Antiplatelet Therapy in Patients With Diabetes Mellitus and Acute Coronary Syndrome
– New Insights from Randomized Trials –
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Patients with diabetes mellitus have increased atherothrombotic risk and elevated rates of recurrent cardiac events, which may be in part attributable to abnormalities of platelet function resulting in increased platelet reactivity. Despite improved clinical outcomes with an antiplatelet strategy of aspirin plus clopidogrel in patients with acute coronary syndrome (ACS), diabetic patients continue to experience relatively high rates of adverse events during follow-up. Thus, strategies using more potent antiplatelet drugs are warranted in diabetic patients with ACS, especially in the presence of an increased coronary angiographic risk profile. The relative benefit of prasugrel has been described as higher in diabetic vs. nondiabetic patients, without increase in the bleeding risk, whereas a reduction in ischemic events was similar with ticagrelor in patients with and without diabetes. Glycoprotein IIb/IIIa inhibitors are indicated in high-risk patients with ACS, but diabetic patients do not benefit from routine administration of such agents. (Circ J 2014; 78: 33–41)

Key Words: Acute coronary syndrome; Antiplatelet agents; Diabetes mellitus

Diabetes mellitus (DM) represents a major public health concern because of its prevalence and the poorer cardiovascular prognosis of patients with this disease; thus, strategies aimed at improving cardiovascular outcomes in patients with DM may have relevant epidemiological, economic and clinical effects. Previous investigations in diabetic patients with acute coronary syndrome (ACS) showed a 1.8-fold increase in cardiovascular deaths and a 1.4-fold increase in myocardial infarctions (MI) at 2 years compared with nondiabetics. Moreover, a gradient in the incidence of these events according to diabetes type has been demonstrated, as patients with insulin-dependent DM (IDDM) have a worse prognosis than those with non-IDDM. Randomized evidence in the setting of ACS indicates that an invasive strategy with systematic coronary angiography and, when indicated, coronary revascularization, compared with a conservative strategy, is associated with more pronounced benefit in patients with vs. those without DM (27% vs. 13% risk reduction of events at 6 months in the TACTICS-TIMI 18 trial, although in that study the P-value for interaction was not significant). Nevertheless, despite diabetic patients gaining the greatest advantage from an invasive strategy, after ACS in the real world they undergo early cardiac catheterization and percutaneous coronary intervention (PCI) less frequently than non-DM patients; it is notable that rates of receiving an invasive approach are the lowest for ACS patients with IDDM.

Biological Bases of Platelet Hyperreactivity in Patients With DM

Different systems involved in the maintenance of vascular integrity and patency are impaired in DM, such as platelet and endothelial function, coagulation pathways and fibrinolysis. Notably, platelets of patients with DM have been proven to be hyperreactive, which leads to intensified adhesion, activation and aggregation.

Several mechanisms are involved in this platelet dysfunction (Figure 1): hyperglycemia enhances platelet aggregation by inducing P-selectin expression, by activating protein kinase C (a mediator of platelet activation) and by glykating platelet surface proteins, with consequent decrease in membrane fluidity and amplification of platelet adhesion. Moreover, insulin resistance and/or deficiency in diabetic patients have been associated with impairment in the response to anti-thrombotic molecules (such as prostacyclin) and contribute to platelet dysfunction by insulin receptor substrate-dependent effects, causing a rise in the intracellular calcium concentration and subsequent enhanced platelet degranulation. Upregulation of glycoprotein (GP) IIb/IIIa surface receptors, amplification of P2Y12 signaling, and overproduction of reactive oxygen species also contribute to the platelet dysfunction of diabetic patients; finally, metabolic conditions frequently associated with DM (ie, obesity, dyslipidemia and systemic inflammation) may also play a role.

Despite the use of long-term dual antiplatelet therapy after
ACS, there are still considerable rates of death, MI and stroke during follow-up of these patients (=10% at 1 year). Because ACS is mainly a platelet-driven process, attention has been recently given to high on-treatment platelet reactivity (HPR) as a possible indicator of adverse cardiac events, which could guide the individualization of antithrombotic strategies. Besides genetic factors (mainly CYP2C19 polymorphisms), acquired conditions have been also associated with HPR (ie, high body mass index), DM and the clinical presentation of ACS. Interestingly, in type 2 DM patients with coronary artery disease on dual antiplatelet therapy, Angiolillo et al found that major adverse cardiovascular events (MACE) at 2 years occurred in 15.2%, 12.2%, 12.2% and 37.7% of platelet reactivity quartiles, respectively, with HPR being the strongest predictor of events (hazard ratio 3.35, P=0.001).

**Oral Antiplatelet Therapy in ACS Patients With DM: Aspirin and Clopidogrel**

As mentioned, patients with ACS, compared with those with stable angina, have increased platelet reactivity persisting after initial clinical stabilization, and this may impair clinical outcome independently of the cardiovascular risk profile.

Aspirin irreversibly inhibits the cyclooxygenase 1 pathway of arachidonic acid metabolism, therefore blocking platelet thromboxane A-2 synthesis and resulting in inhibition of platelet aggregation. Benefit of aspirin has been consistently demonstrated in both non-ST-segment elevation ACS (NSTEMI) and STEMI trials. This drug still represents the first-line antiplatelet therapy for improving cardiovascular outcome in all patients with acute or previous atherothrombotic disease, including those with DM, in whom the recommended daily dose is 75–160 mg. In a large meta-analysis of secondary prevention trials in high-risk patients with acute or previous cardiovascular disease, where aspirin was the most frequently used antiplatelet agent, incidence of MACE by adding aspirin was reduced from 22% to 18% in patients with and from 16% to 13% in those without DM; although the overall incidence of adverse events was higher in diabetic patients, the benefit of antiplatelet therapy was consistent regardless of diabetic status. Of note, low-dose aspirin (75–150 mg/day) was found to be at least as effective as higher daily doses and bleeding complications were reduced with the lower doses. The first large-scale randomized study comparing high- (300–325 mg daily) vs. low-dose (75–100 mg daily) aspirin was the CURRENT-OASIS 7 trial, which included ACS patients scheduled to undergo early coronary angiography. Results did not show significant differences in efficacy between high- and low-dose aspirin for the primary outcome measure of 30-day MACE. As expected, a trend towards higher rates of gastrointestinal bleeds was observed in the high-dose group (0.38% vs. 0.24%; P=0.051).

In previous studies 5–57% of patients have been reported to have suboptimal antiplatelet effects with aspirin treatment. These disparate findings may be attributed to differences in the definition of resistance, type of assay used, variable doses of aspirin as well as the different risk profiles of the included populations. A previous investigation of healthy subjects showed that even low doses of aspirin (as low as 40 mg) once daily cause an almost complete suppression of thromboxane A2 formation and platelet aggregation throughout the entire platelet lifespan; as a consequence, platelet function is only partially restored by newborn, unacetylated platelets produced by megakaryocytes. Recovery of cyclooxygenase 1 activity in patients with type 2 DM receiving low-dose aspirin presents a large interindi-
individual variability; moreover, increased fractions of immature platelets and enhanced platelet turnover have been detected in diabetic patients. A low response to aspirin has been also reported to be more common in diabetic vs. nondiabetic patients, and this is more pronounced in diabetic patients with poor glycemic control. Recent pharmacodynamic studies showed that in diabetic patients on aspirin, the enhancement of platelet turnover can be counteracted by a twice-daily aspirin dose. Increasing the aspirin dose has been also suggested to overcome resistance; however, no study has evaluated the clinical efficacy of doubling the frequency of aspirin administration in diabetic patients and in the CURRENT-OASIS 7 trial the lack of benefit with high-dose aspirin was also observed in the subset with DM.

ACS patients have a high thrombotic risk and, especially if diabetic, may present a low response to aspirin; hence, the rationale for using antiplatelet strategies involving pathways different from thromboxane A2. On top of aspirin therapy, in the CURE trial the use of clopidogrel (300 mg load then 75 mg/day maintenance dose) vs. placebo decreased the incidence of MACE at 1 year in patients with NSTE-ACS. Event reduction with clopidogrel was significant both in nondiabetic and diabetic patients (7.9% vs. 9.9% and 14.2% vs. 16.7%, respectively), but in the latter there was a trend towards lower benefit (although the P-value for interaction was not significant =0.31) (Table); this was consistently confirmed in the PCI-CLARITY study of patients with STEMI undergoing percutaneous revascularization. Thus, patients with DM derive a lesser benefit from standard clopidogrel doses in the setting of ACS, which may be related in part to interindividual variability in the response to this drug; multiple mechanisms are involved in this variability, including differences in individual drug absorption, variations in the rate of biotransformation into active metabolite (because of drug-drug interactions at the site of cytochrome P or cytochrome P genetic polymorphisms) or P2Y12 receptor polymorphisms affecting receptor number and activity. A large patient-level meta-analysis from 6 studies evaluated the relationship between platelet reactivity on clopidogrel treatment measured by a point-of-care assay and cardiovascular outcome in 3,059 patients undergoing PCI. The combined endpoint including death, MI and stent thrombosis at 2 years occurred more frequently in patients with and without DM, which raises the question of whether the optimal level of platelet inhibition by platelet function testing differs between diabetic and nondiabetic patients. This has been suggested by previous investigations showing that the cut-off point for adverse events in patients with DM may differ from that for the overall population and that redefining HPR based on specific thresholds for patients with and without DM improves prediction of adverse events after PCI.

Impaired response to clopidogrel is more evident in patients with DM. Angiolillo et al observed higher platelet aggregation in clopidogrel-treated patients with vs. those without DM; moreover, the proportion of patients with low response to the drug was more elevated among the diabetic patients (38% vs. 8% in nondiabetic patients). This affects the clinical outcome following PCI, with the highest incidence of ischemic events.
OASIS 7 trial also explored the issue of whether a strategy with high-dose clopidogrel (600 mg loading plus 150 mg/day for 1 week) in patients with ACS reduces the incidence of 30-day MACE vs. standard dose (300 mg loading and then 75 mg/day); a prespecified post-hoc analysis of the subgroup undergoing PCI suggested a clinical benefit in the high-dose group, with a significant reduction in the event rate (3.9% vs. 4.5%, P=0.039) and in-stent thrombosis (0.7% vs. 1.3%, P=0.0001), at the expense of excess major bleeding (1.6% vs. 1.1%, P=0.009); reduction of MACE by high-dose clopidogrel was similar in patients with and without DM. Overall results of CURRENT-OASIS 7 showed no difference for the 2 clopidogrel dose regimens and, therefore, caution must be taken when considering subgroup analyses. Increasing the clopidogrel dose does not solve the issue of low response to the drug, especially in patients at higher thrombotic risk because of elevated baseline platelet reactivity. In fact, pharmacodynamic studies of patients with type 2 DM demonstrates that 150 mg/day clopidogrel achieved an average 20% additional reduction of platelet reactivity index by light transmittance aggregometry (LTA) vs. the 75-mg daily dose; however, even with the higher dose regimen, there was a suboptimal response in 60% of the patients with a low response to the conventional daily dose. Hence, the rationale for more pronounced platelet inhibition with newer, more potent antiplatelet agents.

New Oral Antiplatelet Agents in ACS Patients With DM

Prasugrel is an orally administered third-generation thienopyridine; it is a prodrug requiring cytochrome P 450-dependent hepatic metabolism to achieve the active metabolite that irreversibly inhibits the platelet P2Y12 receptor.49 In patients with DM, prasugrel (60 mg plus 10 mg/day), even in comparison with 600 mg plus 150 mg daily dose of clopidogrel occurring in patients having both DM and HPR while on clopidogrel and the lowest in those without DM and without an impaired response to the drug.44 Given the clinical relevance of interindividual variability in the response to standard clopidogrel doses, various studies have investigated the usefulness of higher clopidogrel loading and maintenance doses in patients undergoing PCI. The ARMYDA-2 study first showed that a 600 mg clopidogrel loading dose given 6 h before the procedure is associated with 52% reduction of early ischemic events compared with the conventional 300-mg dose.45 Faster achievement of maximal platelet inhibition, as well as reduction of rates of low-responders, may explain this clinical benefit. In another randomized investigation, we demonstrated that using a 150-mg daily maintenance dose of clopidogrel has a stronger antiplatelet action and decreases the incidence of low-responders vs. the conventional 75-mg daily dose; of note, in the same study the higher dose regimen was also associated with improvement of endothelial function and reduction of inflammatory parameters. The GRAVITAS trial evaluated effects of high-dose (600 mg loading, then 150 mg daily) compared with standard-dose clopidogrel (no additional loading, 75 mg daily thereafter) in patients with HPR after PCI; MACE rates at 6 months were not different between patients receiving high- or standard-dose clopidogrel (2.3% vs. 2.3%, P=0.97) and severe or moderate bleeding rates were also similar. However, levels of on-treatment platelet reactivity significantly decreased over the first 30 days in both arms of the study, with greater reduction in the high-dose group, and as expected, the 6-month incidence of MACE was numerically higher in patients with vs. those without HPR.47 Thus, rather than disproving the concept of guiding therapy by platelet function test, the results of GRAVITAS suggest that doubling the maintenance dose may be inadequate for most patients with a low response to clopidogrel and does not reduce adverse events in patients with a low to moderate clinical risk profile. The CURRENT-OASIS 7 trial also explored the issue of whether a strategy with high-dose clopidogrel (600 mg loading plus 150 mg/day for 1 week) in patients with ACS reduces the incidence of 30-day MACE vs. standard dose (300 mg loading and then 75 mg/day); a prespecified post-hoc analysis of the subgroup undergoing PCI suggested a clinical benefit in the high-dose group, with a significant reduction in the event rate (3.9% vs. 4.5%, P=0.039) and in-stent thrombosis (0.7% vs. 1.3%, P=0.0001), at the expense of excess major bleeding (1.6% vs. 1.1%, P=0.009); reduction of MACE by high-dose clopidogrel was similar in patients with and without DM (Table). Overall results of CURRENT-OASIS 7 showed no difference for the 2 clopidogrel dose regimens and, therefore, caution must be taken when considering subgroup analyses. Increasing the clopidogrel dose does not solve the issue of low response to the drug, especially in patients at higher thrombotic risk because of elevated baseline platelet reactivity. In fact, pharmacodynamic studies of patients with type 2 DM demonstrates that 150 mg/day clopidogrel achieved an average 20% additional reduction of platelet reactivity index by light transmittance aggregometry (LTA) vs. the 75-mg daily dose; however, even with the higher dose regimen, there was a suboptimal response in 60% of the patients with a low response to the conventional daily dose. Hence, the rationale for more pronounced platelet inhibition with newer, more potent antiplatelet agents.

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grel, provides significantly higher platelet inhibition in both the loading and maintenance phases; with prasugrel, rates of low-responders (ie, with inhibition of platelet aggregation ≤20% by LTA) were also decreased from 24% to 3%, because of the single-step activation of prasugrel in the liver into the active metabolite (vs the dual-step activation of clopidogrel), with involvement of a lower number of cytochromes and consequently less influence of cytochrome P genetic polymorphisms or drug-drug interactions. Moreover, after fixed doses of both agents, biotransformation of prasugrel amounts to approximately 70%, whereas only 15% of oral clopidogrel is transformed into the active compound. The molar potency of the respective active metabolites of prasugrel and clopidogrel is identical; thus, the more rapid onset, higher potency and lower interindividual variability of the antiplatelet effects of prasugrel compared with clopidogrel may be explained also in diabetic patients by its more efficient pharmacokinetics (ie, more efficient conversion into the active metabolite).

In the subgroup analysis of the TRITON-TIMI 38 trial, which enrolled 13,608 ACS patients undergoing coronary revascularization, use of prasugrel instead of clopidogrel after assessing the coronary anatomy was associated in diabetic patients with higher reduction of cardiovascular death, stroke and MI at 15 months (primary ischemic endpoint) vs. those without DM (30% relative risk reduction vs. 14%, with P-value for interaction close to the statistical significance, ≈0.09; Table): this beneficial effect of prasugrel was mainly from the prevention of nonfatal MI. In the DM subgroup of TRITON there was a 30% higher risk of major bleeding compared with nondiabetic patients, and, importantly, there was no increase in non-coronary bypass-related major bleeding with the use of prasugrel. In TRITON, the excess bleeding with prasugrel was pronounced in patients aged ≥75 years, weighing <60 kg or with a prior history of stroke, in whom prasugrel did not reduce the occurrence of the primary ischemic endpoint. Importantly, in the subset of patients with DM and without a history of stroke, even with body weight <60 kg and age ≥75 years, prasugrel significantly decreased the incidence of MACE (15% vs. 25% in the clopidogrel group). The results of the efficacy and safety endpoints according to diabetic status observed in the TRITON trial may be explained in the light of recent pharmacodynamic data suggesting a curvilinear relationship between platelet reactivity while on antiplatelet therapy and the incidence of ischemic/bleeding events (Figure 2): Patients with ACS and DM have elevated platelet reactivity and lower response to clopidogrel; thus, when treated with this drug, they have an increased risk of ischemic events, whereas when treated with prasugrel they exhibit higher platelet inhibition and show a significant reduction of ischemic events, without an increase in bleeding (ie, consistently within the therapeutic window).

As expected, in TRITON there was a gradient of benefit with prasugrel in patients without DM (14% relative reduction of the primary ischemic endpoint), those with non-IDDM (26% reduction) and in those with IDDM (37% reduction). Finally, a further analysis showed that using prasugrel, compared with clopidogrel, was associated with a significant decrease in recurrent cardiovascular events, also including cardiovascular death, and this effect was particularly evident in the diabetic population (56% reduction vs. 4% in nondiabetic patients, P-value for interaction ≈0.036).

Ticagrelor is a reversible, direct-acting P2Y12 inhibitor that does not require metabolic activation; it has been associated with earlier and stronger platelet inhibition than clopidogrel, without dependence on cytochrome genetic polymorphism and with few drug-drug interactions because of inhibition or induction of cytochrome P450 enzymes. In agreement with in vitro studies, clinical interaction studies in healthy volunteers demonstrated drug-drug interactions between ticagrelor and CYP 3A4/5 inhibitors (ketocozazole, diltiazem, clarithromycin, nefazodone) or CYP2C9 substrate (tolbutamide). In diabetic patients with ACS who received clopidogrel and underwent PCI, ticagrelor achieved higher platelet inhibition than prasugrel, but both drugs effectively treated HPR. The PLATO trial explored the issue of whether upstream administration of ticagrelor improves clinical outcome vs. clopidogrel in patients with STEMI or NSTE-ACS. In that study, reduction of the primary endpoint, including cardiovascular death, MI or stroke, at 1 year by ticagrelor was significant and similar both in patients with and without DM (12% and 17% relative risk reduction; P-value for interaction ≈0.49; Table). In PLATO the benefit of ticagrelor, irrespective of diabetic status, was also observed among patients planned for an invasive strategy (hazard ration 0.88 in diabetic patients and 0.83 in nondiabetic patients, P-value for interaction =0.72). In the diabetic subgroup, the benefit in mortality with ticagrelor was consistent with the overall cohort, and in patients with HBA1c levels above the median of 6% the primary composite outcome was significantly decreased by 20%. Moreover, in the diabetic population of the PLATO trial, ticagrelor showed similar rates of overall major bleeding compared with clopidogrel, and a numerically higher incidence of non-coronary bypass-related major bleeding.

In the TRITON study, prasugrel significantly prevented the occurrence of any definite or probable stent thrombosis at 15 months; this reduction was higher in patients receiving drug-eluting stents and was independent of diabetic status (48% relative reduction in patients with DM and 55% in those without). In the overall populations of the CURRENT and PLATO trials, a significant risk reduction of definite or probable stent thrombosis was also demonstrated for both high-dose clopidogrel (31% relative reduction) and ticagrelor (28% reduction), but no specific data are available with regard to the incidence of such outcome measures according to diabetic status in either of these studies.

Other Antiplatelet Agents

Cangrelor is a rapid, potent inhibitor of the platelet P2Y12 receptor; after an intravenous bolus platelet inhibition is immediate, the effect is maintained with a continuous infusion and platelet function is restored within 1 h after drug interruption. A recent study evaluated the pharmacodynamic effects of cangrelor in diabetic and nondiabetic, clopidogrel-naïve patients with coronary artery disease on aspirin therapy; cangrelor provided potent, dose-dependent blockade of platelet P2Y12 receptors by both vasodilator-stimulated phosphoprotein (VASP) assay and multiple electrode aggregometry, without differential effects according to diabetic status. A patient-level pooled analysis from the 3 randomized CHAMPION trials recently compared cangrelor with control (clopidogrel or placebo) in PCI patients: cangrelor significantly reduced the odds of ischemic cardiac events at 48 h (19% reduction), at the expense of increased incidence of GUSTO mild bleeding events. No specific interaction between diabetic status and efficacy of cangrelor was found.

Cilostazol is another oral antiplatelet agent that increases cyclic adenosine monophosphate levels by phosphodiesterase inhibition, potentially modulating VASP and intraplatelet P2Y12 signaling and leading to enhanced platelet inhibition.
when used in combination with standard dual antiplatelet therapy. The OPTIMUS-2 study demonstrated in type 2 DM patients a lower P2Y12 reactivity index (measured by VASP assay) with cilostazol vs. placebo. Previous investigations suggested that the clinical benefit of cilostazol in preventing ischemic events after PCI, without increase in bleeding events, may be even greater in patients with DM. In the setting of ACS, triple antiplatelet therapy with the addition of cilostazol for 6 months after successful PCI was associated with a significant 35% relative reduction of MACE vs. the association of aspirin plus clopidogrel, without increase in the overall bleeding risk. Of note, the subgroup of patients with DM had a more pronounced benefit with triple therapy (53% MACE reduction). Finally, in patients undergoing PCI with drug-eluting stent implantation, the adjunctive use of cilostazol was non-inferior to doubling the 75-mg daily dose of clopidogrel with respect to the net primary outcome including cardiac death, nonfatal MI, stent thrombosis, stroke or major bleeding. However, large, ad-hoc studies are needed to specifically establish the clinical safety and efficacy of cilostazol in diabetic patients with ACS.

Evaluation of new platelet inhibitors is an important avenue of investigation, and inhibition of protease-activated-receptor 1 (PAR-1), a key receptor for thrombin on human platelets, represents a novel strategy for reducing platelet activation and thrombosis. Thrombin activates platelets through 2 protease-activated-receptors, PAR-1 and PAR-4; PAR-1 is activated by lower concentrations of thrombin than PAR-4 and mediates a more rapid platelet activation. Binding of thrombin to PAR-1 is relevant for thrombus formation but may not be required for hemostasis, as suggested by preclinical studies; thus, inhibition of PAR-1 might prevent thrombosis without significant inhibitory effects on hemostasis, potentially reducing ischemic events without increasing bleeding complications. Elevated levels of thrombin-receptor agonist peptide have been observed in ACS patients, in whom the attendant prothrombotic milieu might also require use of agents inhibiting the PAR-1 pathway of platelet activation. Vorapaxar is an oral competitive PAR-1 antagonist with rapid absorption and distribution; peak plasma levels are reached in 60–90 min after administration. Vorapaxar has been recently evaluated in patients with NSTE-ACS in addition to standard therapy; in this randomized investigation the use of such agent did not significantly prevent the incidence of MACE at a median follow-up of 502 days vs. placebo (18.5% vs. 19.9%; P=0.07), with a 35% increase of moderate or severe bleeding and a >3-fold higher risk of intracranial hemorrhage, causing premature trial interruption. Furthermore, in patients with a history of MI, vorapaxar decreased by 20% the risk of cardiovascular death or ischemic events at 2.5 years on top of standard antiplatelet treatment, but increased the occurrence of moderate or severe bleeding.

**Glycoprotein IIb/IIIa Inhibitors in Patients With DM**

GP IIb/IIIa inhibitors are intravenous antiplatelet agents that have demonstrated the highest benefit in high-risk patients with ACS undergoing PCI, but questionable efficacy in low- to moderate-risk ACS patients or in those treated with a conservative approach. A meta-analysis of ACS patients published more than 10 years ago showed a 22% reduction of 30-day death in diabetic patients treated with GP IIb/IIIa inhibitors vs. those not receiving these agents (4.6% vs. 6.2%; P=0.007), whereas patients without DM had no benefit in survival, in-deed, in the diabetic population the mortality benefit was greater in those patients undergoing PCI during the index hospitalization. Of note, the studies included in this meta-analysis used conventional doses of clopidogrel (300mg loading and 75mg daily maintenance regimen) as concomitant antiplatelet therapy.

The ISAR-SWEET trial more recently did not show beneficial effects of abciximab over placebo on the risk of death and MI at 1 year in diabetic patients undergoing elective PCI after pretreatment with high-dose (600mg) clopidogrel (8.3% vs. 8.6%; P=0.91). The ISAR-REACT 2 trial demonstrated a significant reduction of 30-day MACE with the use of abciximab vs. placebo in patients with NSTE-ACS undergoing PCI on top of 600mg clopidogrel loading dose (8.9% vs. 11.9%, odds ratio 0.75, 95% confidence interval 0.58–0.97; P=0.03).

This benefit was restricted to patients with elevated baseline troponin levels (29% risk reduction) and was observed across all subgroups, including patients with DM. Furthermore, the EARLY-ACS trial did not find a specific interaction between diabetic status and efficacy of early (=24h before PCI) vs. delayed, provisional use of epifibatide in patients with NSTE-ACS assigned to an invasive strategy; however, absolute reduction of MACE at 96h with early epifibatide was more pronounced in patients with DM vs. those without (2.1% vs. 0.8%). Finally, a recent meta-analysis of randomized trials evaluating the effects of GP IIb/IIIa inhibitors in the setting of primary PCI for STEMI suggested a decrease in mortality, but not in re-infarction, with the use of these agents in diabetic patients. Thus, the benefit of pretreatment with GP IIb/IIIa inhibitors during clopidogrel therapy appears more pronounced in patients with high clinical risk, including those with DM undergoing PCI for both NSTE- and STE-ACS. None of the abovementioned trials of GP IIb/IIIa inhibitors used bivalirudin or the newer, more potent antiplatelet agents, which has led to questions about the actual validity of the data and whether, in the current era of newer antithrombotic strategies, diabetic patients might achieve a lower benefit from the routine addition of GP IIb/IIIa inhibitors in the setting of ACS. In TRITON, the benefit of prasugrel over clopidogrel on the primary ischemic endpoint was irrespective of therapy with GP IIb/IIIa inhibitors during the index hospitalization (11% and 16% risk reduction in patients with and without use of these drugs, respectively). In the subset of the PLATO trial planned for an invasive strategy, the relative reduction of adverse events with ticagrelor was numerically higher in patients not receiving GP IIb/IIIa inhibitors (19% vs. 10% in those receiving such agents), but the P-value for interaction was not significant (=0.37). A major concern with GP IIb/IIIa inhibitors is the increase in the bleeding risk, as bleeding events after ACS have relevant prognostic implications, also including higher mortality; in patients with DM this may be an emerging issue, as diabtes is also considered as a predictor of bleeding complications. This has been confirmed in the diabetic patients in the ACUITY trial, who, in the context of PCI for ACS, experienced higher rates of non-coronary bypass-related major bleeding, especially retroperitoneal and access sites, than non-diabetic patients. Similar to what was obtained in the overall study population, use of bivalirudin monotherapy in the DM subgroup of the ACUITY study was associated with similar protection from ischemic events at 30 days compared with heparin plus GP IIb/IIIa inhibitors (7.9% vs. 8.9%; P=0.39) and less major bleeding (3.7% vs. 7.1%; P=0.001).

Concordant findings have been recently found in a randomized investigation that included older patients with DM or chronic renal failure and undergoing PCI for a variety of coronary syn-
dromes, also including ACS. Thus, according to the available data, bivalirudin may also represent a safer option than heparin plus GP IIb/IIIa inhibitors in diabetic patients with ACS undergoing an invasive treatment strategy.

**Conclusions**

Patients with DM have an increased atherothrombotic risk, which may in part be attributed to abnormalities of platelet function resulting in increased platelet reactivity. The enhanced baseline platelet reactivity in diabetic patients might be a marker rather than the cause of the increased cardiovascular risk; nevertheless it may predispose to poorer future cardiac outcomes. Despite the high level of platelet inhibition achieved with currently available antiplatelet drugs, diabetic patients with ACS remain at higher risk of ischemic events; thus, large, randomized studies are needed to explore whether these patients may derive a further benefit from new-generation antiplatelet drugs or new anticoagulant agents (ie, factor Xa inhibitors), with a decrease in thrombotic events and without significant excess of bleeding.

**Disclosures**

Conflict of interest: none.

**References**


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