Review

Interventional Cardiology

Platelet reactivity and antiplatelet management in diabetic patients with coronary artery disease

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Diabetes mellitus is characterized by enhanced platelet reactivity and impaired response to antiplatelet therapy, with a higher percentage of low responders and an increased risk of thrombotic events following an acute coronary syndrome and/or percutaneous coronary intervention. This evidence was utilized to investigate the effectiveness and safety of higher doses of clopidogrel as well as the use of newer and more potent antiplatelet drugs, such as prasugrel and ticagrelor, in this high-risk subset of patients. The aim of this paper is to systematically report the latest evidence on the prognostic role of diabetes mellitus on responsiveness to antiplatelet treatments and to discuss the most effective therapeutic strategy to be used in such patients.

Keywords: clopidogrel • coronary artery disease • diabetes mellitus • percutaneous coronary intervention • platelet reactivity • prasugrel • ticagrelor

Coronary artery disease (CAD) represents the leading cause of mortality and morbidity in diabetic patients in western countries. Previous studies suggest that the absolute risk for major coronary events in patients with diabetes mellitus (DM) almost equals that of nondiabetic patients with established CAD [1]. Moreover, once patients with diabetes develop clinical CAD, they show a particularly unfavorable prognosis, both acutely, in the postinfarction period, and in long-term follow-up [1]. Interestingly, previous investigations in diabetic patients suffering from acute coronary syndrome (ACS) showed a 1.8-fold increase in cardiovascular death and a 1.4-fold increase in myocardial infarction (MI) at 2 years compared with nondiabetics [2].

Diabetic patients with ACS and/or undergoing percutaneous coronary intervention (PCI) have been demonstrated to be characterized by a significantly enhanced prothrombotic milieu, explained by molecular abnormalities seen in untreated insulin resistance and DM, including an increased incidence of residual on-treatment platelet reactivity after clopidogrel administration and consequently a higher risk of cardiovascular complications and recurrent athero-thrombotic events than nondiabetic patients [3–7]. Prasugrel and ticagrelor are two novel potent and fast-acting P2Y12 receptor antagonists that have extended the cardiologists' armamentarium in the management of patients with ACS treated medically and/or invasively by PCI. Both drugs demonstrated their superiority regarding P2Y12 receptor blockade and subsequently ischemic events reduction compared with clopidogrel [8–10]. However, there is little evidence in the literature about direct clinical outcome and pharmacodynamic comparison between these recently approved antiplatelet agents in the population with DM and ACS undergoing PCI. In this review the authors aim to systematically retrace the prognostic role of diabetes mellitus on platelet reactivity in the setting of ACS and the benefit of newer antiplatelet pharmacological strategies in diabetic patients.

Role of diabetes mellitus in the development of cardiovascular disease & platelet hyper-reactivity

The development of atherosclerosis in patients with blood glucose abnormalities

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such as DM is a progressive process, characterized by early endothelial dysfunction and vascular inflammation leading to monocyte recruitment, foam cell formation and subsequent plaque development over a variable time period [11]. In the presence of this enhanced inflammatory condition, coronary plaques may become unstable and rupture, promoting occlusive thrombus formation. In this setting, in diabetic patients, platelets, the key players of thrombus formation, have been proven to be hyper-reactive and this leads to intensified adhesion, activation and aggregation [6,12]. Moreover, the metabolically active adipose tissue of diabetic and obese patients plays an important role in the development of cardiovascular disease; the increased accumulation of macrophages occurring in obese adipose tissue has emerged as a key process in metabolic inflammation and insulin resistance [11]. In addition, in insulin-resistant patients, macrophages increase expression of the oxidized low-density lipoprotein (LDL) scavenger receptor B, promoting foam cell formation and atherosclerosis [11]. The enhanced production of free fatty acids by the adipose tissue indirectly impairs phosphorylation of endothelial nitric oxide synthase resulting in decreased production of nitric oxide (NO), endothelial dysfunction and vascular remodeling [11]. Hyperglycemia by itself further decreases endothelium-derived NO availability by different pathways, mainly involving overproduction of reactive oxygen species (ROS) [13] and also affects vascular function and platelet activation by inducing P-selectin expression [14], by activating protein kinase C [15] and glycating platelet surface proteins, with consequent alterations in membrane fluidity and amplification of platelet adhesion [16].

Insulin resistance and/or deficiency in diabetic patients not only leads to macrophage dysfunction but also influences molecular mechanisms involved in platelet aggregation: it is associated with significant impairment in the endovascular antithrombotic response (such as diminished sensitivity to prostacyclin) [17] and it contributes to platelet dysfunction by increasing intracellular calcium concentration and enhancing platelet degranulation [18]. Finally, amplification of the P2Y12 signaling [19] and upregulation of glycoprotein (GP) IIb/IIIa surface receptors [20] also have been demonstrated in DM patients.

Impact of platelet reactivity on cardiovascular outcomes in patients with DM & coronary artery disease

Despite the use of a guideline-recommended dual antiplatelet therapy in patients suffering from ACS and/or receiving stent implantation, there is a 10% rate of recurrent cardiovascular events in this subgroup of patients [9,10]. This has been attributed, in part, to the fact that a substantial proportion of patients may have an inadequate response to antiplatelet therapy, which turns into a lower inhibition of platelet activity and reaction, leading to a persistently high platelet reactivity (HPR) [21,22].

Several studies have focused on the assessment of platelet reactivity and its prognostic relevance in patients with CAD [23–26]. Sibbing and colleagues found that patients undergoing PCI with lower response to clopidogrel (>468 AU*min) had significantly higher risk of stent thrombosis [23]. Patti *et al.* demonstrated in the setting of elective PCI, that high preprocedural platelet reactivity levels (measured by the VerifyNow P2Y12 assay) were associated with sixfold increased risk of 30-day major adverse cardiovascular events (MACE; OR: 6.1; 95% CI: 1.1–18.3; p = 0.033), with a pre-PCI platelet reaction unit (PRU) value ≥240 as the optimal cut-off to predict the primary end point [24]. A similar, significant association between PRU and 6-month out-of-hospital cardiovascular death, nonfatal MI or stent thrombosis was described by Price *et al.* in 380 patients undergoing elective drug-eluting stent implantation; a cut-off of PRU ≥235 was predictive for the combined end point [25]. These findings are consistent also in the acute setting; Marcucci *et al.* identified a post-PCI PRU ≥240 as predictor of 12-month cardiovascular death and nonfatal MI in 683 patients with ACS undergoing dual-antiplatelet therapy after bare-metal or drug-eluting stent implantation [26].

Besides genetic factors (mainly *CYP2C19* polymorphisms), other pathological conditions have been associated with HPR, such as high body mass index [27], smoking, renal insufficiency, systemic inflammation, drug-to-drug interaction [28], acute coronary syndrome as clinical presentation [29] and, not least, diabetes mellitus [5–7].

HPR is, in fact, more frequent in diabetic patients compared with nondiabetics, even when treated with dual antiplatelet therapy [6,30–31]. A study by Mangiacapra *et al.* showed that DM patients undergoing PCI have significantly higher platelet reactivity before PCI (assessed using a VerifyNow P2Y12 assay), despite adequate clopidogrel pretreatment, compared with those without DM, with HPR (defined as a PRU >240) being more frequently observed in diabetics (36 vs 22%; p = 0.01) [32]. More interestingly, when the entire population was divided into four groups by the presence or absence of DM and HPR, the combination of DM and HPR resulted in a fourfold increase in periprocedural myocardial infarction (p for trend <0.0008) compared with diabetic patients with normal platelet reactivity, with HPR being an independent predictor for this complication (OR: 8.34; 95% CI:

2.60–26.76; p = 0.0003). Angiolillo *et al.* observed that among diabetic patients with CAD receiving dual antiplatelet therapy, those with an HPR (defined as the upper quartile of maximal platelet aggregation after 20 mmol/l adenosine diphosphate stimuli) in a steady-state phase of therapy with aspirin and clopidogrel had an over threefold increase in 2-year cardiovascular event rates compared with those without HPR [33]. The authors also demonstrated that HPR was the strongest independent predictor of MACE (HR: 3.35; 95% CI: 1.68–6.66; p < 0.001) [33]. Recently another paper by Mangiacapra *et al.* identified a different threshold for high platelet reactivity in diabetic compared with non-diabetic patients that better predict clinical outcomes after PCI in this specific population; in particular, the optimal cut-off to predict 30-day MACE was a PRU value of >256 in diabetics versus a PRU value of >229 in nondiabetic patients [34].

Standard antiplatelet therapy in diabetic patients: clinical benefits & limitations

Aspirin irreversibly inhibits the cyclooxygenase-1 pathway of arachidonic acid metabolism, thus blocking platelet thromboxane A-2 synthesis and resulting in inhibition of platelet aggregation [35]; it represents the first-line antiplatelet therapy for improving cardiovascular outcome in patients with ACS or stable coronary disease, including diabetic patients, in whom the recommended daily dose is 75–160 mg [36]. In a large meta-analysis of secondary prevention trials in high-risk patients with acute or previous cardiovascular events, aspirin reduced the incidence of MACE from 22 to 18% in patients with DM and from 16 to 13% in those without DM. However, previous studies demonstrated a suboptimal antiplatelet effect of aspirin on a variable, 5–57%, range of patients [37]; these figures 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 [38]. A low response to aspirin has been reported to be more common in diabetic versus nondiabetic patients, and this is more evident in patients with DM and poor glycemic control [39]. Recent pharmacodynamic studies on diabetic patients taking aspirin showed that the enhancement of platelet turnover, which is typical of DM patients [40], can be counteracted by a twice-daily aspirin regimen [41]; moreover, a recent observation on diabetic patients with stable coronary artery disease indicated that doubling the frequency of aspirin administration further enhances platelet inhibition [41]. Interestingly, higher aspirin doses (up to 325 mg daily) significantly reduce platelet reactivity in patients with DM, yielding a similar occurrence of aspirin resistance as nondiabetic patients [42]. However, in the CURRENT-OASIS 7 trial [43,44], a large-scale randomized study comparing high- (300–325 mg daily) versus low-dose (75–100 mg daily) aspirin in ACS patients undergoing early coronary angiography, the lack of clinical benefit with high-dose aspirin was also observed in the diabetic population.

Clopidogrel bisulfate is an inactive thienopyridine prodrug that undergoes oxidative biotransformation to its active metabolite by a two-step, CYP450-dependent process. The active metabolite of clopidogrel then selectively and irreversibly inhibits the platelet P2Y12 ADP receptor thus blocking ADP-mediated platelet activation and aggregation.

Despite the known overall benefit of clopidogrel in addition to aspirin in the setting of ACS/PCI patients [45–48], patients with DM derive a lesser benefit from standard doses of this antiplatelet drug. In the CURE trial [45], the use of clopidogrel (300 mg loading dose followed by 75 mg/day maintenance dose) decreased the incidence of MACE at 1 year in patients with NSTE-ACS compared with placebo. Event reduction with clopidogrel was significant both in nondiabetic and diabetic patients (7.9 vs 9.9% and 14.2 vs 16.7%, respectively); however, in the latter there was a trend towards lower benefit (with a nonsignificant p-value for interaction = 0.31). These results were confirmed in the PCI-CLARITY study of patients with STEMI undergoing percutaneous revascularization (event reduction 5.3 vs 2.9% in nondiabetic and 10.1 vs 6.0% in diabetic patients) [48].

Recently, the 1-year outcome associated with clopidogrel treatment after MI in patients with and without DM was reported from a large, Danish, healthcare registry using a cohort of nearly 60,000 patients [49]. Clopidogrel treatment reduced the unadjusted mortality rate (events/100 person-years) in patients with and without DM compared with those not treated with antiplatelet agents. However, in diabetic versus nondiabetic patients, clopidogrel was associated with significantly less relative effectiveness for all-cause (HR: 0.89; 95% CI: 0.79–1.00 vs HR: 0.75; 95% CI: 0.70–0.80; p = 0.001) and cardiovascular mortality (HR: 0.93; 95% CI: 0.81–1.06 vs HR: 0.77; 95% CI: 0.72–0.83; p = 0.01).

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 with CAD. The first study investigating this issue in the setting of elective PCI was the ARMYDA-2 study that demonstrated that a 600 mg clopidogrel loading dose given 4–8 h before elective PCI is associated with 52% reduction of early ischemic events compared with

the conventional 300 mg dose [50]. Faster achievement of maximal platelet inhibition and reduction of rates of low-responders may explain this observed clinical benefit. In another randomized investigation, the authors demonstrated that a 150 mg daily maintenance dose of clopidogrel, given for 30 days following PCI, decreases the incidence of low-responders compared with the conventional 75 mg daily dose; interestingly, in the same study the higher dose regimen was also associated with reduction of inflammatory parameters and improvement of endothelial function [51]. However, a subgroup analysis for patients with DM was not performed in these studies. In the OPTIMUS study, the comparative pharmacodynamic efficacy of high (150 mg) versus standard maintenance dose of clopidogrel (75 mg) in diabetic patients with coronary artery disease and high platelet reactivity was evaluated [52]. In this study, maximal adenosine diphosphate-induced (20 µmol/l) platelet aggregation was significantly reduced in the 150 mg group compared with the 75 mg group (p = 0.002). However, suboptimal clopidogrel response was still present in 60% of patients on the 150 mg regimen, thus providing further evidence that most low responders to clopidogrel, such as DM patients, continue to exhibit increased platelet reactivity despite enhanced dual antiplatelet therapy. These findings are supported by the GRAVITAS trial that compared high-dose clopidogrel (600 mg initial dose and 150 mg daily thereafter for 6 months) versus standard-dose clopidogrel (no additional loading dose and 75 mg daily) in 2214 patients with high on-clopidogrel platelet reactivity (assessed by VerifyNow P2Y12 assay) at 12–24 h after drug-eluting stent implantation [53]. Even though the reduction in the level of on-treatment reactivity was higher in the high-dose clopidogrel group at 30 days after PCI (22% absolute reduction compared with the standard clopidogrel dose), no difference in the 6-month rates of the primary composite end point (cardiovascular death, nonfatal MI or stent thrombosis) or its components was found (2.3% in both groups, HR: 1.01; 95% CI: 0.58–1.76; p = 0.97). The CURRENT-OASIS 7 trial explored the issue of whether a strategy with high-dose clopidogrel (600 mg loading plus 150 mg/day for 1 week, then 75 mg daily) in patients with ACS reduces the incidence of 30-day MACE compared with standard dose (300 mg loading and then 75 mg/day), failing to find a significant difference in the overall study population [43]. However, 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 adverse 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 an excess in major bleedings (1.6 vs 1.1%; p = 0.009) [44]. Notably, it has been observed a similar MACE reduction in patients with and without DM. Interestingly, no significant interactions were found in the overall cohort between clopidogrel dose and diabetes. All these findings may lead to infer that the persistence of increased platelet reactivity in diabetic patients, despite higher dose regimens of antiplatelet therapy with clopidogrel, makes this high-risk group a target population for more powerful antiplatelet drugs.

GP IIb/IIIa inhibitors have shown a significant benefit in high-risk patients with ACS undergoing PCI, but questionable efficacy has been observed with these antiplatelet agents in low-to-moderate risk ACS patients or in those treated with a conservative approach [54]. A dated meta-analysis, including studies with conventional doses of clopidogrel (loading dose 300 mg and maintenance dose 75 mg), showed a 22% reduction of 30-day death in diabetic patients treated with GP IIb/IIIa inhibitors versus those not receiving these agents, whereas patients without DM had no benefit in survival; the highest benefit was found in those patients undergoing PCI during the index hospitalization [55]. The more recent ISAR-SWEET trial did not find beneficial effects of abciximab over placebo on the risk of death and MI at 1 year in DM patients undergoing elective PCI after pretreatment with high-dose (600 mg) clopidogrel [56], whereas the ISAR-REACT 2 trial demonstrated a significant reduction of 30-day MACE with the use of abciximab versus placebo in patients with NSTE-ACS undergoing PCI on top of 600-mg clopidogrel loading dose (8.9 vs 11.9%; p = 0.03) [57]. This benefit, however, was limited to patients with elevated baseline troponin levels and was observed across all subgroups, including patients with DM. Moreover, the EARLY-ACS trial did not demonstrate a significant interaction between diabetic status and efficacy of early (≈24 h before PCI) versus delayed, provisional use of eptifibatide in patients with NSTE-ACS assigned to an invasive strategy [58]; however, absolute reduction of MACE at 96 h with early eptifibatide was more pronounced in diabetic versus nondiabetic patients. It could be inferred that the benefit of pretreatment with GP IIb/IIIa inhibitors during clopidogrel therapy appears more pronounced in high clinical risk patients, including those with DM undergoing PCI for both NSTE- and STE-ACS.

Newer oral antiplatelet drugs: prasugrel & ticagrelor in diabetic patients

Prasugrel is a third-generation thienopyridine that is orally administered as a prodrug and requires cytochrome P 450-dependent hepatic metabolism to achieve the active metabolite that irreversibly inhibits

the platelet P2Y12 receptor [59]. When compared with clopidogrel, prasugrel is more efficiently metabolized in the liver due to the single-step activation into the active metabolite and also to the smaller influence of cytochrome-P genetic polymorphisms and drug–drug interactions [59]. This more favorable pharmacokinetic profile confers to prasugrel a faster onset of action with enhanced inhibition of platelet activity and an overall smaller response variability, even when compared with high-dose clopidogrel (600-mg loading dose/150-mg maintenance dose) in patients undergoing PCI [60]. Serial pharmacodynamic assessments of prasugrel (60 mg load followed by 10 mg) compared with high-dose clopidogrel (600 mg and then 150 mg) in patients with DM and CAD were performed in the OPTIMUS-3 randomized cross-over trial [61]: greater platelet inhibition by different platelet function measures was achieved by prasugrel at 4-h post-loading dose ($p < 0.0001$). The difference in platelet inhibition between prasugrel and clopidogrel was significant from 1 h through 7 days ($p < 0.0001$). Moreover, prasugrel resulted in fewer poor responders at all-time points irrespective of definition used.

The TRITON-TIMI 38 trial evaluated the clinical effectiveness and safety of prasugrel (60-mg/10-mg) compared with clopidogrel (300-mg/75-mg) in 13,608 patients with moderate to high risk ACS and with planned PCI, followed-up for a median time of 14.5 months [10]. A significant 19% relative reduction of the primary efficacy end point (composite of cardiovascular death, nonfatal MI or nonfatal stroke) was observed with prasugrel in the overall population, largely driven by a reduction in MI incidence in the prasugrel group (HR: 0.76; 95% CI: 0.67–0.85; $p < 0.001$). Significant reductions in the rates of urgent target-vessel revascularization (3.7 vs 2.5%; $p < 0.001$) and stent thrombosis (2.4 vs 1.1%; $p < 0.001$) were also found in patients treated with prasugrel. However, these benefits on ischemic events were counterbalanced by an increase in noncoronary artery bypass grafting (CABG)-related TIMI major bleedings (2.4 vs 1.8%; HR: 1.32; 95% CI: 1.03–1.68; $p = 0.03$). Also, the rate of life-threatening bleeding was greater in the prasugrel group (1.4 vs 0.9%; $p = 0.01$). Nevertheless, despite this increased bleeding risk, the net clinical benefit (a composite of death from any cause, nonfatal MI, nonfatal stroke and non-CABG-related major bleeding) was in favor of prasugrel (12.2 vs 13.9%; HR: 0.87; 95% CI: 0.79–0.95; $p = 0.004$), except in patients older than 75 years of age, weighing <60 kg and with a previous history of stroke. A prespecified subgroup analysis compared prasugrel with clopidogrel among 3146 subjects with DM in TRITON-TIMI 38 [62]. Also in the diabetic population, prasugrel compared with clopidogrel significantly reduced the rate of the primary efficacy end point, resulting in a 30% relative reduction (vs 14% relative reduction in nondiabetic patients). This difference was mainly driven by the significant lower incidence of MI with prasugrel; however, stent thrombosis rate also exhibited a significant reduction in diabetic patients treated with the new antiplatelet agent (48% relative risk reduction). The rates of TIMI major bleeding were similar among subjects with DM for clopidogrel and prasugrel (2.6 vs 2.5%; HR: 1.06; $p = 0.81$, P interaction = 0.29). The beneficial effect of prasugrel on the primary end point was consistent in patients with (14.3 vs 22.2%; HR: 0.63; 95% CI: 0.44–0.89; $p = 0.009$) and without insulin treatment (11.5 vs 15.3%; HR: 0.74; 95% CI: 0.59–0.93; $p = 0.009$). Substantial benefits in ischemic events were observed, including a 44% relative reduction in MI (9.9 vs 17.3%; $p < 0.005$) for DM on insulin and a 38% relative reduction for MI in DM without insulin (11.9 vs 7.7%; $p < 0.001$); moreover, a 69% relative reduction in stent thrombosis for DM on insulin (1.8 vs 5.7%; $p < 0.008$) and a 34% reduction among diabetic subjects without insulin therapy (2.0 vs 3.0%; $p = 0.14$) was reported. Hemorrhage rates were similar regardless of DM treatment type. The combination of a relatively greater reduction in ischemic end points and no increase in major bleedings among subjects with DM led to a statistically greater net clinical benefit for prasugrel among diabetic subjects. Specifically, among subjects without DM, a nonsignificant 8% reduction in the composite of all-cause mortality, nonfatal MI, nonfatal stroke, or nonfatal major bleeding was observed, whereas a statistically greater 26% reduction in this composite outcome was seen for diabetic subjects ($p = 0.001$, p interaction = 0.05). In the attempt to solve the increased bleeding risk associated with prasugrel, another study evaluating the effectiveness of reduced dose of this drug was concluded, however it did not confirm the positive results of TRITON-TIMI 38. In fact, in the TRILOGY ACS trial, enrolling 9326 ACS patients without ST-segment elevation managed medically [63], the clinical efficacy and safety of prasugrel (30-mg load and 10- or 5-mg maintenance dose in patients <75 years and ≥75 years of age, respectively) was compared with clopidogrel (300-mg/75-mg). In this study, prasugrel did not significantly reduce the frequency of the primary end point of cardiovascular death, MI or stroke in the overall population (18.7 vs 20.3%; HR: 0.96; 95% CI: 0.86–1.07; $p = 0.45$) and in the subgroup of patients with DM (n = 2811) aged younger than 75 years (17.8 vs 20.4%; HR: 0.90; 95% CI: 0.73–1.09; $p = 0.71$). Nonetheless, it must be noted that, in these large randomized studies, prasugrel was compared with a lower clopidogrel loading dose

(300 mg) than that recommended, in the first place, by current guidelines on myocardial revascularization [64].

Ticagrelor, a cyclo-pentyl-triazolo-pyrimidine is a reversible, direct-acting P2Y12 inhibitor that does not require metabolic activation, as it is not a prodrug; it has been associated with more rapid onset and offset of action and stronger platelet inhibition than clopidogrel, without dependence on cytochrome genetic polymorphism and with few drug–drug interactions caused by inhibition or induction of CYP450 enzymes [65,66]. The clinical effectiveness and safety of ticagrelor (180-mg loading dose followed by 90-mg b.i.d. maintenance dose) compared with clopidogrel (300–600-mg followed by 75 mg daily) has been evaluated in the PLATO trial enrolling patients (n = 18,624) with moderate-to-high risk ACS (non-ST elevation ACS invasively or medically managed or ST-elevation MI managed with primary PCI) [9]. Over a median follow-up of 12 months, a 16% relative reduction of the primary end point (a composite of death from vascular causes, MI or stroke) was observed with ticagrelor compared with clopidogrel (9.8 vs 11.7%, respectively, HR: 0.84; 95% CI: 0.77–0.92; p < 0.001). Of note, a 22% relative reduction for cardiovascular death (p < 0.001) and a 23% relative reduction for stent thrombosis (p < 0.01) favored ticagrelor in the overall population. No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6 and 11.2%, respectively; p = 0.43); however, the former was associated with a higher rate of major bleeding not related to CABG (4.5 vs 3.8%, p = 0.03). In a predefined subgroup analysis of the DM cohort (n = 4662) of the PLATO trial [67], a significant reduction in the primary composite end point (HR: 0.88; 95% CI: 0.76–1.03), all-cause mortality (HR: 0.82; 95% CI: 0.66–1.01) and stent thrombosis (HR: 0.65; 95% CI: 0.36–1.17) was observed, with no increase in major bleeding (HR: 0.95; 95% CI: 0.81–1.12), without significant diabetes status-by-treatment interactions. The benefit of ticagrelor was more pronounced in the group of patients with worse glycemic control, defined as HbA1c levels above the median of 6%, in which the rates of the primary end point (11.4 vs 14.2%; HR: 0.80; 95% CI: 0.70–0.91), all-cause mortality (5.6 vs 7.4%; HR: 0.78; 95% CI: 0.65–0.93) and stent thrombosis (1.3 vs 2.0%; HR: 0.62; 95% CI: 0.39–1.00) were significantly reduced, with similar bleeding rates (HR: 0.98; 95% CI: 0.86–1.12).

As for GP IIb/IIIa inhibitors, both in TRITON and in the subset of the PLATO trial planned for an invasive strategy, the clinical benefit of both prasugrel and ticagrelor over clopidogrel was irrespective of the use of GP IIb/IIIa inhibitors [8,10,68].

As discussed above, the more favorable pharmacodynamics profiles of prasugrel and ticagrelor have been shown to translate in higher clinical efficacy with respect to clopidogrel in patients with ACS and/or undergoing PCI, both among diabetic and nondiabetic subgroups. Although greater relative reductions in ischemic events seemed to be associated with the use of prasugrel (when compared with a nonoptimal clopidogrel loading dose), both prasugrel and ticagrelor, compared with clopidogrel, reduced ischemic events at the expense of an increased risk of non-CABG-related major bleeding. Therefore, a careful assessment of the ischemic and bleeding risks should be made when choosing more potent antiplatelet drugs. The presence of diabetes, as well as the clinical presentation of a moderate-to-high risk ACS should suggest to shift the balance toward the ischemic risk, guiding the therapeutic decision toward more aggressive antithrombotic strategies.

On a pharmacodynamic level, prasugrel and ticagrelor have been directly compared in few studies. Alexopoulos *et al.* [69] evaluated platelet reactivity (assessed by VerifyNow) and bleeding events in 512 patients with ACS undergoing PCI treated with ticagrelor 90 mg b.i.d or prasugrel 10 mg daily for one month. At 30 days, platelet reactivity was lower with ticagrelor compared with prasugrel (p < 0.001). HPR rate was higher for prasugrel-treated patients (5.4 vs 0%, p < 0.001). However, more Bleeding Academic Research Consortium (BARC) type 1 bleeding events were observed with ticagrelor compared with prasugrel (36.7 vs 28.2%; p = 0.047), while more severe bleeding events frequency did not differ between the two agents. Of interest, DM had a significant effect on platelet reactivity in prasugrel treated patients compared with nondiabetics, whereas, no factor significantly affected platelet reactivity under ticagrelor. The same study group designed another prospective, crossover, randomized study with specific regard to the diabetic population [70]. They compared the pharmacodynamic action of ticagrelor 90 mg b.i.d versus prasugrel 10 mg daily for a 15-day treatment period in 30 ACS patients with DM who had been pretreated with clopidogrel. Platelet reactivity was significantly lower after ticagrelor (45.2 PRU [95% CI: 27.4–63.1]) compared with prasugrel (80.8 PRU [95% CI: 63.0–98.7]), while HPR rate was 0% for ticagrelor and 3.3% among patients treated with prasugrel (p = 1.0). Laine *et al.* performed a single-center prospective open-label randomized trial enrolling 100 patients with DM suffering from ACS and undergoing PCI, in order to compare the level of platelet reactivity inhibition achieved by prasugrel and ticagrelor loading dose (assessed by VASP index) [71]. Ticagrelor achieved a significantly

lower platelet reactivity compared with prasugrel loading dose (17.3 ± 14.2 vs 27.7 ± 23.3%; p = 0.009). In addition, the rate of high on-treatment platelet reactivity, defined by a VASP ≥ 50%, tended to be lower in the ticagrelor group although the difference did not reach statistical significance (6 vs 16%; p = 0.2).

These pharmacodymanic findings suggest ticagrelor may be more effective compared with prasugrel in reducing HPR in diabetic patients suffering from an ACS; however, whether the higher potency of ticagrelor could translate into a clinical benefit should be further investigated. To date, no clinical direct comparison data are available.

Conclusion

DM represents a major risk factor for the development of coronary artery disease with a significant impact on long-term prognosis. Moreover, patients with DM have increased baseline platelet reactivity and impaired response to antiplatelet drugs compared with nondiabetics, that evidently may make pharmacological management difficult in the setting of acute coronary events and/or invasive coronary procedures. A higher percentage of low responders has been observed among patients with DM, clinically associated with an increased risk of thrombotic events during follow-up, suggesting also the need for different thresholds for high platelet reactivity that predict clinical outcomes after PCI, in this specific high-risk population. All these findings strongly confirm that diabetic patients may benefit from more aggressive antiplatelet strategies such as prasugrel and ticagrelor, that, at the moment, have been demonstrated to be more effective in diabetic patients compared with standard clopidogrel treatment. However, further ad hoc randomized studies are needed to establish whether prasugrel or ticagrelor may

Executive summary

Introduction

- Diabetes mellitus (DM) is a major risk factor for cardiovascular events; diabetic patients suffering from acute coronary syndrome (ACS) have been shown to have a 1.8-fold increase in cardiovascular death and a 1.4-fold increase in myocardial infarction at 2 years, compared with nondiabetics.
- Diabetic patients with ACS and/or undergoing percutaneous coronary intervention (PCI) have been demonstrated to be characterized by a significantly enhanced prothrombotic milieu and impaired response to antiplatelet therapy.

Role of diabetes mellitus in the development of cardiovascular disease & platelet hyper-reactivity

- In diabetic patients platelets have been proven to be hyper-reactive, leading to intensified adhesion, activation and aggregation.
- The increased accumulation of macrophages in the adipose tissue of DM patients is a key process in vascular inflammation, foam cell formation and atherosclerosis.
- Hyperglycemia and insulin resistance and/or deficiency in diabetic patients is associated with vascular function impairment and enhanced platelet aggregation.

Impact of platelet reactivity on cardiovascular outcomes in patients with DM & coronary artery disease

- High residual platelet reactivity (HPR) despite antiplatelet therapy is associated with higher rates of major adverse cardiovascular events (MACE) after ACS and/or PCI.
- HPR is more frequently observed in DM patients.
- Following ACS and/or PCI, the combination of HPR and DM result in a significant increase in cardiovascular events and specific thresholds for platelet reactivity are being identified as predictive for MACE.

Standard antiplatelet therapy in diabetic patients: clinical benefits & limitations

- Despite the known overall benefit of clopidogrel in addition to aspirin in the setting of ACS/PCI, patients with DM derive a lesser benefit from standard doses of this antiplatelet drug.
- Several studies have explored the antiplatelet effect of higher loading dose and maintenance dose of clopidogrel in patients with ACS and/or undergoing PCI, finding a significant reduction in the measured on-treatment platelet reactivity; this phenomenon, however, was less evident in diabetic patients and not always led to a net clinical benefit in terms of MACE reduction.

Newer oral antiplatelet drugs: prasugrel & ticagrelor in diabetic patients

- In the diabetic population with a moderate-high risk ACS and a planned PCI, prasugrel compared with standard-dose clopidogrel significantly reduced the rate of the primary efficacy end point, resulting in a 30% relative reduction, with similar rates of TIMI major bleeding.
- Ticagrelor was associated with significant reduction in the primary ischemic composite end-point compared with clopidogrel in diabetic patients with moderate-high risk ACS and PCI, with similar bleeding rates.
- Pharmacodynamic studies directly comparing ticagrelor and prasugrel in DM patients suggest ticagrelor may have a more pronounced antiplatelet effect leading to lower rates of high on-treatment platelet reactivity. However, direct clinical comparison randomized studies are warranted in the future.

be considered the treatment of choice in patients with diabetes mellitus and to investigate which of the two drug is superior in this specific subset of patients.

Future perspective

Despite the high level of platelet inhibition achieved with currently available antiplatelet drugs, diabetic patients with ACS and/or undergoing PCI remain at higher risk of ischemic events. Hence, the rationale for the development of newer and more potent antiplatelet drugs to use as first antiplatelet line in this specific subset of patients. Impressive results have been observed in the diabetic population with the use of prasugrel and ticagrelor compared with standard clopidogrel therapy, however, other new antiplatelet agents are under investigation. Cangrelor is an inhibitor of the platelet P2Y12 receptor that is administered intravenously; it has an immediate, potent platelet inhibition after a single bolus and a rapid offset of action (i.e., platelet reactivity is restored) within 1 h of continuous intravenous infusion interruption [72]. In a recent pharmacodynamic study comparing the antiplatelet effect of this drug in diabetic and nondiabetic, clopidogrel-naive patients with CAD on aspirin therapy [73], cangrelor provided potent, dose-dependent blockade of platelet P2Y12 receptors, without differential effects according to diabetic status. A pooled analysis from the three randomized trials recently compared cangrelor with control (clopidogrel or placebo) in PCI patients, demonstrating a significant 19% reduction in the odds of ischemic cardiac events at 48 h, at the expense of increased incidence of GUSTO mild bleeding events [74]. No specific interaction between diabetic status and efficacy of cangrelor was found in this meta-analysis. This new drug, possibly offering great benefit in terms of survival and MACE rate reduction in high-risk ACS patients treated with PCI, may also serve as bridging therapy for those patients with recent ACS and/or coronary stent implantation scheduled for major surgery. In conclusion, large randomized studies are needed to explore whether DM patients may derive a further benefit from new-generation antiplatelet drugs, with a decrease in thrombotic events and without significant excess of bleeding. Also, a better risk stratification based on the metabolic status of patients with ACS and/or undergoing PCI would be of great importance in order to choose the antiplatelet drugs that better fit the specific ischemic/bleeding risk.

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