopidogrel is currently the thienopyridine of choice because it has an efficacy similar to that of ticlopidine and a favorable safety profile.[107] In addition, clopidogrel has a faster onset of action through administration of a loading dose.[108] The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial evaluated the efficacy of clopidogrel (75 mg daily) versus aspirin (325 mg daily) in reducing the risk of ischemic outcomes in patients (n=19 185) with a history of recent MI, recent ischemic stroke, or established peripheral artery disease. The global results showed a significantly lower annual rate of the composite end point (ischemic stroke, MI, or vascular death) with clopidogrel (5.32% versus 5.83%; $P=0.043$).[109] The benefit with clopidogrel therapy was higher in the DM subgroup (15.6% versus 17.7%; $P=0.042$), leading to 21

Table. Large-Scale Randomized Placebo-Controlled Clinical Trials Evaluating the Efficacy of Dual Antiplatelet Therapy With Aspirin and Clopidogrel Versus Aspirin Alone in ACS/PCI Patients in the Overall Study Population and in DM Patients

Study	n (Overall)	Scenario	Primary End Point	% of Events and Association Measure in the Overall Population	n (DM)	% of Events and Association Measure in DM
CURE[7]	12 562	UA/NSTEMI	Cardiovascular death, nonfatal MI or stroke at 1 y	9.3 vs 11.4	2840	14.2 vs 16.7
RR (95% CI)				0.80 (0.72–0.90)		0.84 (0.70–1.02)
PCI-CURE[111]	2658	CURE patients undergoing PCI	Cardiovascular death, MI, or urgent TVR at 30 d	4.5 vs 6.4	504	12.9 vs 16.5
RR (95% CI)				0.70 (0.50–0.97)		0.77 (0.48–1.22)
CREDO[112]	2116	Elective PCI	Death, MI, or stroke at 1 y	8.5 vs 11.5	560	NR
RRR (95% CI), %				26.9 (3.9–44.4)		11.2 (−46.8–46.2)
COMMIT[113]	45 852	Acute MI (93% STEMI)	Death, reinfarction, or stroke at discharge or 28 d	9.2 vs 10.1	NR	NR
OR (95% CI)				0.91 (0.86–0.97)		
CLARITY[114]	3491	STEMI with fibrinolysis	Occluded infarct-related artery on angiography or death or recurrent MI before angiography	15.0 vs 21.7	575	NR
OR (95% CI)				0.64 (0.53–0.76)		
PCI-CLARITY[115]	1863	CLARITY patients undergoing PCI	Cardiovascular death, recurrent MI, or stroke at 30 d	3.6 vs 6.2	282	6.0 vs 10.1
OR (95% CI)				0.54 (0.35–0.85)		0.61 (0.24–1.53)

CURE indicates Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial; CREDO, Clopidogrel for the Reduction of Events During Observation; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; UA, unstable angina; TVR, target vessel revascularization; NR, not reported; RR, relative risk; RRR, relative risk reduction; and OR, odds ratio.

vascular events prevented for every 1000 DM patients treated (38 among insulin-treated patients).[110] Of note, the reduction in the rates of the primary end point did not reach statistical significance in non-DM patients.

Currently, the American Diabetes Association recommends the use of clopidogrel in very high-risk DM patients or as an alternative therapy in patients intolerant to aspirin.[90] In line with this, current guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel as the antiplatelet treatment of choice for patients with ACS, including patients with unstable angina or NSTEMI,[80] those with STEMI,[81] and patients undergoing PCI.[91] The recommended dose of clopidogrel is a 300-mg loading dose (up to 600 mg in the setting of PCI) followed by a maintenance dose of 75 mg daily. These recommendations have been made in light of the results of several large-scale clinical trials that have shown a clear benefit of clopidogrel in addition to aspirin in terms of preventing recurrent ischemic events, including stent thrombosis, compared aspirin alone.[7,111–115] The Table summarizes ACS/PCI trials comparing dual antiplatelet therapy with aspirin and clopidogrel versus aspirin alone, highlighting the relative benefits in the overall study population and in patients with DM.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showed that in high-risk but non-ACS patients (n=15 603) with either clinically evident cardiovascular disease or multiple risk factors, clopidogrel and aspirin were not significantly more effective than aspirin alone in reducing the rate of cardiovascular death, MI, or stroke (6.8% versus 7.3%; $P=0.22$).[116] Being a high-risk feature, DM was an important inclusion criterion for this study and represented 42% (n=6555) of the population. Consistent with the results in the overall population, no benefit of combined therapy was observed in the DM subgroup. Therefore, long-term dual antiplatelet therapy with aspirin and clopidogrel should not be advocated, not even in DM patients, outside the ACS/PCI setting.

The CURRENT/OASIS-7 trial, which compared the efficacy of high-dose (600-mg loading dose and then 150 mg once a day for 7 days followed by 75 mg daily) or standard-dose (300-mg loading dose followed by 75 mg daily) clopidogrel for 1 month in ACS patients (n=25 087) scheduled to undergo angiography within 72 hours of hospital arrival, failed to find a statistical difference for the primary end point (cardiovascular death, MI, or stroke at 30 days) in the overall study population.[99] However, in the subgroup of patients undergoing PCI (n=17 232), the high-dose clopidogrel regimen significantly reduced the rates of the primary efficacy end point (3.9% versus 4.5%; hazard ratio [HR]=0.85; $P=0.036$), as well as the risk of stent thrombosis, but at the expense of an increase in study-defined major bleedings.[99a] No differences in efficacy were observed among DM patients undergoing PCI (4.9% versus 5.6%; HR=0.87; 95% confidence interval [CI], 0.66 to 1.15).[99]

Prasugrel is a third-generation thienopyridine that was recently approved for clinical use in ACS patients undergoing PCI. It is orally administered and, like all thienopyridines, is a prodrug that requires hepatic metabolism to give origin to its active metabolite that irreversibly inhibits the $P2Y_{12}$ receptor.[117] Prasugrel has a more rapid onset of action than clopidogrel and provides greater platelet inhibition because of

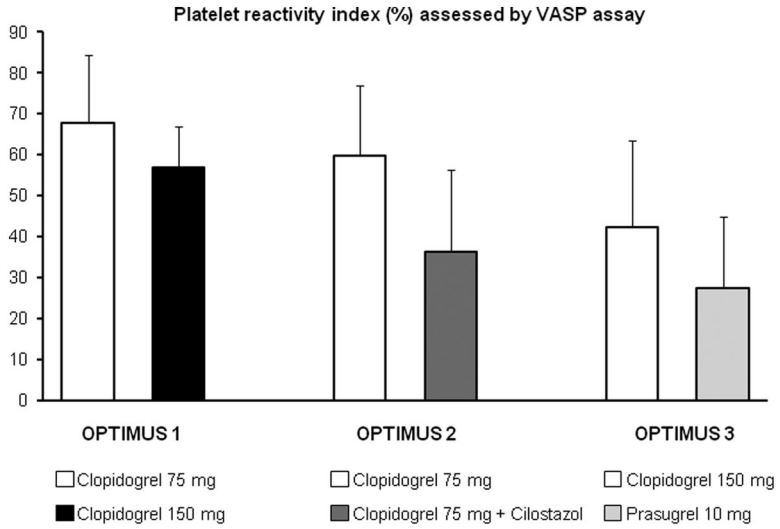

Figure 2. Antiplatelet effects of different treatment strategies to optimize platelet inhibition in diabetes mellitus (DM). The OPTIMUS studies were performed in patients with DM and coronary artery disease and evaluated platelet inhibition achieved by different antiplatelet treatment strategies using multiple pharmacodynamic measures. The platelet reactivity index (PRI), which is obtained by the flow cytometric analysis of the phosphorylation status of vasodilator-stimulated phosphoprotein (VASP) and is a specific measure of the degree of blockade of the $P2Y_{12}$ receptor signaling pathway, is illustrated. The OPTIMUS-1[124] study compared the effect of a high maintenance dose of clopidogrel (150 mg daily) and standard dosing at 30 days among suboptimal responders while on standard doses of dual antiplatelet therapy. The OPTIMUS-2[125] study compared the effect of adding cilostazol (100 mg BID) vs placebo at 2 weeks in patients on standard doses of dual antiplatelet therapy. The OPTIMUS-3[123] study compared the efficacy of prasugrel (60-mg loading dose and 10-mg daily maintenance dose) vs high-dose clopidogrel (600-mg loading dose and 150-mg daily maintenance dose) up to 1 week in patients on long-term aspirin therapy.

its more effective conversion into its active metabolite.[118] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) examined the efficacy and safety of prasugrel (60-mg loading dose followed by 10 mg daily) versus standard clopidogrel therapy (300-mg loading dose followed by 75-mg/d maintenance dose) in patients (n=13 608) with moderate- to high-risk ACS undergoing PCI.[119] A significant reduction in the rates of the primary end point (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) favoring prasugrel (9.9% versus 12.1%; HR=0.81; $P<0.001$) was found, as well as a reduction in the rates of stent thrombosis,[120]over a follow-up period of 15 months at the expense of an increased risk of major bleeding in the prasugrel group. Of note, no net clinical benefit was observed in the aged patients (≥75 years of age) and in those weighing <60 kg; in fact, a net harm was found in patients with history of stroke or transient ischemic attack.[119] However, particular subgroups appeared to have a higher benefit with prasugrel therapy such as patients with STEMI[121] and, importantly, DM patients.[122] The primary end point was reduced significantly with prasugrel in subjects with DM (12.2% versus 17.0%; HR=0.70; $P<0.001$). This benefit was consistent in patients with (14.3% versus 22.2%; HR=0.63; $P=0.009$) and without (11.5% versus 15.3%; HR=0.74; $P=0.009$) insulin treatment. Importantly, although major bleeding was higher overall in DM patients, which is consistent with the fact that DM per se is a risk factor for bleeding, there were no differences in major bleeding among DM patients treated with prasugrel compared with clopidogrel (2.6% versus 2.5%; HR=1.06; $P=0.81$). Prasugrel also improved the risk of stent thrombosis in the DM subgroup (overall DM cohort: 2.0% versus 3.6%; HR=0.52; $P=0.007$; insulin-dependent patients: 1.8% versus 5.7%; HR=0.31; $P=0.008$). Recently, the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS)-3 study showed that prasugrel (60-mg loading dose followed by 10-mg maintenance dose daily for 1 week) achieved significantly greater platelet inhibition compared with double-dose clopidogrel (600-mg loading dose followed by 150-mg maintenance dose) in DM patients with coronary artery disease on long-term aspirin treatment using multiple pharmacodynamic measures (Figure 2).[123–125] These observations overall suggest that greater clinical benefit is derived by achieving higher platelet inhibition in DM patients. The clinical efficacy of prasugrel in medically managed patients with unstable angina/NSTEMI is being evaluated in the ongoing Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS; NCT00699998) trial.

GP IIb/IIIa Inhibitors

Currently, 3 different GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) are approved for clinical use, all of them administered intravenously. The efficacy of these agents correlates directly with the severity and the risk of the ACS, being questionable in low- to moderate-risk patients or in those in whom a conservative approach is chosen.[126] These agents can be administered only intravenously; thus, despite their potent inhibitory effects on platelets, their utility is limited to the acute phase of treatment.

A meta-analysis of 6 large trials evaluating the effect of GP IIb/IIIa inhibitors in ACS patients observed a 22% reduction of mortality at 30 days in DM patients (n=6458) associated

with the use of GP IIb/IIIa blockers compared with those not receiving these agents (4.6% versus 6.2%; $P=0.007$), whereas non-DM patients (n=23 072) had no benefit in survival.[5] Of note, the benefit among DM patients was greater in those patients (n=1279) who underwent PCI during the index hospitalization (1.2% versus 4%; $P=0.002$). However, the fact that these trials did not use regimens of high clopidogrel loading dose, which are associated with more potent antiplatelet effects and have become the standard of care in clinical practice, but instead used ticlopidine or standard-dose clopidogrel has led to questions about validity of these data in today's practice. In fact, a more recent study, the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) trial did not show a benefit of abciximab over placebo on the 1-year risk of death and MI in DM patients (n=701) undergoing elective PCI after pretreatment with a 600-mg loading dose of clopidogrel at least 2 hours before the procedure.[127] Therefore, these results do not support the routine use of GP IIb/IIIa inhibitors in elective PCI. Conversely, the Intracoronary Stenting and Antithrombotic: Regimen Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial showed a significant reduction in the risk of adverse events with abciximab treatment compared with placebo in patients with high-risk ACS undergoing PCI after pretreatment with 600 mg clopidogrel.[128] This benefit, however, was restricted to patients with elevated troponin levels and was observed across all subgroups, including DM patients. These results support the use of GP IIb/IIIa receptor antagonists in high-risk ACS patients, in particular those with DM, as recommended in current guidelines.[80]

Few studies have evaluated the use of GP IIb/IIIa inhibitors in DM patients with STEMI undergoing PCI. In a small-scale study performed before the clopidogrel era, abciximab was associated with lower mortality and reinfarction rates across the DM subgroup (n=54) compared with placebo.[129] The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Combinations (CADILLAC) trial did not find a benefit in terms of death, reinfarction, or stroke with the use of abciximab in low-risk DM patients (n=346) with acute MI treated with balloon angioplasty or stenting.[10] However, a recent meta-regression of randomized trials evaluating the effect of GP IIb/IIIa inhibitors in STEMI patients treated with primary PCI showed a benefit in terms of death, but not reinfarction, associated with the use of these agents in high-risk patients, including those with DM.[130]

The major limitation associated with GP IIb/IIIa inhibitors is the increased risk of bleeding. Of note, bleeding has an important impact on prognosis after an ACS, including mortality.[131,132] Bivalirudin, a direct thrombin inhibitor, may be a valid alternative because it has been shown to provide similar protection from ischemic events with lower major bleeding rates compared with GP IIb/IIIa inhibitors, as observed in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial.[133] In a subgroup analysis performed in the DM cohort (n=3852), bivalirudin monotherapy was associated with a similar rate of composite ischemia (death, MI, or unplanned ischemic revascularization) compared with GP IIb/IIIa plus heparin (7.9% versus 8.9%; $P=0.39$) and a lower rate of major bleedings (3.7% versus 7.1%; $P<0.001$), resulting in fewer net adverse clinical outcomes (10.9% versus 13.8%; $P=0.02$).[134] This reduction of ischemic risk is of special importance because DM is a predictor of bleeding complications in patients with ACS and/or PCI.[135]

Limitations of Current Treatment Strategies: Antiplatelet Drug Resistance and DM

Numerous reports have described a possible relationship between variability in response to antiplatelet therapy and clinical outcomes, thus suggesting that "resistance" to oral antiplatelet drugs may play a role in the risk of adverse cardiovascular events.[136–138] Because the risk of recurrent ischemic events is elevated in DM patients, there has been particular interest in understanding antiplatelet drug response in these high-risk subjects. In "resistant" patients, the antiplatelet drug fails to block its specific platelet target (eg, aspirin to block the COX-1 enzyme and clopidogrel to block the $P2Y_{12}$ receptor).[136] Therefore, it is a laboratory finding and should not be confused with "treatment failure," which means the recurrence of ischemic events despite treatment.[137,138]

Several clinical studies have shown an association between aspirin resistance and a higher risk of recurrent ischemic events.[139,140] However, the prevalence of aspirin resistance is widely variable among reported studies. These disparate findings are due mainly to differences in test used, definition of resistance, aspirin dose, and patient population considered. When COX-1–specific tests (eg, determination of serum or urine thromboxane and assays with arachidonic acid as agonist) are used, aspirin resistance is an infrequent phenomenon (<5% of patients).[141,142] The fact that the prevalence of aspirin resistance is higher when assays that are not specific to COX-1 signaling are used suggests that these results not only are derived from COX-1 degree of inhibition but also reflect aspirin-induced COX-1–independent effects.[136] The main cause of aspirin resistance, when assessed by COX-1–specific tests, is poor patient compliance.[137] Population selection is another factor that contributes to inadequate aspirin effects. DM patients have very high rates of inadequate response to aspirin when assessed by non–COX-1–specific methods[13,143]; in these patients, increasing aspirin dose has been suggested to overcome resistance.[144] This is in line with findings from a subanalysis of the Aspirin-Induced Platelet Effect (ASPECT) study, which compared the pharmacodynamic effect of different doses of aspirin in patients with and without DM and showed a higher percentage of aspirin resistance in the DM subgroup with the lower dose (81 mg daily). Interestingly, increasing aspirin dose (162 and 325 mg daily) significantly reduced platelet reactivity in patients with DM, resulting in similar rates of aspirin resistance in both groups.[142]

To date, there are no published studies specifically designed to assess the clinical efficacy of aspirin and the implications of aspirin resistance in DM patients with ACS. In addition, few studies have investigated the mechanisms of aspirin resistance that are inherent in patients with DM. Hyperglycemia has been proposed to play a role because an

interaction between glycation and acetylation has consistently been observed.[145] In addition, TXA_2 synthesis is increased in DM patients, and tight metabolic control may lead to a reduction in TXA_2 concentrations.[146] This may be related to the reduced response to aspirin observed in DM patients with poor metabolic control.[147] Elevated TXA_2 synthesis may also be attributed to increased platelet turnover in DM; thus, although aspirin may irreversibly inhibit COX-1, the introduction into the systemic circulation of newly generated platelets not exposed to aspirin continues to generate TXA_2, which may allow TP receptor activation despite COX-1 inhibition.[77] TP receptor activation has led to interest in developing pharmacological agents that can also block TP receptors. Picotamide is an inhibitor of both TXA_2 synthase and TP receptors, being able to block the effect of TXA_2 generated through COX-1 escape mechanisms, which may represent a pathway involved in inadequate aspirin-induced effect in DM patients. The Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics (DAVID) trial randomized DM patients with peripheral artery disease (n=1209) to receive either picotamide (600 mg twice daily) or aspirin (320 mg once daily plus placebo once daily) for 24 months. In this trial, the cumulative incidence of the 2-year overall mortality (primary end point) was significantly lower among patients treated with picotamide compared with those receiving aspirin (3.0% versus 5.5%; $P=0.0474$). No statistical difference was observed in the secondary combined end point of mortality and morbidity (death and nonfatal vascular events, including MI, ischemic stroke, and major amputation).[148] Other novel agents targeting the TXA_2 pathway, including ridogrel (a combined TXA_2 synthase inhibitor and TP receptor blocker), ramatroban (a TP receptor inhibitor), NCX 4016 (an NO-releasing aspirin derivative), and Si8886/terutroban (a TP receptor inhibitor), have been evaluated. Some of them have been compared with aspirin in different settings with variable success and might be of future interest for specifically targeting DM platelets.[149–152]

Clopidogrel therapy, in addition to aspirin, has shown an undisputed clinical benefit in patients with ACS/PCI (the Table). However, a substantial number of recurrent cardiovascular events continue to occur. Accumulating evidence shows that variability in individual response is involved in this limited efficacy, even among DM patients.[138,153,154] The prevalence of clopidogrel low responsiveness reported in the literature varies considerably and is related to differences in definitions, type of test used, dose of clopidogrel, and patient population studied. Genetic, cellular, and clinical mechanisms have been observed to contribute to inadequate clopidogrel responsiveness.[138,153] The presence of DM is an important clinical factor that contributes to decreased clopidogrel-induced effects; a lower response to clopidogrel has repeatedly been shown in DM patients compared with non-DM patients in both the immediate and maintenance phases of therapy.[13,16,17] Among patients with DM, those at the most advanced stage who require insulin therapy have the highest degree of platelet reactivity while on dual antiplatelet therapy.[155] DM is also a risk factor for developing chronic kidney disease, which may affect platelet function and response to antiplatelet agents. The presence of moderate or severe chronic kidney disease is associated with impaired response to clopidogrel among DM patients on maintenance dual antiplatelet therapy.[156] This is in line with the findings of a recently reported posthoc analysis of the CHARISMA trial suggesting that clopidogrel use might be harmful in patients with diabetic nephropathy.[157] Overall, these findings contribute to an explanation of why DM is associated with a higher risk of recurrent ischemic events in patients with ACS[7] and is a strong predictor of stent thrombosis.[158–160]

Numerous mechanisms may play a role in the inadequate clopidogrel response observed in DM patients. Several small-scale in vitro or ex vivo studies have reported the following factors as possible causes of the impaired clopidogrel response present in DM patients: lack of response to insulin in platelets,[75] alterations in calcium metabolism,[42,65] upregulation of $P2Y_{12}$ receptor signaling,[75] increased exposure to ADP,[161] and increased platelet turnover.[79]

Future Directions

The persistence of high platelet reactivity in DM patients despite the use of standard recommended antiplatelet treatment regimens has raised interest in identifying strategies able to optimize platelet inhibitory effects in these high-risk subjects (Figure 2). The OPTIMUS study evaluated the effect of a 150-mg maintenance dose of clopidogrel versus standard dose of clopidogrel (75 mg) in a cohort of type 2 DM patients with coronary artery disease and high platelet reactivity while in their maintenance phase of clopidogrel therapy. Use of the high maintenance dose was associated with a marked improvement in platelet inhibition, although a significant number of patients remained with elevated platelet reactivity.[124] The efficacy and safety of tailored treatment with high clopidogrel maintenance dose in patients with inadequate response to standard clopidogrel dose are being evaluated in the ongoing Gauging Responsiveness With a VerifyNow Assay: Impact on Thrombosis and Safety (GRAVITAS; NCT00645918) trial, which will comprise a considerable number of DM patients.

Although modifying doses of currently approved drugs represents an option to optimize platelet inhibition in DM patients, the future will likely include newer agents, many of which are currently under clinical development. They may include agents that block multiple pathways involved in platelet adhesion, activation, and aggregation (Figure 3).[162] Among these agents, encouraging results have emerged from clinical trials evaluating novel and more potent $P2Y_{12}$ receptor inhibitors, which represent attractive treatment alternatives in high-risk patients such as those with DM (Figure 4).

Ticagrelor, a cyclopentyltriazolopyrimidine, is an orally administered, direct, reversible $P2Y_{12}$ inhibitor that has recently completed phase III clinical testing.[164] Ticagrelor is a direct-acting drug with no need for hepatic biotransformation into an active metabolite, which is an advantage over thienopyridines. In addition, ticagrelor achieves higher inhibition of platelet aggregation than clopidogrel in ACS patients.[165] The Platelet Inhibition and Patient Outcomes (PLATO) trial evaluated the benefit of ticagrelor (180-mg loading dose followed by 90 mg twice daily) compared with clopidogrel (300- to 600-mg loading dose followed by 75 mg daily) in

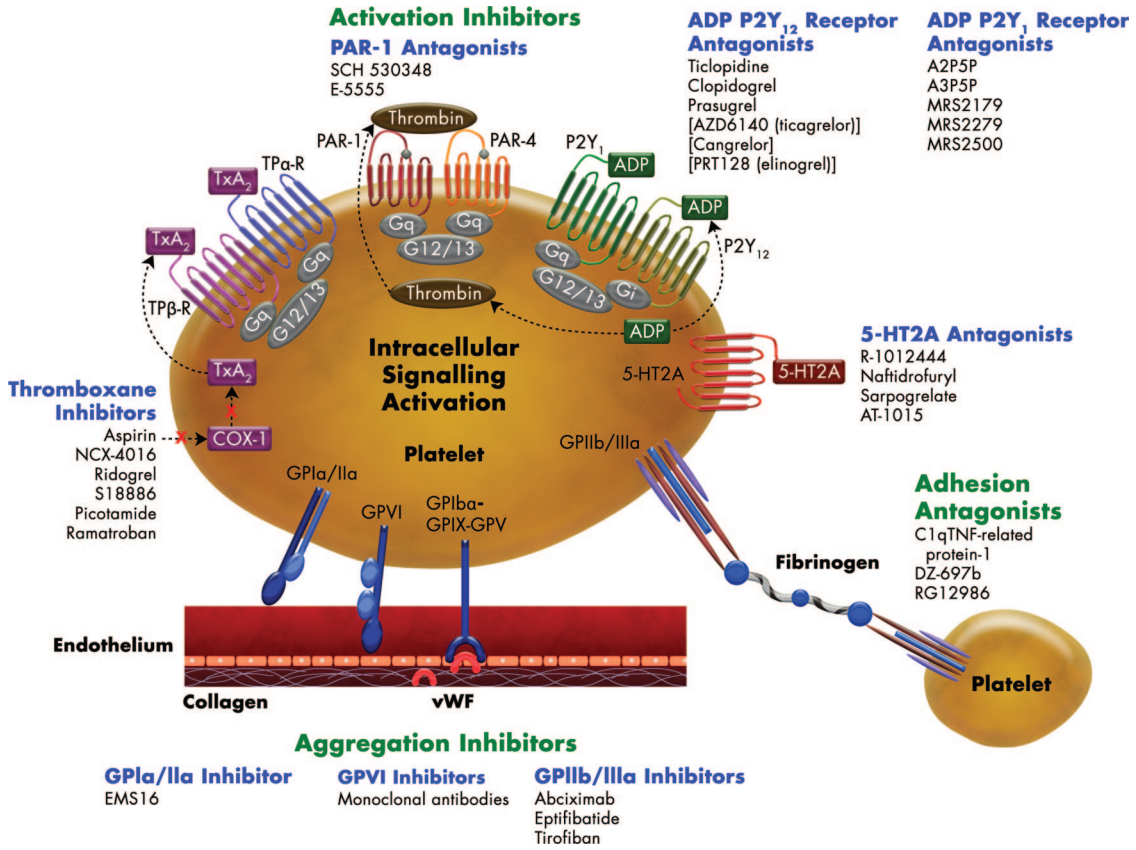

Figure 3. Currently available and novel antiplatelet agents under development. Platelet adhesion to the endothelium occurs at sites of vascular injury through the binding of GP receptors to exposed extracellular matrix proteins (collagen and von Willebrand factor [vWF]). Platelet activation occurs via intracellular signaling processes and causes the production and release of multiple agonists, including TXA_2 and ADP, and local production of thrombin. These factors bind to their respective G protein–coupled receptors, mediating paracrine and autocrine mechanisms. In addition, they potentiate each other's actions (eg, $P2Y_{12}$ signaling modulates thrombin generation). The major platelet integrin GP IIb/IIIa mediates the final common step of platelet activation by undergoing a conformational shape change and binding fibrinogen and von Willebrand factor, leading to platelet aggregation. The net result of these interactions is thrombus formation, resulting platelet/platelet interactions with fibrin. Current and emerging therapies inhibiting platelet receptors, integrins, and proteins involved in this process include thromboxane inhibitors, ADP receptor antagonists, GP IIb/IIIa inhibitors, and the novel protease-activated receptor (PAR) antagonists and adhesion antagonists. Reversible-acting agents are indicated by brackets. Reproduced with permission from Angiolillo DJ, Capodanno D, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J*. 2010;31:17–28.[162] 5-HT2A indicates 5-hydroxytryptamine 2A receptor.

preventing cardiovascular events in ACS patients (n=18 624) with or without ST-segment elevation. The rate of the primary end point (death resulting from vascular causes, MI, or stroke) at 12 months was significantly decreased in the ticagrelor arm (10.2% versus 12.3%; HR=0.84; P=0.0001), as were the rates of cardiovascular death and stent thrombosis in the subgroup of PCI patients. Importantly, ticagrelor was not associated with an increase in protocol-defined major bleeding, although a higher rate of major bleeding not related to coronary artery bypass grafting was observed (4.5% versus 3.8%; HR=1.19; P=0.03). Side effects occurring more frequently with ticagrelor included dyspnea, ventricular pauses, and an increase in creatinine and uric acid levels.[163] In patients with DM (n=4662), the reduction in the primary composite endpoint (HR=0.88; 95% CI, 0.76 to 1.03), all-cause mortality (HR=0.82; 95% CI, 0.66 to 1.01), and stent thrombosis (HR=0.65; 95% CI, 0.36 to 1.17) with no increase in major bleeding (HR=0.95; 95% CI, 0.81 to 1.12) with ticagrelor was consistent with the overall cohort and without significant diabetes status-by-treatment interactions.[163a] There was no heterogeneity between patients with or without insulin therapy. Further, ticagrelor reduced the primary endpoint (HR=0.80; 95% CI, 0.70 to 0.91), all-cause mortality (HR=0.78; 95% CI, 0.65 to 0.93), and stent thrombosis (HR=0.62; 95% CI, 0.39 to 1.00) in patients with HbA1c above the median with similar bleeding rates (HR=0.98; 95% CI, 0.86 to 1.12). Ticagrelor has been recently approved in Europe, but it is not yet approved for clinical use by the FDA.

Cangrelor, an intravenous ATP analog, is a direct-acting and reversible $P2Y_{12}$ receptor inhibitor.[164] Phase II trials showed cangrelor to be a potent antiplatelet agent; it achieves a great degree of platelet inhibition (>90%) with extremely rapid onset and offset of action and has a relatively safe profile.[166] The results from the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) program, which included CHAMPION-PCI (which randomized 8716 ACS patients to receive cangrelor or 600 mg of clopidogrel administered before PCI) and the CHAMPION-PLATFORM (which randomized 5362 patients not treated with clopidogrel to receive either cangrelor or

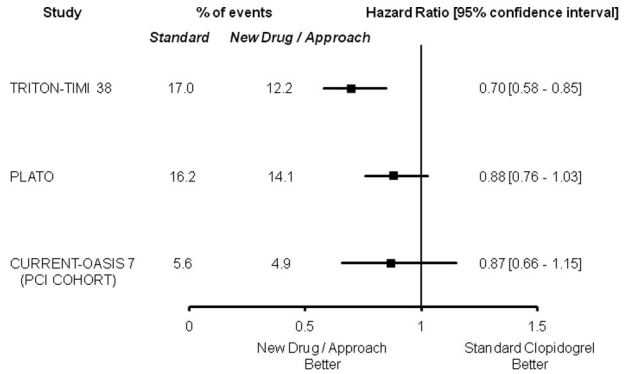

Figure 4. Efficacy in reducing adverse outcomes of new drugs and approaches tested in large-scale clinical trials in diabetes mellitus (DM) patients. Novel strategies to enhance platelet inhibition with the aim of improving outcomes (composite of cardiovascular death, myocardial infarction [MI], or stroke) include the use of prasugrel, ticagrelor, and high-dose clopidogrel. The data presented represent the composite of cardiovascular death, MI, or stroke in the DM cohort of these studies. The TRITON-TIMI 38 study[122] compared prasugrel (60-mg loading dose followed by a 10-mg maintenance dose) with standard clopidogrel therapy (300-mg loading dose followed by 75-mg daily maintenance dose) in patients with moderate- to high-risk acute coronary syndromes undergoing percutaneous coronary intervention (PCI) with up to 15 months of follow-up. The PLATO[163a] trial compared ticagrelor (180-mg loading dose followed by 90 mg twice daily) with clopidogrel (300- to 600-mg loading dose followed by 75 mg daily) with up to 12 months of follow-up. The CURRENT-OASIS 7[99a] trial evaluated 30-day outcomes comparing high (600-mg loading dose and then 150 mg once a day for 7 followed by 75 mg daily) and standard (300-mg loading dose followed by 75 mg daily) clopidogrel dosing in acute coronary syndromes ACS patients scheduled to undergo angiography within 72 hours of hospital arrival (results were obtained in the cohort of patients undergoing PCI).

placebo at the time of PCI, followed by 600 mg of clopidogrel) trials, have been recently published.[167,168] Both trials failed to show superiority in reducing the primary end point (composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours) of cangrelor over clopidogrel (7.5% versus 7.1%; odds ratio=1.05; 95% CI, 0.88 to 1.24; P=0.56) in CHAMPION-PCI and over placebo (7.0% versus 8.0%; odds ratio=0.87; 95% CI, 0.71 to 1.07; P=0.17) in CHAMPION-PLATFORM. A subgroup analysis (n=2702) performed in CHAMPION-PCI showed that results were consistent among the cohort of DM patients (odds ratio=1.08; 95% CI, 0.80 to 1.46).

Despite the use of dual antiplatelet therapy with aspirin and a $P2Y_{12}$ blocker in the ACS setting as described previously, patients, particularly those with DM, may continue to have recurrent events. The reason may be that only 2 signaling pathways, COX-1 and $P2Y_{12}$, are blocked, leaving multiple other signaling pathways, many known to be upregulated in DM patients, uninhibited. Therefore, future strategies may include the use of antiplatelet agents that block pathways other than COX-1 and $P2Y_{12}$. Several drugs have been suggested for use as an adjunctive treatment to aspirin and $P2Y_{12}$ inhibitors. Agents that have the potential to be part of such "triple therapy" strategies include cilostazol, protease-activated receptor-1 antagonists, and new oral anticoagulants.

Cilostazol, a phosphodiesterase III inhibitor that increases intraplatelet cAMP concentration, in addition to standard dual antiplatelet therapy may be considered in the maintenance phase of therapy. The benefit of this triple antiplatelet treatment regimen has consistently been observed in patients undergoing PCI, mainly as a reduction in the rates of target lesion revascularization and even in stent thrombosis.[119,170] This benefit in ischemic outcomes, which is not accompanied by an increased risk of bleeding, is greater in patients with DM.[171,172] The latter is in line with the findings of the OPTIMUS-2 study, in which adjunctive treatment with cilostazol markedly increased the inhibition of platelet $P2Y_{12}$ signaling in DM patients on dual antiplatelet therapy.[125] Recently, the efficacy of cilostazol in the setting of ACS was evaluated in a clinical trial that randomized ACS patients (n=1212) to either standard dual-antiplatelet treatment with aspirin and clopidogrel or triple antiplatelet therapy with the addition of cilostazol for 6 months after successful PCI. In this study, triple antiplatelet treatment was associated with a significantly lower incidence (10.3% versus 15.1%; HR=0.65; P=0.011) of the primary end point (composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization at 1 year after randomization), and importantly, no significant differences were found in the risks for major and minor bleeding.[173] In this study, the DM subgroup (n=263) had a particular benefit with triple therapy (9.9% versus 18.9%; HR=0.47; 95% CI, 0.23 to 0.96). The use of cilostazol, however, is limited by the high frequency of side effects (eg, headache, palpitations, and gastrointestinal disturbances) that often lead to withdrawal.

Thrombin is the link between plasmatic and cellular components of the thrombotic process because it plays a role in the coagulation cascade and is a potent agonist of platelet aggregation. Of note, thrombin generation processes are enhanced in patients with DM.[174] To date, 2 oral thrombin receptor antagonists that block the platelet protease-activated receptor-1 subtype, Vorapaxar (SCH530348) and atopaxar (E5555), are under advanced clinical development.[162] Atopaxar is still in an early stage of development; vorapaxar was recently compared with placebo in a large phase II safety and dose-ranging trial performed in patients (n=1030) undergoing nonurgent PCI or coronary angiography with planned PCI. Importantly, vorapaxar showed an excellent safety profile; concomitant administration with aspirin and clopidogrel was not associated with any significant increase in bleeding across all doses tested.[175] Currently, 2 large-scale phase III trials are evaluating the efficacy and safety of vorapaxar: the Trial to Assess the Effects of vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P; NCT00526474) in patients with atherosclerosis and the Trial to Assess the Effects of vorapaxar in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome (TRACER; NCT00527943) in ACS patients. Results from these trials in which DM patients will be highly represented will provide important insights into the future utility of these new agents.

Atherothrombotic complications are the result not only of platelet reactivity but also of dysregulation of coagulation processes. Importantly, DM patients are also characterized by several coagulation abnormalities, including increased plasma coagulation factors (eg, factor VII and thrombin) and

lesion-based coagulants (eg, tissue factor), decreased endogenous anticoagulants (eg, protein C and thrombomodulin), and increased production of plasminogen activator inhibitor-1, a fibrinolysis inhibitor.[11] These procoagulant abnormalities, coupled with the platelet hyperreactivity discussed previously, enhance the thrombotic risk of DM patients. Several new oral anticoagulants, including anti–factor IIa (eg, dabigatran) and anti–factor Xa (eg, rivaroxaban, apixaban), are currently in different stages of clinical development.[176] In addition to being studied as an alternative to warfarin in settings such as atrial fibrillation or venous thrombosis disorders,[177] many of these newer oral anticoagulant agents are currently being tested for long-term use in ACS populations as an adjunct to dual antiplatelet therapy, in which DM patients represent a cohort of particular interest.

Conclusions

DM patients have an increased atherothrombotic risk and elevated rates of recurrent ischemic events. This may be attributed in part to the abnormalities in platelet function that characterize this patient population and result in increased platelet reactivity. These findings underscore the importance of platelet-inhibiting drugs in DM patients. Although currently approved antiplatelet treatment strategies have proven successful in improving outcomes in ACS, DM patients continue to experience high rates of adverse cardiovascular events. The high prevalence among DM patients of suboptimal response to currently used oral antiplatelet agents may contribute to these impaired outcomes. Therefore, more potent antithrombotic treatment strategies are warranted in DM patients. The large number of novel antithrombotic agents, including antiplatelet and anticoagulant drugs, that are currently under advanced clinical development may represent important treatment alternatives in the near future to tackle the thrombotic burden of patients with DM.

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