Antiplatelet Therapy in Diabetes: Efficacy and Limitations of Current Treatment Strategies and Future Directions

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Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes (1). The concomitant presence of multiple classical cardiovascular risk factors in diabetic subjects contributes to enhanced atherothrombotic risk (2). However, other risk factors may be important such as abnormal platelet function (3). Platelets, in fact, play a key role in atherogenesis, and its thrombotic complications and measures, which lead to blockade of one or multiple pathways modulating platelet activation and aggregation processes, are pivotal in reducing ischemic risk in diabetic subjects (4). This article reviews currently available antiplatelet agents on ischemic events in diabetic patients, limitations of currently available treatment strategies, and antiplatelet agents currently under clinical development that may potentially overcome these limitations.

Antiplatelet therapy

There are three different classes of platelet-inhibiting drugs: cyclooxygenase-1 (COX-1) inhibitors (aspirin), ADP $P2Y_{12}$ receptor antagonists (thienopyridines), and platelet glycoprotein (GP) IIb/IIIa inhibitors, which are mostly used for the prevention and treatment of atherothrombotic disorders (4) (Fig. 1). Aspirin inhibits the COX-1 enzyme and therefore blocks platelet thromboxane A_2 synthesis (5). However, patients on aspirin therapy, particularly those at high risk, may continue to have recurrent thrombotic events. GP IIb/IIIa inhibitors are very potent antiplatelet agents, which exert effects through inhibition of the final common pathway that mediates platelet aggregation processes, and have been shown to be effective in preventing thrombotic complications in high-risk

patients undergoing percutaneous coronary interventions (PCI) (4). However, these agents are available only for parenteral use and have a short duration of action, which impedes their use for long-term protection. The need for alternative antiplatelet treatment strategies led to the evaluation of effects obtained from a combination of oral antiplatelet agents inhibiting other platelet-activating pathways. Ticlopidine is a first-generation thienopyridine, which irreversibly blocks the platelet ADP $P2Y_{12}$ receptor (6). Its combination with aspirin is associated with a more enhanced inhibition of platelet function and better clinical outcomes in patients undergoing coronary stenting compared with aspirin monotherapy or aspirin plus warfarin (6). However, the limited safety profile of ticlopidine and its inability to achieve antiplatelet effects rapidly have led clopidogrel, a second-generation thienopyridine, to become the ADP $P2Y_{12}$ receptor antagonist of choice (6–7).

Aspirin. Aspirin selectively acetylates the COX-1 enzyme, thereby blocking the formation of thromboxane A_2 in platelets (5). This effect is irreversible because platelets are enucleate and, thus, unable to resynthesize COX-1. In addition to being the antiplatelet agent of choice for secondary prevention of ischemic events in patients with atherosclerotic disease, aspirin may also be used for primary prevention of ischemic events. In fact, although this indication in the general population is controversial, there is an expert consensus for aspirin usage in the primary prevention setting in diabetic patients.

Aspirin as a primary prevention strategy in diabetes. The American Diabetes Association (ADA) recommends the use

of low-dose aspirin (75–162 mg/day) as a primary prevention strategy in patients with type 1 or type 2 diabetes at increased cardiovascular risk, including those >40 years of age or who have additional risk factors (family history of cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria) (8). However, aspirin therapy should not be recommended for patients aged <21 years because this may increase the risk of Reye's syndrome. The role of aspirin in diabetic patients aged <30 years remains unclear because it has not been investigated.

Several clinical trials have evaluated the efficacy of aspirin in diabetic patients (9–12). Most of these studies showed a benefit of aspirin in diabetic patients (9–11). However, these outcomes were based on post hoc analyses because these trials were not specifically designed for diabetic patients. In addition, the obtained results were based on small numbers of subjects, which may explain why aspirin was not always shown to be beneficial in the primary prevention setting in diabetic patients (12).

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (clinical trial reg. no. NCT00110448) was the first prospectively designed trial to evaluate the use of aspirin (81 mg or 100 mg) in the primary prevention of cardiovascular events in patients with type 2 diabetes ($n = 2,539$) aged 30–85 years in Japan (13). After a median follow-up of 4.37 years, there was a 20% difference between the aspirin and nonaspirin arms in the primary end point (5.4 vs. 6.7%, respectively) that failed to achieve statistical significance ($P = 0.16$). Among patients aged >65 years ($n = 1,363$), aspirin was associated with a 32% reduction in the risk of the primary end point (6.3 vs. 9.2%; $P = 0.047$). Furthermore, in aspirin-treated patients, the incidence of fatal coronary and cerebrovascular events (a secondary end point) was significantly lower by 90% (0.08 vs. 0.8%; $P = 0.0037$); however, there were no differences in nonfatal coronary and cerebrovascular events. Aspirin was well tolerated, with no significant increase in the composite of hemorrhagic stroke and
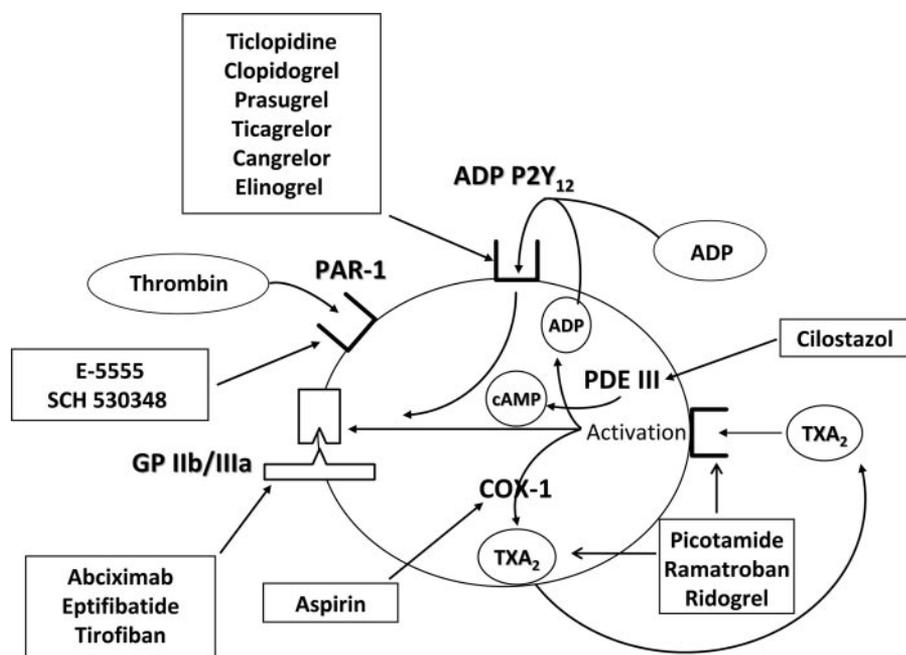
Figure 1— *Mechanisms of action of antiplatelet agents. Aspirin inhibits thromboxane A_2 (TXA_2) synthase through blockade of the COX-1 enzyme. Picotamide, ramatroban, and ridogrel inhibit both TXA_2 synthase and TXA_2 receptors. Thienopyridines, ticlopidine, and clopidogrel are inhibitors of ADP $P2Y_{12}$ receptor and block intracellular pathways leading to platelet activation. Prasugrel, ticagrelor, cangrelor, and elinogrel are $P2Y_{12}$ receptor antagonists currently under clinical investigation. Aspirin and $P2Y_{12}$ receptor antagonists have synergistic effects in blocking the final common pathway leading to platelet aggregation represented by GP IIb/IIIa receptor, which may be directly inhibited by intravenous GP IIb/IIIa receptor antagonists. Cilostazol is an inhibitor of phosphodiesterase (PDE) III, which inhibits platelets through an increase in intraplatelet cAMP levels. E5555 and SCH 530348 are thrombin receptor antagonists that block the PAR-1 subtype. (Adapted from Schafer AI: Antiplatelet therapy. Am J Med 101:199–209, 1996.)*

severe gastrointestinal bleeding. Limitations of this trial include the open-label assignment to aspirin and the low event rate. Therefore, the study may have been underpowered to demonstrate a significant effect of aspirin on the primary end point. The results of this trial have questioned the validity of current guideline recommendations on aspirin usage in primary prevention in diabetic patients. However, there are other ongoing trials, which will provide further insights to the appropriateness of aspirin usage in the primary prevention setting in diabetic subjects. These include A Study of Cardiovascular Events iN Diabetes (ASCEND) (clinical trial reg. no. NCT00135226) and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) (clinical trial reg. no. ISRCTN48110081).

Recently, the results of the Prevention Of Progression of Arterial Disease And Diabetes (POPADAD) trial have been reported (14). In this trial, patients ($n = 1,276$) with type 1 or type 2 diabetes aged >40 years with an ankle-brachial pressure index ≤0.99 but no symptomatic cardiovascular disease were randomized to aspirin (100 mg) and antioxidants in a double-blind, 2×2 factorial, placebo-controlled fashion. This trial failed to show any benefit with aspirin or antioxidants in primary prevention of cardiovascular events. The overall small number of patients with low event rates could have played a role in the outcomes of the study. Although patients in this trial were asymptomatic, this should not be considered a primary prevention study because subjects had some degree of peripheral arterial disease (PAD).

Aspirin as a secondary prevention strategy in diabetes. ADA recommends the use of low-dose aspirin (75–162 mg/day) for secondary prevention of cerebrovascular and cardiovascular events in all diabetic patients (8). This position is supported by the results of two large meta-analyses of major secondary prevention trials by the Antithrombotic Trialists' Collaboration (ATC), which showed oral antiplatelet agents, mostly aspirin, to be protective in patients at high risk for car-

diovascular disease, including those with diabetes (15–16). The meta-analyses included 287 secondary prevention trials involving 212,000 high-risk patients with acute or prior vascular disease or another condition that increased their risk of vascular disease. Aspirin in doses ranging from 75 to 325 mg/day was the most frequently used antiplatelet agent. In the major high-risk groups (acute myocardial infarction, past history of myocardial infarction, past history of stroke or transient ischemic attack, acute stroke, and any other relevant history of vascular disease), antiplatelet therapy reduced the incidence of vascular events by 23%. Of note, a low dose of aspirin (75–150 mg/day) was found to be at least as effective as higher daily doses. Furthermore, bleeding complications were reduced with the lower doses. In more than 4,500 diabetic patients studied in the ATC, the incidence of vascular events was also reduced from 23.5 in the control group to 19.3% in the group treated with antiplatelet therapy ($P < 0.01$) and from 17.2 to 13.7% in the ~42,000 nondiabetic patients ($P < 0.00001$). Although the overall incidence of vascular events was much higher in diabetic patients, the benefit of antiplatelet therapy in both diabetic and nondiabetic patients was consistent (42 vascular events were prevented for every 1,000 diabetic patients and 35 events for every 1,000 nondiabetic patients).

$P2Y_{12}$ receptor antagonists
Clopidogrel is currently the thienopyridine of choice because it has a more favorable safety profile compared with that of ticlopidine (6–7). The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial examined the effects of clopidogrel (75 mg/day) versus aspirin (325 mg/day) in a large secondary prevention population ($n = 19,185$) of patients with a history of recent myocardial infarction, recent ischemic stroke, or established PAD (17). The annual incidence of the primary end point (combined incidence of vascular death, myocardial infarction, or ischemic stroke) was 5.32% with clopidogrel and 5.83% with aspirin, representing an 8.7% relative risk reduction in favor of clopidogrel ($P = 0.043$). Bhatt et al. (18) retrospectively analyzed the results of the diabetic subgroup in the CAPRIE study, which represented 20% of the study population. The composite vascular primary end point occurred in 15.6 and 17.7% of patients randomized to clopidogrel and as-

pirin, respectively ($P = 0.042$). For every 1,000 diabetic patients treated, this led to 21 vascular events prevented, which increased to 38 among insulin-treated diabetic patients. Of note, the reduction in the composite vascular primary end point with clopidogrel (11.8%) compared with aspirin (12.7%) was not statistically significant in nondiabetic patients. ADA currently recommends the use of clopidogrel therapy in very high-risk diabetic patients or as an alternative therapy in aspirin-intolerant patients (8).

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study examined outcomes with clopidogrel plus aspirin versus aspirin alone in patients ($n = 12,562$) with unstable angina or non–ST-elevation myocardial infarction (NSTEMI) (19). Patients were randomized to treatment with either clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) or placebo in addition to standard aspirin therapy (75–325 mg/day) for up to 1 year. Patients assigned to treatment with dual antiplatelet therapy (aspirin and clopidogrel) had a significant 20% relative reduction in the first primary outcome (composite vascular death, myocardial infarction, or stroke) compared with that in patients treated solely with aspirin (9.3 vs. 11.4%, respectively; $P < 0.001$). Although the enhanced degree of platelet inhibition associated with dual antiplatelet therapy reduced ischemic events, this was associated with a higher incidence of major bleeding (3.7 vs. 2.7%; $P = 0.001$). However, there were no significant differences in life-threatening bleeding (2.2 vs. 1.8%; $P = 0.13$). In the CURE study, there were 2,840 diabetic patients who experienced ~17% reduction in the first primary outcome when treated with combined aspirin and clopidogrel therapy compared with aspirin alone (14.2 vs. 16.7%). However, the CI 0.70–1.02 shows that, although dual antiplatelet therapy with aspirin and clopidogrel provided beneficial effects in the diabetic subgroup (as in the overall study population), this achieved a borderline statistical significance. It is important to note that the event rate was much higher in the diabetic than in the nondiabetic subgroup despite more intense antiplatelet therapy with the adjunctive use of clopidogrel. In fact, the primary composite cardiovascular end point was almost twofold higher in diabetic than in nondiabetic patients (14.2 vs. 7.9%, respectively) (19). These findings emphasize that more specific an-

tiplatelet treatment regimens, which may include more potent agents or a combination with other antiplatelet drugs, are warranted in diabetic patients (20).

The current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of unstable angina and NSTEMI recommend the addition of clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) to aspirin in patients presenting with unstable angina and NSTEMI (21). Recently, the use of clopidogrel in patients with ST-elevation myocardial infarction (STEMI) has been approved by the U.S. Food and Drug Administration and endorsed by the current ACC/AHA guidelines on the management of STEMI patients (22). In acute coronary syndrome (ACS) patients, guidelines state that clopidogrel should be used regardless of the treatment strategy adopted (invasive or noninvasive) and should, ideally, be continued for up to 1 year. The prognostic implications of compliance with adjunctive clopidogrel therapy are underscored by a rebound increase in death and myocardial infarctions following its withdrawal (23). This phenomenon is particularly apparent in diabetic patients and may be attributed to a more marked increase in platelet reactivity in these patients following clopidogrel withdrawal (23–24).

In contrast to the clear benefit seen with dual antiplatelet therapy across the spectrum of patients with ACS, including those undergoing PCI, the results of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showed that in high-risk but nonacute patients ($n = 15,603$) with clinically evident cardiovascular disease ($n = 12,153$) or multiple cardiovascular risk factors ($n = 3,284$), treatment with clopidogrel plus aspirin was not significantly more effective than that with aspirin alone in reducing the rate of cardiovascular death, myocardial infarction, or stroke (6.8 vs. 7.3%, respectively; $P = 0.22$) (25). Although a subgroup analysis in a higher-risk group ($n = 9,478$) with prior myocardial infarction, ischemic stroke, or symptomatic PAD ("CAPRIE-like" population) showed a 17% relative risk reduction ($P = 0.01$) with dual antiplatelet therapy (26), the opposite findings were observed in patients in the lower-risk cohort who were enrolled in the study based on the presence of multiple cardiovascular risk factors in which an increase in

mortality was observed. Importantly, a large number of patients enrolled in this latter subgroup had diabetes, as diabetes diagnosis represented one of the key inclusion criteria. Therefore, dual antiplatelet therapy with aspirin and clopidogrel should not be advocated in the primary prevention setting for diabetic individuals.

GP IIb/IIIa receptor antagonists

Numerous studies have been performed comparing various GP IIb/IIIa inhibitors. Currently, three different GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) are approved for clinical use. In a meta-analysis of six trials of intravenous GP IIb/IIIa inhibitors in ACS patients, 22% of whom had diabetes ($n = 6,458$), GP IIb/IIIa blockers significantly reduced mortality at 30 days from 6.2 to 4.6% ($P = 0.007$) in diabetic patients (27). Among more than 22,000 patients in these trials who did not have diabetes, GP IIb/IIIa inhibitors did not improve survival. The effect of GP IIb/IIIa inhibitors in diabetic individuals was even greater in 1,279 patients who underwent percutaneous coronary intervention during the index hospitalization; in these individuals, GP IIb/IIIa inhibitors reduced 30-day mortality from 4 to 1.2% ($P = 0.002$). Of note, these trials were performed in an era of limited use of clopidogrel that has challenged the need for a GP IIb/IIIa receptor antagonist in diabetic patients. In fact, the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics? (ISAR-SWEET) trial did not show any effect of abciximab on 1-year risk of death and myocardial infarction in diabetic patients ($n = 701$) undergoing PCI after pretreatment with a 600-mg loading dose of clopidogrel at least 2 h before the procedure (28). However, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial clearly showed that abciximab safely reduces the risk of adverse events in patients with NSTEMI ACS undergoing PCI after pretreatment with 600 mg of clopidogrel, which was administered to patients with elevated troponin levels but not to patients with electrocardiogram changes (29). The benefit was observed across all subgroups, including patients with diabetes. Overall, in accordance with current guidelines, these results continue to support the use of GP IIb/IIIa receptor antagonists

in ACS patients, in particular those with diabetes (21).

Increased bleeding rates represent the major limitation of GP IIb/IIIa agents. There is increasing evidence that bleeding has an important impact on prognosis, including long-term mortality (30). Compared with GP IIb/IIIa inhibitors, bivalirudin (a direct thrombin inhibitor) has been shown to provide similar protection from ischemic events with less major bleeding in ACS patients, resulting in a significant reduction in net adverse clinical outcomes (31). These findings were corroborated in a recent subgroup analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial performed in the diabetic cohort ($n = 3,852$). In particular, bivalirudin monotherapy compared with GP IIb/IIIa plus heparin resulted in a similar rate of composite ischemia (7.9 vs. 8.9%, respectively; $P = 0.39$) and less major bleeding (3.7 vs. 7.1%; $P < 0.001$), yielding fewer net adverse clinical outcomes (10.9 vs. 13.8%; $P = 0.02$) (32).

Limitations of currently available antiplatelet drugs

Aspirin and clopidogrel represent the cornerstone of treatment for secondary prevention of ischemic events in patients, including those with diabetes, presenting with either stable or unstable atherosclerotic cardiovascular disease. However, a considerable number of patients continue to experience recurrent atherothrombotic events despite the use of these antiplatelet agents. These observations have led over the course of recent years to the development of the concept of antiplatelet drug resistance. The term "resistance" derives from a laboratory finding consisting in failure of an antiplatelet agent to adequately block its specific target on the platelet (33). Therefore, thrombotic events cannot be attributed to drug resistance if the efficacy of the antiplatelet agent was not tested in affected patients. For aspirin, resistance involves inadequate or lack of inhibition of the COX-1–mediated thromboxane A_2 pathway, whereas for clopidogrel, resistance involves $P2Y_{12}$ receptor signaling (33). Antiplatelet drug resistance should not be confused with treatment failure, which is defined by recurrence of an ischemic event despite treatment. Indeed, antiplatelet drug resistance can lead to a treatment failure, but not all treatment failures can be attributed to antiplatelet drug resistance. This is in line with the multifacto-

rial nature of atherothrombosis, which implies the existence of multiple mechanisms that can lead to recurrence of events. **Aspirin resistance.** Numerous studies have correlated aspirin resistance with long-term adverse clinical outcomes not only in patients with coronary artery disease but also in individuals with ischemic stroke or peripheral arterial disease (33). The prevalence of aspirin resistance described in the literature varies considerably (in 0% of patients in some studies and >50% of patients in others); the disparate findings can be attributed to differences in the definition of resistance, type of assay used, dose of aspirin, and patient population under consideration. Many of the studies used assays that are not COX-1 specific (e.g., PFA-100, light transmittance aggregometry using agonists other than arachidonic acid), and the results obtained may be reflective of multiple platelet-signaling pathways. These tests typically lead to a higher prevalence of aspirin resistance, particularly in diabetic patients (34). There is accumulating evidence, however, that when tests that specifically assess COX-1 activity are used to determine aspirin responsiveness, aspirin resistance is encountered very infrequently (in <5% of patients) (35–36). Even though the relevance of different assays testing aspirin sensitivity (specific and nonspecific for COX-1 inhibition) still needs to be better defined, meta-analyses using various laboratory assays support the poor prognostic implications of inadequate aspirin-induced effects (37–38). However, there are no published studies specifically designed to evaluate the implications of biochemical aspirin resistance in diabetic patients.

The foremost reason for aspirin resistance when using COX-1–specific assays is poor patient compliance (33,35). Interactions with drugs, such as ibuprofen, that interfere with aspirin–induced COX-1 acetylation may also be a cause of inadequate or absent effects of aspirin (39). The latter may also be responsible for an increased risk of ischemic events despite aspirin use. In addition, the overall prevalence of inadequate aspirin effects may be influenced by the patient population under investigation. Patients with diabetes are typically characterized by platelet hyperreactivity. Although aspirin may lead to complete blockade of COX-1 as assessed by assays specific to this target, high residual platelet reactivity may persist in these patients as a result of upregulation of other signaling pathways,

which are not blocked by aspirin. This becomes more evident when non–COX-1 specific assays are used, and diabetic patients are more likely to be resistant using these tests (34).

Only a limited number of studies have investigated the potential mechanisms of aspirin resistance intrinsic to diabetic patients. Diabetic individuals are characterized by increased platelet reactivity and an increased level and activity of prothrombotic clotting factors (4), which may explain their predisposition to inadequate aspirin-induced effects. Hyperglycemia may be considered a diabetes-specific mechanism for inadequate aspirin-induced effects (40). In fact, an interaction between glycation and acetylation has been repeatedly shown. Also, increased glycation of platelet and coagulation factor proteins may interfere with the acetylation process, thereby contributing to inadequate aspirin-induced antiplatelet effects in diabetic patients. However, it still remains undetermined whether improved glycemic control enhances the efficacy of aspirin or whether increased doses of aspirin are beneficial in the presence of poor glycemic control. **Clopidogrel resistance.** Clopidogrel is a specific, irreversible antagonist of the platelet $P2Y_{12}$ ADP receptor and, thus, inhibits platelet activation in an entirely distinct manner compared with that of aspirin. Similarly to aspirin, the prevalence of clopidogrel resistance reported in the literature varies considerably and is related to differences in the definitions used, type of assay used, dose of clopidogrel, and patient population (41). Nonetheless, interindividual variability in platelet response to clopidogrel is a well-established concept. Genetic, cellular, and clinical causes can all contribute to inadequate clopidogrel responsiveness (41). The presence of diabetes may contribute to inadequate clopidogrel-induced effects through various mechanisms (Table 1). Clopidogrel nonresponsiveness is more prevalent in diabetic compared with nondiabetic patients and is highest among patients requiring insulin therapy (42–44) (Fig. 2). These findings may explain why diabetic patients, particularly those at the most advanced state of their disease (e.g., insulin-requiring diabetes), continue to have recurrent atherothrombotic events, including stent thrombosis (41,45). Platelet-function profiling performed exclusively in type 2 diabetic patients receiving aspirin and clopidogrel therapy has shown that even though these pa-

Table 1—*Mechanisms of clopidogrel response variability*

Clinical factors
    Failure to prescribe/poor compliance
    Underdosing
    Poor absorption
    Drug–drug interactions involving intestinal P-glycoprotein (MDR1 gene product)
    Drug–drug interactions involving CYP3A4
    Acute coronary syndrome
    Diabetes/insulin resistance*
    Elevated BMI*
Cellular factors
    Accelerated platelet turnover*
    Reduced CYP3A metabolic activity*
    Increased ADP exposure*
    Upregulation of the $P2Y_{12}$ pathway*
    Upregulation of the $P2Y_1$ pathway*
    Upregulation of P2Y-independent pathways*
Genetic factors
    Polymorphisms of CYP
    Polymorphisms of GPIa
    Polymorphisms of $P2Y_{12}$
    Polymorphisms of GPIIIa
    Polymorphisms of MDR1

*Factors potentially leading to reduced clopidogrel-induced effects in diabetic subjects. CYP, cythochrome P450; MDR1, multidrug resistance protein 1. (Adapted from ref. 41.)

tients compared with nondiabetic subjects have higher degrees of platelet reactivity, there is still a broad range of responsiveness (46). Importantly, within this cohort composed only of diabetic patients, those with high platelet reactivity had a more than threefold risk of long-term adverse events (Fig. 3) (46). These patients were also characterized by a general dysfunctional status of their platelets, as revealed by the presence of high platelet reactivity using agonists testing for multiple signaling pathways.

Numerous mechanisms may account for inadequate clopidogrel response in diabetic patients, in particular type 2 diabetic subjects. Human platelets are targets of insulin, which interacts with its own receptor on the surface of the platelet, leading to loss of G_i activity. This results in suppression of cAMP, inhibition of $P2Y_{12}$ signaling, and reduced platelet reactivity (47–48). However, platelets of type 2 diabetic patients are also affected by the insulin resistance phenomenon that characterizes these patients, which results in decreased sensitivity to insulin (9). This results in upregulation of the $P2Y_{12}$ pathway and increased platelet reactivity. Other mechanisms linked to clopidogrel nonresponsiveness in diabetic patients include increased exposure to ADP, increased cytosolic levels of calcium, and increased platelet turnover (4,41).

Future directions
The limitations of currently available antiplatelet agents that are used for preven-
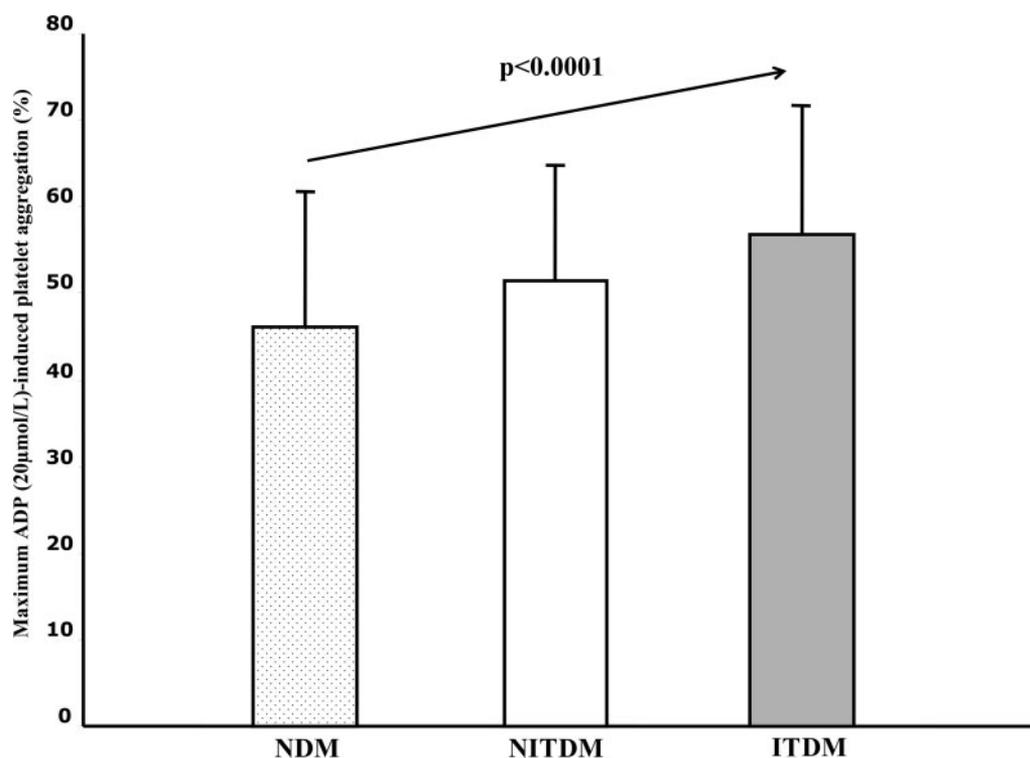
Figure 2— *Platelet aggregation following ADP (20 μmol/l) stimuli in nondiabetic patients (NDM) (n = 65), non–insulin-treated diabetic patients (NITDM) (n = 133), and insulin-treated diabetic patients (ITDM) (n = 68). Platelet aggregation is higher in diabetic than in nondiabetic patients, and insulin-treated diabetic patients have the highest degree of platelet reactivity. Platelet aggregation progressively increases across nondiabetic, non–insulin-treated, and insulin-treated patients, respectively. (Adapted from ref. 43.)*
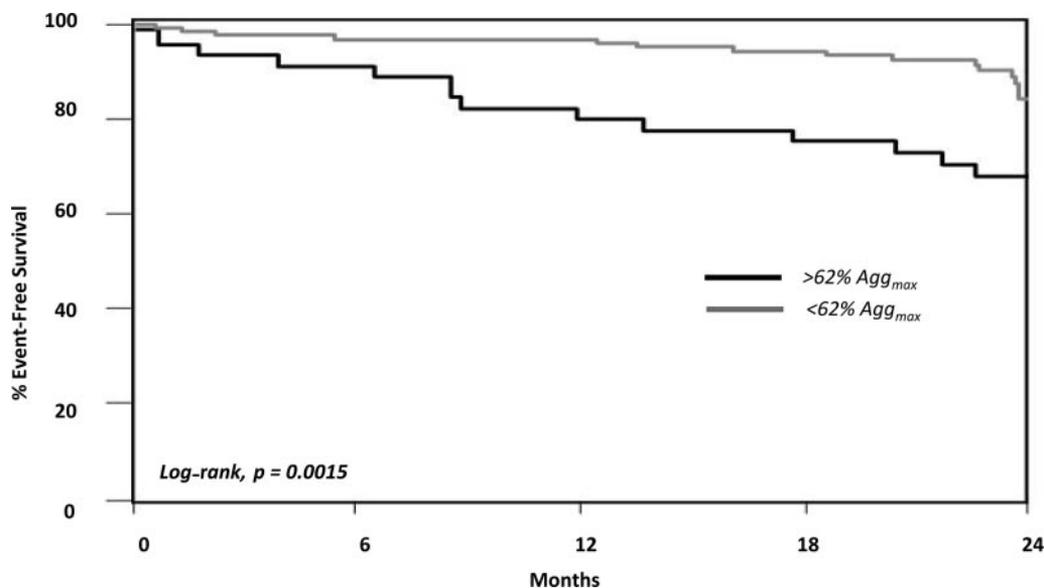
Figure 3— *Cumulative event-free survival from cardiovascular events in diabetic patients* (n = 173) *with and without high platelet reactivity. The cutoff value to define high platelet reactivity using receiver operating characteristic analysis was 62% maximum ADP (20 μmol/l)-induced platelet aggregation (Agg$_{max}$). The major adverse cardiac event rate was significantly higher in patients with platelet reactivity above the cutoff value compared with those below this cutoff value (37.7 vs. 13.3%, respectively; odds ratio 3.96 [95% CI 1.8–8.7]; P < 0.0010). Multivariate Cox regression analyses showed high platelet reactivity (HR 3.35 [95% CI 1.68–6.66]; P = 0.001) to be the strongest independent predictor of major adverse cardiac events. (Adapted from ref. 46.)*

tion of atherothrombotic events and that have been shown to be of greater magnitude among diabetic patients underscore the need for more specific antiplatelet treatment regimens, particularly in these patients. Three strategies are proposed to achieve this goal and include dose modification, adjunctive antiplatelet drug usage, and use of newer agents.

Antiplatelet drug dose modification. The rationale behind increasing the dose of currently available antiplatelet agents is that this strategy may potentially increase the bioavailability of the drug and therefore enhance platelet inhibition. The dose of aspirin used in clinical practice broadly varies (75–325 mg/daily). Although there are no randomized studies assessing which of these doses is most effective, the ATC clearly shows that higher aspirin doses are not associated with better clinical outcomes (15–16). On the contrary, aspirin dose is associated with a higher risk of adverse effects, mainly gastrointestinal bleed (5). Although functional studies have shown that aspirin dosing may have an impact on its COX-1–independent effects, the significance of which is unknown, this does not affect the degree of COX-1 blockade, which requires that low doses of aspirin be fully inhibited (5). Given that diabetic platelets are characterized by increased turnover rates (4), it has been advocated that multiple daily dosing

rather than an increase in a once-daily dose may be more beneficial in these patients. Aspirin, in fact, has a very short half-life and therefore will not achieve blockade of newly generated platelets. However, the functional and clinical implications of once-daily versus multiple daily aspirin administrations are unknown.

Several studies have focused on how to overcome clopidogrel nonresponsiveness by increasing the dose (49–50). The Optimizing Anti-Platelet Therapy in Diabetes MellitUS (OPTIMUS) study selectively examined type 2 diabetic patients with high platelet reactivity in their chronic phase of clopidogrel treatment (50). The use of a 150-mg clopidogrel maintenance dose resulted in greater platelet inhibition than use of a 75-mg dose. Recent findings have shown that enhanced P2Y$_{12}$ inhibition achieved with high-dose clopidogrel in diabetic patients also reduces thrombin generation (51). However, despite this strategy, a significant number of patients remained above the therapeutic threshold of posttreatment platelet reactivity adopted in this study (50,52). Despite the lack of large-scale clinical trial data sufficiently powered to assess the safety and efficacy of high-dose clopidogrel, PCI guidelines provide a class I recommendation (level of evidence C) for high (600 mg) clopidogrel

loading doses (53). A class IIb level of evidence C is available for 150-mg maintenance dose. The ongoing Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS (CURRENT/OASIS7) trial will evaluate whether high loading and maintenance dosing of clopidogrel achieves better clinical outcomes than standard dosing in ACS patients undergoing PCI (clinical trial reg. no. NCT00335452). In addition, all patients will be randomized to receive low (75–100 mg) or high (300–325 mg) doses of aspirin.

Use of adjunctive antiplatelet agents. Using additional antiplatelet therapy on top of therapies currently used for secondary prevention of ischemic events may be a way of achieving enhanced platelet inhibition in diabetic patients. However, there are limited options to reach this goal. GP IIb/IIIa inhibitors usage is limited to the acute phase of therapy. These drugs have been shown to be particularly beneficial in ACS patients undergoing PCI, in particular diabetic patients (27). However, in the current era of high-dose clopidogrel usage, GP IIb/IIIa inhibitors failed to show any clinical benefit in non-ACS settings, including in diabetic patients (28). It has been recently suggested that GP IIb/IIIa inhibitors, however, may be beneficial in non-ACS

settings in patients undergoing nonurgent PCI with aspirin or clopidogrel resistance. However, a subgroup analysis of the Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study failed to show any significant differences associated with this strategy among diabetic subjects (54). Another approach to improve platelet inhibition in diabetic patients is with the adjunctive use of cilostazol, a phosphodiesterase III inhibitor (Fig. 1). Several studies have shown the benefit of triple antiplatelet therapy with aspirin, clopidogrel, and cilostazol, particularly in diabetic patients treated with bare-metal as well as drug-eluting stents (55–56). These findings may be attributed to a greater degree of platelet inhibition achieved with adjunctive treatment with cilostazol in diabetic patients, as shown in the OPTIMUS-2 study (57). This study showed that cilostazol, which increases intraplatelet cAMP levels, enhances phosphorylation of vasodilator-stimulated phosphoprotein (VASP), thereby increasing $P2Y_{12}$ inhibitory effects (57). However, the major drawback of cilostazol therapy is its high prevalence of side effects (e.g., migraine, palpitations, and gastrointestinal disturbances), which frequently lead to drug withdrawal (57).

Use of new agents. The development of newer antiplatelet agents that can effectively and safely inhibit platelet activation and aggregation processes appears to be the most promising strategy in view of a hypothetical future in which antiplatelet drug regimens will be used according to individual need. This may imply use of drugs that may target pathways that are dysfunctional in a particular patient population, such as subjects with diabetes. Accordingly, picotamide has been suggested as a treatment alternative to aspirin (58). Picotamide, in fact, inhibits both thromboxane A_2 synthase and thromboxane A_2 receptors and, therefore, is able to block the effect of thromboxane A_2 that is generated through COX-1 escape mechanisms, which may represent a pathway leading to an inadequate aspirin-induced effect in diabetic patients (Fig. 1). In the Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics (DAVID) study, a total of 1,209 adults aged 40–75 years with type 2 diabetes and PAD were randomized to receive picotamide (600 mg b.i.d.) or aspirin (320 mg o.d.) for 24 months (58). The cumulative incidence of the 2-year overall mortality was significantly lower among patients treated with picotamide (3.0%) than in those who received aspirin (5.5%), with a relative risk ratio for picotamide versus aspirin of 0.55 (95% CI 0.31–0.98). However, although the combined end point of mortality and morbidity had a slightly lower incidence in the picotamide group, this difference did not reach statistical significance. Other thromboxane inhibitors, such as ramatroban, ridogrel, and S18886, are also currently under clinical investigation and may represent future treatment alternatives (59) (Fig. 1).

There are several $P2Y_{12}$ receptor antagonists under advanced clinical investigation (60). These include prasugrel, ticagrelor (AZD6140), cangrelor, and elinogrel (PRT128) (Fig. 1). Prasugrel and ticagrelor are administered orally, cangrelor is for intravenous use, and elinogrel can be administered via both routes. Prasugrel is an irreversible agent, whereas ticagrelor, cangrelor, and elinogrel are reversible. All agents have increased potency and are associated with less response variability compared with clopidogrel (60). The pharmacodynamic and pharmacokinetic profiles of these drugs and the preclinical and early-phase clinical data go beyond the scope of this review and are described in detail elsewhere (60). Encouraging clinical outcome data from large-scale phase III testing is available for prasugrel (61). Prasugrel is a third-generation thienopyridine that, like clopidogrel, selectively and irreversibly blocks the ADP $P2Y_{12}$ receptor (62). However, prasugrel has a more favorable pharmacokinetic profile because, compared with clopidogrel, it is more efficiently transformed into its active metabolite, which leads to more prompt, potent, and predictable degrees of platelet inhibition as shown in numerous pharmacodynamic studies even when compared with platelet inhibition associated with both high and maintenance dosing of clopidogrel (62). The clinical implications of these more favorable pharmacological properties were evaluated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) comparing prasugrel with clopidogrel in patients ($n = 13,608$) with moderate- to high-risk ACS who underwent PCI (62). After a median duration of 14.5 months, the primary end point (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 12.1 vs. 9.9% of clopidogrel- vs. prasugrel-treated patients, respectively (hazard ratio [HR] 0.81; $P < 0.001$). However, there was an increased risk of major bleeding observed in 2.4% of the patients receiving prasugrel compared with 1.8% of the patients receiving clopidogrel (HR 1.32; $P = 0.03$). Despite the increased bleeding risk, the prespecified net clinical benefit analysis, defined as the composite of efficacy and bleeding end points, still favored prasugrel (12.2 vs. 13.9% of prasugrel- and clopidogrel-treated patients, respectively; HR 0.87; $P = 0.004$). Of note, the patients who benefited most from prasugrel therapy were diabetic (63). There were 3,146 subjects with a preexisting history of diabetes, of whom 776 were receiving insulin therapy. The primary end point was reduced significantly with prasugrel in diabetic subjects compared with patients without diabetes (12.2 vs. 17.0%, respectively; HR 0.70; $P < 0.001$). A benefit of prasugrel was observed in diabetic subjects on insulin (14.3 vs. 22.2%; HR 0.63; $P = 0.009$) and those not on insulin (11.5 vs. 15.3%; HR 0.74; $P = 0.009$) (Fig. 4). Myocardial infarction was reduced with prasugrel by 40% in diabetic subjects (8.2 vs. 13.2%; HR 0.60; $P < 0.001$). Similar TIMI major hemorrhage rates were observed in diabetic subjects receiving clopidogrel or prasugrel (2.6 vs. 2.5%, respectively; HR 1.06; $P = 0.81$). The net clinical benefit with prasugrel was greater for subjects with diabetes (14.6 vs. 19.2%; HR 0.74; $P < 0.001$) than without diabetes (11.5 vs. 12.3%; HR 0.92; $P = 0.16$). The OPTIMUS-3 trial is currently evaluating the pharmacodynamic differences between prasugrel (60-mg loading dose and 10-mg maintenance dose) and clopidogrel (600-mg loading dose and 150-mg maintenance dose), specifically in patients with type 2 diabetes (clinical trial reg. no. NCT00642174). This study will provide mechanistic insights into the clinical benefits achieved with clopidogrel observed in the TRITON-TIMI 38 study, particularly in diabetic patients.

Ultimately, antiplatelet agents that inhibit targets other than COX-1 and $P2Y_{12}$ are currently under advanced clinical development. These are warranted in order to overcome the multitude of stimuli leading to enhanced platelet reactivity, which characterizes diabetic patients. Thrombin is the most potent platelet stimulus, and thrombin generation is pronounced in diabetic patients. Several thrombin receptor antagonists that block the protease-
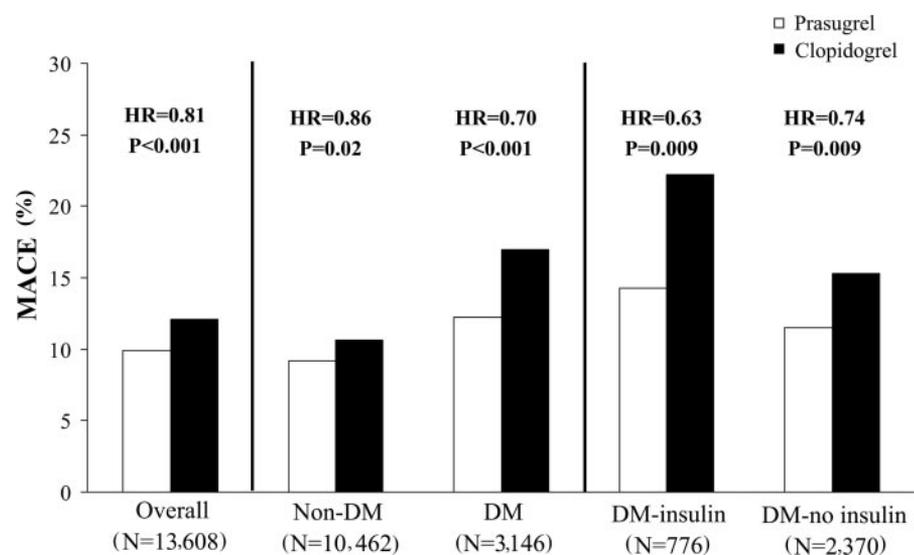
Figure 4— *The major adverse cardiac event (MACE) rate representing the primary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in the TRITON trial comparing prasugrel with clopidogrel in the overall study population according to the presence or absence of diabetes (DM) and use of insulin therapy among diabetic patients.*

activated receptor (PAR)-1 subtype (E5555, SCH 530348) are currently under clinical investigation (64) (Fig. 1). It is important to emphasize that thrombotic processes are the result of not only platelets but also plasmatic factors. Therefore, a better understanding of how these plasmatic components contribute to adverse outcomes in high-risk patients, including those with diabetes, is pivotal for the development of tailored treatment strategies (65). Indeed, the large number of agents specifically targeting various plasmatic components involved in thrombotic processes will be useful as this field further develops.

Conclusions

Diabetic patients have an increased risk of atherothrombotic events in part attributed to platelet dysfunction, which characterizes this patient population. In particular, diabetic patients have increased platelet reactivity warranting use of platelet-inhibiting strategies in order to reduce their ischemic risk. Although currently approved antiplatelet treatment strategies have proven useful in improving outcomes, diabetic patients continue to have a higher risk of adverse cardiovascular events compared with that in nondiabetic patients. Reduced antiplatelet drug responsiveness, including resistance to currently used oral antiplatelet agents, has been suggested to play a role in these worse outcomes. These findings underscore the need of individualized antiplatelet treatment regimens in diabetic patients. Novel and more potent antiplatelet agents currently under clinical development will be useful in efforts to reach these therapeutic goals.

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