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Antithrombotic Therapy for Atherosclerotic Cardiovascular Disease Risk Mitigation in Patients With Coronary Artery Disease and Diabetes Mellitus

ABSTRACT: Patients with diabetes mellitus (DM) are characterized by enhanced thrombotic risk attributed to multiple mechanisms including hyperreactive platelets, hypercoagulable status, and endothelial dysfunction. As such, they are more prone to atherosclerotic cardiovascular events than patients without DM, both before and after coronary artery disease (CAD) is established. In patients with DM without established CAD, primary prevention with aspirin is not routinely advocated because of its increased risk of major bleeding that largely offsets its ischemic benefit. In patients with DM with established CAD, secondary prevention with antiplatelet drugs is an asset of pharmacological strategies aimed at reducing the risk of atherosclerotic cardiovascular events and their adverse prognostic consequences. Such antithrombotic strategies include single antiplatelet therapy (eg, with aspirin or a $P2Y_{12}$ inhibitor), dual antiplatelet therapy (eg, aspirin combined with a $P2Y_{12}$ inhibitor), and dual-pathway inhibition (eg, aspirin combined with the vascular dose of the direct oral anticoagulant rivaroxaban) for patients with chronic ischemic heart disease, acute coronary syndromes, and those undergoing percutaneous coronary intervention. Because of their increased risk of thrombotic complications, patients with DM commonly achieve enhanced absolute benefit from more potent antithrombotic approaches compared with those without DM, which most often occurs at the expense of increased bleeding. Nevertheless, studies have shown that when excluding individuals at high risk for bleeding, the net clinical benefit favors the use of intensified long-term antithrombotic therapy in patients with DM and CAD. Several studies are ongoing to establish the role of novel antithrombotic strategies and drug formulations in maximizing the net benefit of antithrombotic therapy for patients with DM. The scope of this review article is to provide an overview of current and evolving antithrombotic strategies for primary and secondary prevention of atherosclerotic cardiovascular events in patients with CAD and DM.

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Diabetes mellitus (DM) is a global and growing pandemic. Based on statistics from the World Health Organization, the worldwide estimated number of people with DM has risen from 108 million in 1980 to 422 million in 2014, and the overall prevalence from 4.7% to 8.5% within the same period.[1] Among its numerous adverse prognostic consequences, DM is well established as a major risk factor for coronary artery disease (CAD) and CAD-related complications, including myocardial infarction (MI), cerebrovascular events and cardiovascular death.[2] Recently, there has been a growing amount of literature providing an unparalleled increase in evidenced for health care providers caring for patients with DM.[2] Despite some degree of undeniable progress, however, the toll of DM on cardiovascular risk remains substantial.

The higher risk of atherosclerotic cardiovascular disease (ASCVD) in patients with DM stems, at least in part, from their enhanced prothrombotic risk profile. In fact, people with DM present with hyperreactive platelets that are more prone to adhesion, activation, aggregation and, eventually, thrombus formation.[3] Other factors, including a hypercoagulable status and endothelial dysfunction, also contribute the prothrombotic milieu that characterizes patients with DM. Antithrombotic therapy with antiplatelet and/or anticoagulant drugs is thus the asset of pharmacological interventions aimed at preventing the adverse prognostic consequences of such prothrombotic status. Because antithrombotic therapy carries an unavoidable increased risk of bleeding complications, health care professionals that consider intensifying the antithrombotic management of patients with DM (ie, to lower their heightened ASCVD risk) should also be aware of the net clinical benefit of their desired strategy based on patients' individual risk profiles, values and clinical setting.

Several trials conducted in patients without apparent CAD and in patients with established ASCVD or CAD (eg, chronic coronary syndromes [CCS], acute coronary syndromes [ACS], or recent percutaneous coronary intervention [PCI]) are available to define the role of antithrombotic therapy in primary and secondary ASCVD prevention, respectively. The availability of results from more recent trials conducted in cohorts with DM, or in cohorts that include a sizeable proportion of patients with DM, affords the opportunity for a reappraisal of the current evidence (Figure 1). The scope of this review article is to provide the reader with an updated summary

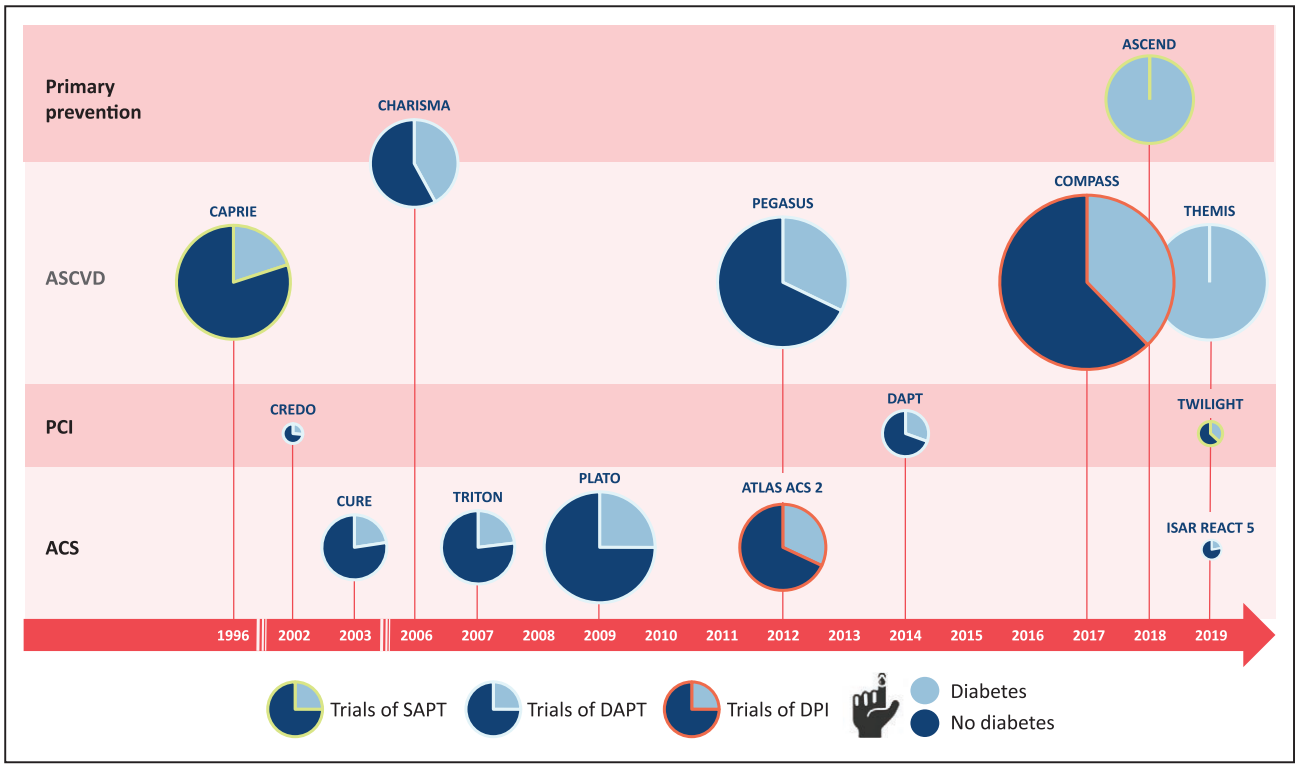

Figure 1. Timeline of landmark studies of antithrombotic therapy and proportion of patients with diabetes mellitus.
The size of the circles is proportional to the number of patents randomized. ACS indicates acute coronary syndromes; ASCEND, A Study of Cardiovascular Events in Diabetes; ASCVD, atherosclerotic cardiovascular disease; ATLAS ACS 2, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CREDO, Clopidogrel for the Reduction of Events During Observation; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; DAPT, dual antiplatelet therapy; DPI, dual-pathway inhibition; ISAR REACT 5, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; PCI, percutaneous coronary intervention; PEGASUS, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; PLATO, Platelet Inhibition and Patient Outcomes; SAPT, single antiplatelet therapy; THEMIS, Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel; and TWILIGHT, Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

of the latest clinical evidence on primary and secondary ASCVD prevention with antithrombotic pharmacotherapy for patients with DM with or at high risk for CAD.

GENERAL CONSIDERATIONS ON PLATELET FUNCTION AND ANTITHROMBOTIC THERAPY IN DIABETES

The mechanisms underlying the prothrombotic milieu that characterizes patients with DM is complex and multifactorial. A detailed description of these mechanisms goes beyond the scope of this review and is described in detail elsewhere.[4] In brief, platelets of DM individuals typically display a hyperreactive phenotype where several mechanisms are synergistically involved (Figure 2).[4] These include increased platelet turnover attributable to higher generation activity in the bone marrow,[5] leading to younger circulating platelets that are hyperreactive per se, and a series of other factors that are intrinsic and characteristic of the diabetic platelet, such as upregulation of platelet signaling pathways that can be a consequence of genetic variants of the insulin receptor substrate 1 gene,[6] increased expression of receptors (eg, purinergic $P2Y_{12}$ receptor and glycoprotein IIb/IIIa),[7–9] and higher levels of platelet-derived microvesicles.[10,11] Factors extrinsic to the platelet also contribute to their hyperreactive phenotype such as increased circulating levels of procoagulant factors (eg, von Willebrand factor) or endothelial dysfunction.[3,4,12,13] Overall, these factors may also determine impaired pharmacodynamic response to antithrombotic agents with modest potency, as broadly described for clopidogrel.[14] However, impaired drug metabolism because of reduced hepatic activity of the cytochrome P450 system in patients with DM may also explain reduced plasma levels of active metabolites of antiplatelet drugs such as thienopyridines that require hepatic oxidation to become functional.[15–17] Notably, the category of patients with DM is sufficiently broad that subsets of patients with different thrombotic risk have been identified, such as those on insulin therapy,[18] with impaired renal function or elevated fibrinogen levels.[19–22] In fact, while patients with DM as a category are known to have an increased prevalence of high platelet reactivity while on treatment with certain antiplatelet agents, high platelet reactivity rates are of greater prevalence in those with the aforementioned conditions.

Because high platelet reactivity is associated with an enhanced risk of long-term adverse ASCVD events in

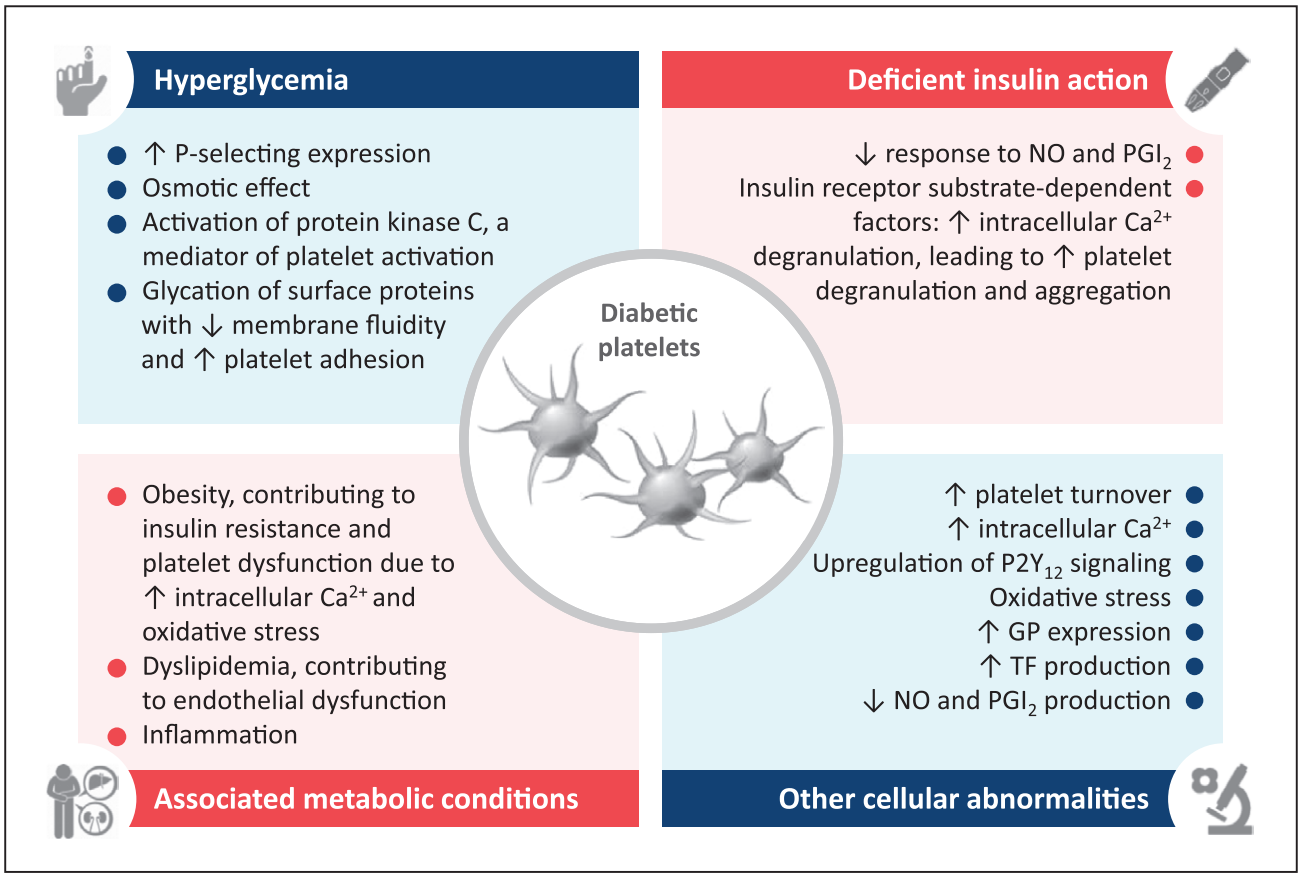

Figure 2. Mechanisms involved in platelet dysfunction in patients with diabetes mellitus.
Several mechanisms contribute to platelet dysfunction in diabetes mellitus patients, including hyperglycemia, insulin deficiency, associated metabolic conditions, and other cellular abnormalities. GP indicates glycoprotein; NO, nitric oxide; $P2Y_{12}$, purinergic $P2Y_{12}$ receptor; PGI_2, prostaglanding I2; and TF, tissue factor.

patients with DM and CAD,[23,24] strategies aimed at increasing the degree of platelet inhibition obtained with antiplatelet drugs are of outmost interest. For example, the use of drugs administered twice-daily may have greater pharmacodynamic efficacy given the high platelet turnover rates in patients with DM compared with once daily administration. To this extent, results from several studies have shown that a bis in die regimen of low-dose aspirin is associated with better platelet inhibitory effects compared with a standard once-daily regimen in patients with DM.[25,26] A number of antiplatelet drugs may exert varying pharmacodynamic effects in patients with DM. This is particularly the case for clopidogrel for the reasons mentioned above. In light of the considerable number of patients treated with dual antiplatelet therapy (DAPT) consisting of the combination of aspirin and a $P2Y_{12}$ inhibitor for the prevention of ischemic recurrences and given that clopidogrel is the most commonly prescribed $P2Y_{12}$ inhibitor, identifying strategies associated with optimized antiplatelet effects in patients with DM has been subject of extensive investigation. Ticagrelor and prasugrel are newer generation $P2Y_{12}$ inhibitors that achieve a faster onset and greater magnitude of platelet inhibition compared with clopidogrel.[27–29] Pharmacodynamic studies conducted selectively in patients with DM have shown that standard dosing regimens of ticagrelor (administered twice-daily) exerts similar or greater $P2Y_{12}$ inhibition of platelet reactivity in comparison with prasugrel (administered once-daily).[30,31] Importantly, the antiplatelet effect of $P2Y_{12}$ inhibitors may be sensitive not only to the type of drug, but also to the dose and possibly the proportion of receptor occupancy.[32] Of note, the lower 60-mg BID dose of ticagrelor yields a high level of platelet inhibition that is consistent with the 90-mg BID dose, regardless of DM status.[33] Recently, the pharmacodynamic superiority of the ticagrelor 60-mg BID dosing regimen compared with clopidogrel 75-mg once daily was also shown in a study selectively conducted in patients with DM undergoing elective PCI.[34] Given the multiple pathways leading to enhanced platelet reactivity in patients with DM, alternative strategies aimed at optimizing platelet inhibition have consisted in the addition of a third antiplatelet agent (ie, triple antiplatelet therapy) to standard DAPT with aspirin and clopidogrel that can thus modulate these alternative pathways. Such strategies include adding cilostazol, which by inhibiting phosphodiesterase III increases intraplatelet cAMP levels and enhances platelet inhibition, or vorapaxar, which by inhibiting the protease-activated receptor (PAR)-1 prevents thrombin-mediated platelet activation that is among the most potent of platelet stimuli.[35,36] The clinical implications of these pharmacodynamic findings are described in the following sections.

PRIMARY ATHEROSCLEROTIC CARDIOVASCULAR RISK PREVENTION WITH ANTITHROMBOTIC DRUGS IN DIABETES MELLITUS

The impact and role of antithrombotic therapy for primary prevention is controversial and of challenging interpretation because (1) the benefits, if present, must be weighed against the risk of bleeding, but (2) it is difficult to compare the severity of the vascular events avoided and the bleeding events caused. Intuitively, individuals in whom a more favorable benefit:risk ratio is anticipated are those at higher baseline ischemic or thrombotic risk, including those with DM.

Among commercially available antithrombotic agents, aspirin is the only drug that has been widely investigated in the setting of primary ASCVD prevention. In studies published before 2018, the risk of bleeding with aspirin clearly exceeded its modest benefit in both patients with and without DM.[3] In the 10-year follow-up study of the JPAD (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) trial, published in 2017, aspirin was not found to affect the risk for cardiovascular events but increased the risk for gastrointestinal bleeding in 2539 patients with DM.[37] Of 3 large trials published in 2018, 1 (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) did not include participants with DM,[38] 1 (ASPREE [Aspirin in Reducing Events in the Elderly]) included only 11% DM participants,[39] and the third (ASCEND [A Study of Cardiovascular Events in Diabetes]) included only DM participants.[40]

In ASCEND, 15 480 participants with DM were randomized to enteric-coated aspirin at a dose of 100 mg once daily or placebo.[40] The primary efficacy end point, a composite of death from any vascular cause (excluding confirmed intracranial hemorrhage), MI, stroke (excluding confirmed intracranial hemorrhage), or transient ischemic attack was significantly reduced by 12% in the aspirin arm during a mean follow-up of 7.4 years (8.5% versus 9.6%; rate ratio, 0.88; 95% CI, 0.79–0.97; *P*=0.01). However, major bleeding events were increased by 29% (4.1% versus 3.2%; rate ratio, 1.29; 95% CI, 1.09–1.52; *P*=0.003), particularly at the level of the gastrointestinal tract and other extracranial sites. The results of ASCEND are relevant to the topic of primary prevention in DM not only because of the highly specific study design, but also because they were obtained in a contemporary era of patients on high rates of statins and blood pressure–lowering drugs.[41] However, it should be noted that only 1 in 4 patients was treated with a proton pump inhibitor, the use of which could potentially amplify the net benefit of aspirin in this setting. In fact, studies have shown that patients with DM may be more vulnerable to gastrointestinal bleeding induced by aspirin because of the presence of

vascular disease impairing mucosal integrity.[42] On this background, the number of patients needed to treat (NNT) to prevent 1 primary end point event was 91, and the number of patients needed to treat to cause a major bleeding event (ie, number needed to harm [NNH]) was 111, with a NNT:NNH ratio of 0.8, indicating only a marginal benefit in the overall ASCEND cohort (Figure 3). Yet, the risk of causing bleeding surpassed or closely balanced the potential benefit across all categories of baseline ischemic risk, including patients who had a predicted 5-year vascular risk of 10% or more, which makes the ASCEND strategy not routinely recommended.[40]

In ASPREE, aspirin did not reduce the risk of all-cause death and a secondary end point of cardiovascular disease defined as fatal coronary heart disease, MI, stroke, or hospitalization for heart failure.[39,43] In a subgroup analysis, no significant interaction between DM and the treatment effect for such secondary end point was observed (*P* for interaction = 0.74). After the publication of ASCEND and ASPREE, the APPRAISE (Aspirin in Primary Prevention of Cardiovascular Disease in Diabetes) consortium conducted an updated meta-analysis of 34 227 participants with DM and no known ASCVD from 12 published trials.[44] Comparing aspirin use with no aspirin at a median treatment duration of 5.0 years, there was

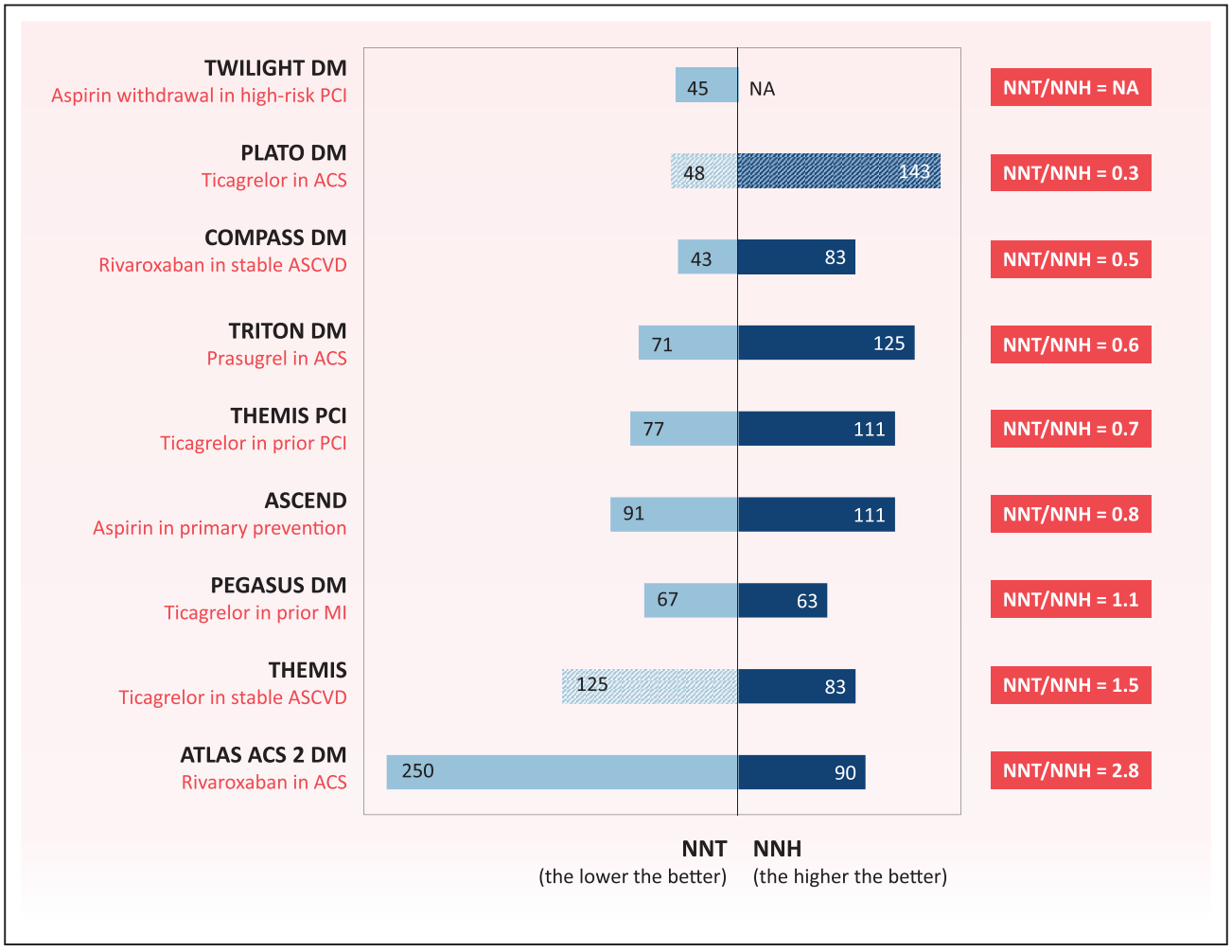

Figure 3. Trade-offs of benefit and harm in patients with diabetes mellitus from landmark trials of antithrombotic therapy.
Number needed to treat (NNT) and number needed to harm (NNH) are reported. Dashed bars refers to outcomes that were not significantly different between experimental and control arms. The ratio between NNT and NNH indicates treatments in which the benefit exceeded the harm (<1.0) or treatment in which the harm exceeded the benefit (>1.0). Ratios for PLATO (Platelet Inhibition and Patient Outcomes) and THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) are reported for exploratory purposes and should be interpreted with caution. In addition, THEMIS-PCI (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study–Percutaneous Coronary Intervention) is a subgroup analysis of THEMIS. In TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients After Coronary Intervention) the benefit was significantly in favor of the investigational strategy for the bleeding outcome and nonsignificantly for the ischemic outcome, hence the NNT:NNH ratio calculation is not applicable. Outcomes refer to primary efficacy and safety end point as defined in the respective trials. Because these definitions varied considerably across trials, particularly with respect to bleeding, this graph should not be intended as a ranking of the different antithrombotic strategies illustrated. ACS indicates acute coronary syndrome; ASCEND, A Study of Cardiovascular Events in Diabetes; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CVD, cardiovascular disease; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; PEGASUS, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; and TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel.

a 11% significant reduction in the risk of major adverse cardiovascular events (a combination of cardiovascular mortality, MI, and stroke outcomes), with a NNT of 95. These figures are consistent with those of ASCEND. Aspirin did not reduce mortality but significantly reduced stroke in analyses restricted to doses ≤100 mg once daily and treatment durations >5 years.[44] In the context of multiple statistical tests for interaction conducted, the results of such subgroup analyses should be interpreted with caution and require replication in other studies. Similarly, although there were no statistically significant effects of aspirin use on major bleeding and other bleeding events, the confidence intervals for these estimates were large and such results potentially imprecise. The results of this analysis support that the use of low dose aspirin for primary ASCVD prevention should be individualized and based on individual baseline ASCVD and bleeding risks.

Current Recommendations

Current recommendations from contemporary guidelines for primary ASCVD prevention with aspirin in patients with and without DM are cautious and largely based on risk assessment. The 2020 guidelines on the primary prevention of ASCVD from the American College of Cardiology and the American Heart Association do not provide DM-specific recommendations on aspirin use.[45] The 2019 guidelines from the European Society of Cardiology on DM, pre-DM, and ASCVD, developed in collaboration with the European Association for the Study of Diabetes, do not recommend aspirin in patients with DM at moderate ASCVD risk (defined as young patients with DM duration <10 years and without other risk factors).[46] However, selective use of aspirin may be considered in individuals at high or very high risk or individuals at high risk in the absence of clear contraindications (Figure 4).[46] Interestingly, the European Society of Cardiology guidelines acknowledges the need to assess the effect of body mass, especially of moderate-to-severe obesity, on antiplatelet drug responsiveness and effectiveness in patients with DM, and with a call to investigate higher dose strategies for such patients.[46,47] Of note, in a meta-analysis of individual patient data from 10 primary prevention trials, the ability of low dose aspirin (ie, 75–100 mg) to reduce cardiovascular events decreased with increasing weight, with benefit seen in people weighing 50 to 69 kg, but not in those weighing 70 kg or more. Higher doses of aspirin (≥325 mg) had the opposite interaction with body weight, reducing cardiovascular events only at higher weight. Importantly, stratification by body size also revealed harms attributable to excess dosing, further suggesting the opportunity to tailoring the dose of aspirin.[47] In this context, it should be noted, however, that there was no evidence of superior efficacy of low-dose aspirin in low-weight individuals compared with high-weight individuals in the ASCEND trial.[41]

Future Directions

Another randomized investigation of aspirin from primary ASCVD prevention is ongoing. ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) is an open-label trial assessing whether 100 mg once daily of aspirin prevents ASCVD events in DM individuals ≥50 years without clinically manifested ASCVD and treated with simvastatin (starting dose 20 mg/once daily).[48] The primary combined end-point will include cardiovascular death, MI, stroke, and hospital admission for ASCVD causes (ie, ACS, transient ischemic attack, unplanned revascularization procedures, peripheral artery disease). This trial is of interest because it may clarify the putative additive effects of aspirin and statins in DM. According to the trial protocol, a total of 515 first events will be necessary to 90% power the trial for detecting a reduction in the risk of major cardiovascular events of 25%.[48] The recruitment of ACCEPT-D has been completed and the results are pending, with no anticipated date because of the event-driven nature of the investigation.

SECONDARY ATHEROSCLEROTIC CARDIOVASCULAR RISK PREVENTION WITH ANTITHROMBOTIC DRUGS IN DIABETES MELLITUS

The role of antithrombotic therapy after an ASCVD event is well established. The risk of increased bleeding is largely offset by the benefit in reducing ischemic and thrombotic outcomes. However, the intensity of antithrombotic therapy in terms of, eg, number of drugs, doses, frequency and duration, is more controversial and still a matter of debate. In particular, the tendency of patients with DM to experience more ischemic or thrombotic events may favorably alter the net benefit of antithrombotic strategies as compared with non-DM or all-comers populations. In this context, 3 strategies have been tested that will be discussed herein: single antiplatelet therapy, DAPT, and dual-pathway inhibition (DPI). A description of intravenous therapies goes beyond the scope of this manuscript.

Single Antiplatelet Therapy

In 1994, the first meta-analysis of the Antiplatelet Trialists' Collaboration found that antiplatelet therapy (mostly with aspirin) is similarly effective in patients with ASCVD, regardless of the presence of DM.[49] There are no large-scale investigations specifically comparing other antiplatelet agents with aspirin selectively in

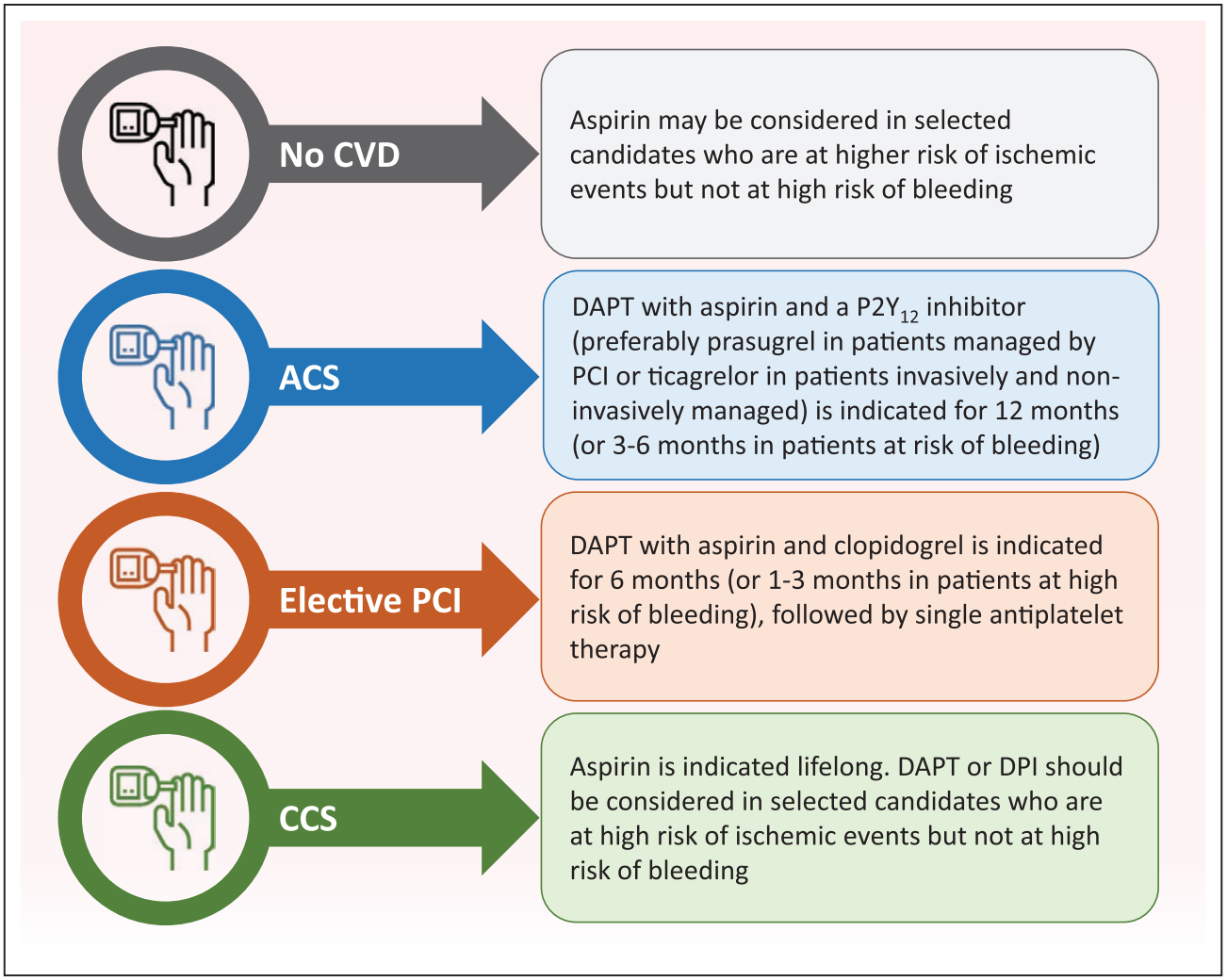

Figure 4. Antithrombotic strategies for patients with diabetes mellitus.
Options for intensified antithrombotic therapy in selected patients with CCS include DAPT with aspirin plus any of the $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor or prasugrel) or DPI with aspirin plus the vascular dose of rivaroxaban. The treatment options represent a summary of general guidelines recommendations from the American College of Cardiology (ACC)/American Heart Association (AHA) or the European Society of Cardiology (ESC). ACS indicates acute coronary syndromes; CCS, chronic coronary syndromes; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DPI, dual-pathway inhibition; and PCI, percutaneous coronary intervention.

patients with DM. In CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events), a head-to-head comparison of aspirin and clopidogrel in patients with preexisting ASCVD manifested as either recent ischemic stroke, recent MI, or symptomatic peripheral artery disease, the superiority of clopidogrel was amplified in patients with DM with greater absolute benefit, who represented 20% of the study population.[50] In particular, for every 1000 patients with DM treated with clopidogrel, 21 vascular events were prevented, which increased to 38 among those who were insulin-treated. Conversely, the absolute reduction in the composite vascular primary end point with clopidogrel compared with aspirin was not statistically significant in patients without DM. Although the relative risk reduction achieved with clopidogrel was similar in patients with and without DM (*P* for interaction=0.36), the absolute risk reduction was larger in those with DM because of their higher event rates. In the overall trial, gastrointestinal bleeding occurred less frequently with clopidogrel. Despite these results, clopidogrel has never really found its way in clinical practice to replace aspirin as a single antiplatelet agent of choice for long-term secondary prevention in patients with established ASCVD.

In a meta-analysis of 42 108 patients from 9 randomized trials comparing $P2Y_{12}$ inhibitors (ie, clopidogrel or ticagrelor) and aspirin in patients with established ASCVD, patients who received a $P2Y_{12}$ inhibitor had a borderline reduction for the risk of MI (OR, 0.81; 95% CI, 0.66–0.99), with an NNT of 244.[51] Conversely, the risks of stroke, all-cause death, vascular death, and major bleeding did not differ between groups. These findings were consistent regardless of the type of $P2Y_{12}$ inhibitor used and suggest that the benefit of $P2Y_{12}$ inhibitor

monotherapy when compared head to head with aspirin may be of debatable clinical relevance, particularly in view of the high NNT to prevent a MI and the absence of any effect on all-cause and vascular mortality.

In the field of PCI, several investigations recently compared a strategy of single antiplatelet therapy (eg, clopidogrel or ticagrelor) with DAPT in patients at lower risk and/or treated with more potent $P2Y_{12}$ inhibitors, in the attempt to reduce the risk of bleeding after the initial period from the procedure, while preserving a sufficient degree of ischemic or thrombotic protection (Figure 5).[52] The GLOBAL LEADERS trial, the first completed large-scale trial of such an aspirin-free strategy, failed to demonstrate a significant reduction in death or Q-wave MI at 2 years with ticagrelor monotherapy after 1 month of DAPT,[53] and this result was consistent in patients with DM (*P* for interaction=0.33).[54] The trial did not show a reduction in bleeding with ticagrelor monotherapy, both in patients with and without DM (*P* for interaction=0.53), but bleeding events were not centrally adjudicated, which may result into some degree of under-reporting and bias. Nevertheless, GLOBAL LEADERS did not display any significant adverse safety harm on ischemic endpoints with the single antiplatelet strategy.

Contrary to the results from GLOBAL LEADERS, 3 subsequent trials successfully demonstrated a benefit of $P2Y_{12}$ inhibitor monotherapy started at 1 or 3 months from PCI.[55–57] In STOP-DAPT 2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent 2), the primary end point, a composite of ischemic and bleeding outcomes, was noninferior with clopidogrel monotherapy compared with DAPT, which was consistent in patients with and without DM (*P* for interaction=0.65).[55] Clopidogrel monotherapy was not only noninferior but also superior in the overall cohort (relative risk reduction [RRR], 36%; *P*=0.04), driven by less bleeding, with no difference in efficacy in the DM (RRR, 30%; *P*=0.26) and non-DM (RRR, 42%; *P*=0.07) subgroups.[55] In SMART-CHOICE (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents), clopidogrel monotherapy was noninferior (but not superior) to DAPT at 12 months for ischemic events, and no heterogeneity was observed by DM status (*P* for interaction=0.84).[56] Bleeding was reduced by clopidogrel monotherapy, with no apparent heterogeneity (*P* for interaction=0.17).[56] In TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) ticagrelor monotherapy was associated with a lower incidence of clinically relevant and particularly severe bleeding than DAPT with ticagrelor plus aspirin.[57] Patients with DM comprised 37% of the randomized cohort. The RRRs for clinically significant bleeding were 35% (*P*=0.01) and 50% (*P*<0.001) in patients with and without DM, respectively, with no significant heterogeneity (*P* for interaction=0.23).[58] Some potential heterogeneity, in the context of no adjustment for multiple testing, was observed for a composite of ischemic outcomes, with a RRR of 23% (*P*=0.14) and a relative risk increase of 24% (*P*=0.21) in patients with and without DM, respectively (*P* for interaction=0.05).[58] An exploratory analysis of net adverse clinical events which included severe bleeding and ischemic events showed a 39% decrease (*P*=0.001) in patients with DM treated with ticagrelor monotherapy with a statistically significant interaction (*P* for interaction=0.004), suggesting an enhanced benefit of this approach in DM compared with patients without DM. These findings have been suggested to be attributed to the greater potential for gastrointestinal toxicity, and hence its associated negative prognostic implications, associated with standard enteric-coated formulations of aspirin in DM compared with patients without DM.[42] Moreover, standard enteric-coated formulations of aspirin have shown to be more susceptible to impaired absorption leading to reduced bioavailability, particularly among patients with DM, which may potentially affect its clinical efficacy.[59] Overall, these results point toward reduced bleeding without any ischemic harm of clopidogrel or ticagrelor monotherapy after a short period of DAPT in patients with DM undergoing PCI. However, these data need to be considered as hypothesis generating because patients with DM were only a proportion of patients and the power for subgroup analyses was low. Moreover, randomization was not stratified according to DM status. It is also important to note that the lack of an aspirin-only arm prevents a clear understanding of the respective merits of $P2Y_{12}$ inhibitor versus aspirin monotherapies in these investigations.

Dual Antiplatelet Therapy

In patients with ACS, DAPT with clopidogrel was superior to placebo in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, and DAPT with prasugrel and ticagrelor were superior to clopidogrel in the TRITON TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) and PLATO (Platelet Inhibition and Patient Outcomes) trials, respectively (Figure 5).[60–62] In CURE, the reduction in clinical events with clopidogrel was directionally consistent in patients with and without DM, although the reduction in patients with DM was not formally significant likely as the reflection of the smaller sample size of the subgroup (*P* for interaction is not available).[60] In TRITON TIMI 38, prasugrel significantly reduced the primary ischemic end point by 30% in patients with DM and by 14% in patients without DM (*P* for interaction=0.09).[63] Major bleeding not related to coronary artery bypass

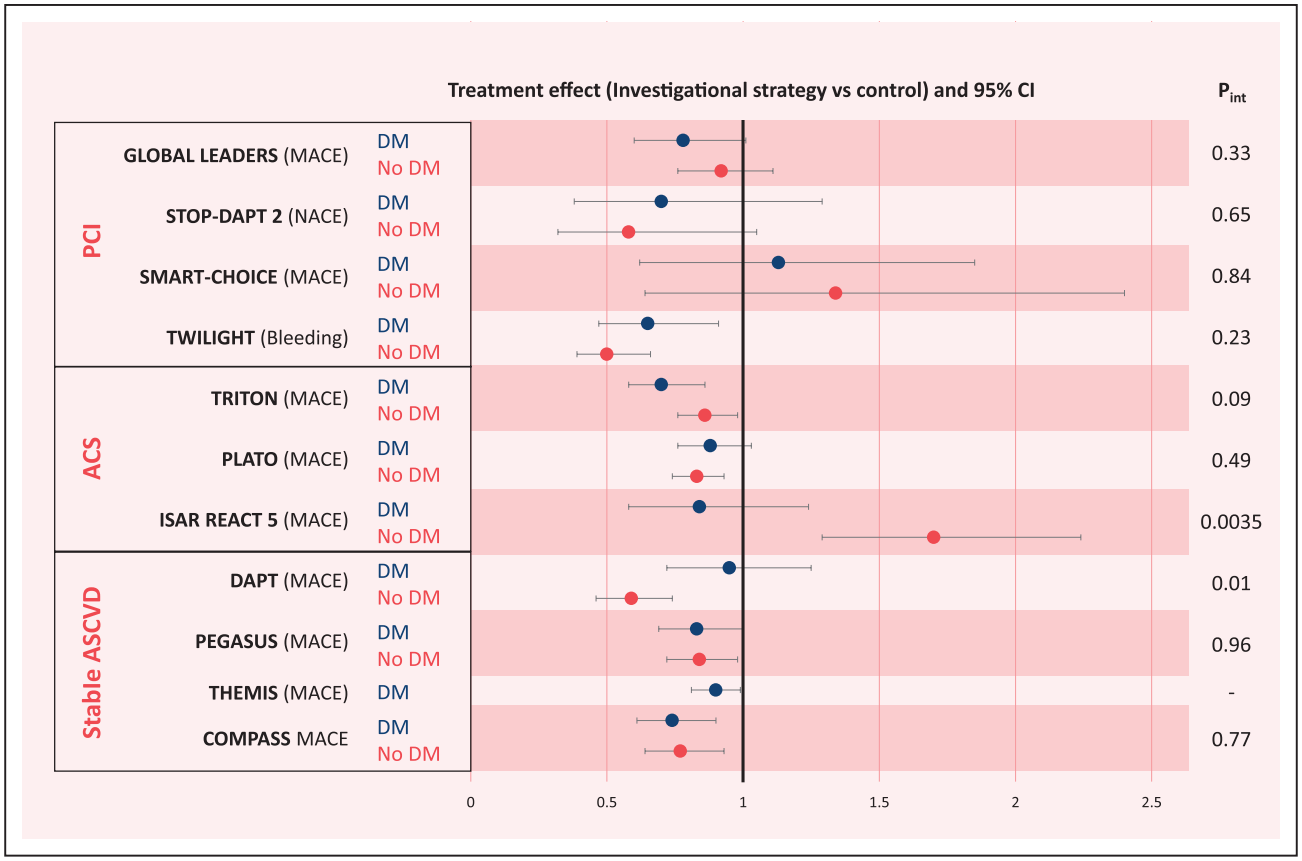

Figure 5. Outcomes by diabetes mellitus status in landmark trials of secondary prevention with $P2Y_{12}$ inhibitor monotherapy after percutaneous coronary intervention, DAPT after an acute coronary syndrome, and DAPT or DPI in patients with stable atherosclerosis.
Outcomes of PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) are reported for comparison of DAPT with aspirin and the approved dose of ticagrelor 60 mg twice daily. Outcomes of COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) are reported for comparison of DPI with rivaroxaban 2.5 mg once daily. ACS indicates acute coronary syndrome; CI, confidence interval; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; DPI, dual-pathway inhibition; ISAR REACT 5, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; MACE, major adverse cardiovascular events; NACE, net adverse cardiovascular events; PCI, percutaneous coronary intervention; Pint, *P* for interaction; PLATO, Platelet Inhibition and Patient Outcomes; SMART-CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOP-DAPT 2, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent 2; THEMIS, Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel; and TWILIGHT, Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

grafting was significantly increased in the overall trial and particularly in patients without DM, but the *P* for interaction between major bleeding and DM status was 0.29, meaning the lack of significant heterogeneity between patients with and without DM.[63] In patients with DM from TRITON TIMI 38, the NNT and NNH were 71 and 125, respectively, with a favorable NNT/NNH ratio of 0.6 (Figure 3). Similarly, in PLATO, ticagrelor significantly reduced the primary ischemic end point with no apparent heterogeneity in patients with and without DM (*P* for interaction=0.49).[64] There was no heterogeneity between patients with or without ongoing insulin treatment, while ticagrelor more markedly reduced the primary end point in patients with HbA1c above the median. Major bleeding was not increased in either patients with or without DM (*P* for interaction=0.21), but this result was sensitive to the bleeding definition adopted.[64] In patients with DM from PLATO, the NNT and NNH were 48 and 143, respectively, with a potentially favorable NNT/NNH ratio of 0.3 (Figure 3). In a subanalysis of PLATO, a gradient of risk was observed according to the presence or absence of DM and chronic kidney disease, showing the greatest absolute risk reduction in patients with both conditions.[65] Ticagrelor and prasugrel were then compared head-to-head in ACS patients in the phase 4 ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, where the incidence of ischemic events was significantly lower among those who received prasugrel and no difference in bleeding was observed between treatment groups.[66] Increased ischemic event rates with ticagrelor were observed in patients without DM, while the point estimate of the hazard ratio versus prasugrel went in the opposite direction in patients without DM, displaying a significant treatment-by-DM status interaction (*P* for interaction=0.0035; Figure 5).[67]

In patients with ASCVD or at high risk of ASCVD events from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, DAPT with clopidogrel and aspirin was not superior to aspirin alone and there was a trend toward more bleeding events particularly in patients with no established ASCVD.[68] A post hoc analysis of CHARISMA suggested that DAPT may actually increase overall and cardiovascular death in patients with DM with microalbuminuria.[69] No formal interaction analysis was provided, but the magnitude of the treatment effect of DAPT was visually larger in patients without DM than in those with DM. Because CHARISMA included also candidates to primary prevention (80% with DM), where the effect of antiplatelet therapy is potentially detrimental as discussed above, a better role for DAPT in higher risk candidates could not be excluded.

The concept of DAPT for secondary prevention has been abandoned for years and then renewed by the PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial, where DAPT with ticagrelor and aspirin proved superior to aspirin alone in reducing ischemic events in patients with previous MI.[70] The RRR in the primary ischemic end point with ticagrelor was consistent for the pooled 90 mg and 60 mg twice daily doses versus placebo in patients with DM (RRR, 16%; *P*=0.035) and without DM (RRR, 16%; *P*=0.013; *P* for interaction=0.99).[71] Because patients with DM were at higher risk of ischemic events, the absolute risk reduction tended to be greater in patients with versus without DM (1.5% versus 1.1%). Additionally, in patients with DM, ticagrelor reduced cardiovascular death by 22% and coronary heart disease death by 34%.[71] This result was consistent in the analysis restricted to the now approved dose of ticagrelor 60 mg twice daily and aspirin (*P* for interaction=0.96; Figure 5). Bleeding was increased with the 60-mg dose in both patients with and without DM (*P* for interaction=0.79).[71] In patients with DM from PEGASUS, the NNT and NNH were 67 and 63, respectively, with an almost neutral NNT:NNH ratio of 1.1 (Figure 3).

Finally, a well-powered specific comparison of DAPT and aspirin for secondary prevention in patients with DM with CAD but without a previous MI was realized in the THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) trial (Figures 3 and 5).[72] Patients were initially randomized to assume ticagrelor at a dose of 90 mg BID or placebo but, during the study, based on the newly available results of the PEGASUS trial, the protocol was amended and the dose of ticagrelor reduced from 90 mg BID to 60 mg BID. At a median follow-up of 39.9 months, the primary composite efficacy end point was significantly lower with ticagrelor compared with placebo (7.7% versus 8.5%; *P*=0.04), corresponding to Kaplan–Meier estimates of 6.9% and 7.6%, respectively, at 36 months. This result was driven by a significant reduction in MI and stroke, with no differences in cardiovascular death and all-cause death.[72] A significantly higher rate of major bleeding events was observed with ticagrelor (2.2% versus 1.0%, respectively; *P*<0.001). Ticagrelor also increased the risk of spontaneous intracranial bleeding, while it did not increase fatal bleeding.[72] The NNT:NNH ratio in THEMIS was 1.5, suggesting more harm than benefit (Figure 3). A predefined analysis of patients with history of previous PCI enrolled in the THEMIS trial, encompassing 58% of the overall trial population called THEMIS-PCI, represents a cohort of particular interest given that this population had been previously exposed to DAPT and thus potentially considered to have enhanced benefit compared with patients who had not been previously treated with DAPT. In THEMIS-PCI, at a median follow-up of 3.3 years, fewer patients receiving ticagrelor and aspirin had a primary efficacy end point event compared with placebo and aspirin (7.3% versus 8.6%; HR, 0.85; 95% CI, 0.74–0.97; *P*=0.01), a finding that was not replicated in patients without previous PCI (*P* for interaction=0.16).[73] Major bleeding was increased 2-fold, but there were no differences in intracranial and fatal bleeding. The net clinical benefit of DAPT with ticagrelor and aspirin was significant in patients with previous PCI in contrast to patients without (*P* for interaction=0.012). This benefit was present irrespective of time from most recent PCI.[73] Overall, the results of PEGASUS and THEMIS-PCI point toward a benefit of prolonged DAPT with the 60-mg BID regimen of ticagrelor in addition to aspirin in selected patients (eg, at low risk of bleeding) with DM. This includes those with a previous MI (PEGASUS-like) or those without a previous major cardiovascular event (THEMIS-PCI–like). On the contrary, the benefit in lower risk THEMIS-like patients without previous PCI is offset by the increased risk of major bleeding, including intracranial bleeding. Based on the results of the THEMIS trial, the US Food and Drug Administration has approved ticagrelor 60 mg BID for patients with CAD without a previous ACS event independent of DM status and independent of previous PCI, thus extrapolating the trial results to a broader patient population.

Patients undergoing PCI or with previous PCI partially overlap with the ACS and ASCVD scenarios previously discussed. After a 12-month course of DAPT, the DAPT trial demonstrated that prolonging the combination of clopidogrel or prasugrel and aspirin for additional 18 months reduces the risk of ischemic events compared with aspirin alone in patients undergoing PCI.[74] In the DM cohort of the DAPT trial (N=3037), continued DAPT resulted only in a trend toward a reduction of MI, with clearly attenuated effect compared with patients without DM, where this reduction was significant (*P* for interaction=0.01; Figure 5).[74,75] These observations may question the efficacy of clopidogrel in high-risk patients with

DM with previous PCI. Indeed, these clinical observations may be attributed to the well-established pharmacodynamic observations of impaired clopidogrel-induced antiplatelet effects in patients with DM.[14–17] To this extent, the use of a ticagrelor 60 mg BID in addition to aspirin as described above represents a treatment option with clear efficacy, albeit the risk of bleeding should be taken into consideration. Identifying patients at high risk for bleeding in whom prolonging intensified antithrombotic regimens, including DAPT, can be associated with potential harm and should thus be avoided is critical. Standardized definitions of high bleeding risk are now available that may be helpful in decision-making after PCI.[76] If a $P2Y_{12}$ inhibitor monotherapy regimen with ticagrelor at a 60-mg BID dose (ie, without aspirin) can reduce bleeding complications while maintaining efficacy is unknown and a topic of ongoing investigation.

Dual-Pathway Inhibition

The rationale of adding a direct oral anticoagulant to antiplatelet therapy is that of achieving a synergistic effect by reducing the circulating levels of thrombin, a potent platelet activator that is also involved in the coagulation cascade.[77] This approach has been tested in a number of trials using different direct oral anticoagulants, but only those conducted with rivaroxaban used at a so-called vascular dose regimen (2.5 mg BID) have been completed and met their primary endpoints in large cohorts of patients with ACS and ASCVD in the ATLAS ACS 2 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2) and COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trials, respectively.[78,79] In ATLAS ACS 2, there was no apparent heterogeneity in the treatment effect of the rivaroxaban-based strategy between the DM and non-DM subgroups (*P* for interaction=0.14). However, the absolute magnitude of reduction in the primary ischemic end point was larger in patients without DM. Major bleeding was significantly increased regardless of DM status (*P* for interaction=0.58). The NNT:NNH ratio was 2.8, indicating more harm than benefit. Because of these bleeding concerns, the strategy of adding rivaroxaban to DAPT, although approved by some drug regulating authorities, but not by the US Food and Drug Administration, has not been widely embraced in clinical practice. In COMPASS, among patients with ASCVD defined as CAD or peripheral artery disease, those assigned to DPI with rivaroxaban plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone.[79] In the DM subanalysis of COMPASS, there was a consistent and similar RRR for the 3-year benefit of rivaroxaban plus aspirin versus placebo plus aspirin in patients with (RRR, 26%; *P*=0.002) and without (RRR, 23%; *P*=0.005) DM (*P* for interaction=0.77; Figure 5).[80] Given their higher baseline risk, the absolute benefits appeared larger in patients with DM. Also, because the bleeding hazards were similar among patients with and without DM, the prespecified net benefit for rivaroxaban appeared particularly favorable in patients with DM (*P* for interaction=0.001).[80]This is consistent with the observation of a favorable NNT:NNH ratio of 0.5, indicating more benefit than arm in the DM cohort (Figure 3).

Current Recommendations

Based on studies discussed above, a 2020 scientific statement from the American Heart Association appraises a number of antithrombotic strategies on clinical management of CCS patients with type 2 DM, without issuing formal recommendations.[81] The 2019 European Society of Cardiology guidelines on DM, pre-DM, and ASCVD currently recommends aspirin at a dose of 75 to 160 mg for secondary prevention.[46] In light of the available evidence and the available guidelines, we endorse that ticagrelor or prasugrel be preferentially given in combination with aspirin in patients with DM and ACS for 1 year, and in those who undergo PCI or coronary artery bypass grafting. Prolongation of DAPT beyond 12 months with clopidogrel or the reduced ticagrelor dose, for up to 3 years, is also advised in patients with DM who have tolerated DAPT without major bleeding complications. The 2019 European Society of Cardiology guidelines on CCS provides a more general recommendation about the opportunity to add a second antithrombotic drug on top of aspirin for long-term secondary prevention in patients at high or moderate risk of ischemic events and without high bleeding risk.[46] These guidelines do not provide recommendations on which option (DAPT or DPI) should be preferred. An understanding of the study entry criteria for the PEGASUS and COMPASS trials and the specific outcomes prevented, particularly in the DM cohorts of these studies, may help discern the choice of a DAPT versus DPI strategy if intensified antithrombotic therapy is desired.[70,71,79,80] Building on guidelines recommendations, treatment suggestions for secondary prevention in patients undergoing PCI and those with ACS or ASCVD are summarized in Figure 4.

Alternative Strategies and Future Directions

The established efficacy of aspirin for secondary prevention, as well as its broad access, have prompted a number of pharmacodynamic investigations aimed at understanding strategies or formulations that can overcome some of the shortcomings with current regimens. Increasing the maintenance dose of aspirin of aspirin has been suggested as a strategy to optimize platelet inhibitory effects in patients with DM.[82] The safety and efficacy of 81-mg versus 325-mg once-daily aspirin

used for secondary prevention in patients with ASCVD is currently being evaluated in the ongoing ADAPT-ABLE (Aspirin Dosing-A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial.[83] Although the study is not being selectively conducted in patients with DM, its large sample size may offer important insights into this population. However, the high platelet turnover rates that characterize patients with DM raises challenges in achieving adequate antiplatelet protection by simply increasing the dose of aspirin. In fact, aspirin has limited systemic bioavailability after oral ingestion (the pharmacokinetic half-life of aspirin is only 15 minutes).[5] Therefore, if aspirin is administered only once daily, irrespective of dose, this will not allow for newly generated platelets released into circulation to be exposed to aspirin and inevitably lead to incomplete cyclooxygenase-1 blockade of the circulating platelet pool and enhanced platelet reactivity. Administering aspirin twice daily would have the theoretical advantage of overcoming this limitation as also demonstrated in a number of pharmacodynamic studies selectively conducted in patients with DM showing enhanced antiplatelet effects compared with once daily aspirin administration.[25,26] The clinical implications of these pharmacodynamic observations are being investigated in 2 ongoing clinical studies selectively conducted in patients with DM with or without coronary artery disease (Table). The ANDAMAN (Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome) trial is comparing treatment with enteric-coated aspirin twice a day versus enteric-coated aspirin once per day on a composite end-point of ischemic events at 18 months in patients with DM and ACS (NCT02520921). The CARING (Chronotherapy With Low-dose Aspirin for Primary Prevention of Cardiovascular Events in Subjects With Impaired Fasting Glucose or Diabetes) trial is exploring the hypothesis that aspirin exerts administration time–dependent effects in participants with impaired fasting glucose or type 2 DM (NCT00725127). Participants are randomized to aspirin at different circadian times (ie, on awakening or at bedtime), with a primary end point of combined cardiovascular, cerebrovascular and renal events at 5 years.

The peculiarities of platelet biology in patients with DM have also led to the development of novel aspirin formulations. An extended-release acetylsalicylic acid formulation was developed to provide 24-hour antithrombotic effects with once-daily dosing.[84] This formulation provided sustained antiplatelet effects during 24 hours in patients with type 2 DM. However, such extended release formulation cannot be used when rapid onset of antiplatelet effects is required for which an immediate-release aspirin formulation should be used. Moreover, despite these measures to enhance the efficacy of aspirin, aspirin leads to gastrointestinal mucosal injury.[85] Gastrointestinal toxicity associated with aspirin therapy can determine direct mucosal injury, leading to a variety of consequences ranging from dyspeptic symptoms affecting drug adherence to gastrointestinal bleeding.[86,87] An approach to reduce gastrointestinal toxicity induced by aspirin is to modify its formulation,[88] such as using enteric coated tablets. Enteric-coated aspirin tablets, which dissolve pH dependently in the small intestine rather than the stomach, are the most commonly used aspirin formulation. Although endoscopy studies have shown that short term-treatment with anti-inflammatory doses of enteric-coated aspirin reduce the risk of acute mucosal lesions and microbleedings in healthy volunteers compared with immediate release aspirin, subsequent studies conducted in patients chronically consuming low-dose aspirin (enteric coated or buffered formulations) for cardioprotection failed to demonstrate a reduction in the risk of clinically relevant ulcer complications, including bleeding. These observations can indeed be attributed also to the systemic nature of aspirin effects which inhibits cyclooxygenase-derived prostaglandins production that are key in epithelial mucus production, microvascular

Table. Ongoing Randomized Clinical Trials of Antithrombotic Therapy Selectively in Participants With Diabetes Mellitus

Study Name	Participants	Intervention	Control	Outcome	Time	Expected primary completion
ACCEPT-D (ISRCTN48110081)	5170 participants with DM treated with statins	Aspirin 100 mg once daily	No aspirin given	Cardiovascular death, MI, stroke, hospitalization attributable to cardiovascular causes	End of the study period	Event-driven
ANDAMAN (NCT02520921)	2574 participants with DM and ACS	Aspirin 100 mg twice daily	Aspirin 100 mg once daily	Death, MI, stroke, urgent coronary revascularization and/or stent thrombosis, acute arterial thrombotic event	18 mo	2021
CARING (NCT00725127)	3200 participants with impaired fasting glucose or type 2 DM	Aspirin 100 mg on awakening	Aspirin 100 mg at bedtime	Composite of cardiovascular, cerebrovascular, and renal events	5 yr	2025

Source: clinicaltrials.gov. ACCEPT-D indicates Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; ACS, acute coronary syndromes; ANDAMAN, Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome; CARING, Chronotherapy With Low-dose Aspirin for Primary Prevention of Cardiovascular Events in Subjects With Impaired Fasting Glucose or Diabetes; DM, diabetes mellitus; and MI, myocardial infarction.

mucosal perfusion and wound healing in the gastrointestinal tract.[89] Moreover enteric coated formulations are associated with delayed and impaired aspirin absorption, contributing to variability in its pharmacokinetic and pharmacodynamic profile, particularly in patients with DM.[59,90] Reduced pharmacological efficacy may contribute to reduced cardiovascular protection.[91] Overall, these observations emphasize the need for aspirin formulations with a more favorable safety profile while maintaining pharmacological efficacy. PL-ASA is a novel lipid–aspirin complex liquid formulation developed to mitigate disruption of the epithelial phospholipid layer of the gastric mucosa without delaying absorption. PL-ASA was shown to be bioequivalent from a pharmacokinetic and pharmacodynamic perspective to immediate release aspirin in healthy volunteers[92] and, importantly, in patients with DM.[59] Bioavailability of PL-ASA does not appear to be affected by food that is known to impact enteric-coated aspirin.[93] Ultimately, PL-ASA has been associated with reduced acute gastric mucosal lesion formation during short-term exposure compared with immediate release aspirin.[94] The long-term safety and cardiovascular efficacy of PL-ASA is unknown.

Cilostazol is a phosphodiesterase III inhibitor that increases intraplatelet cAMP levels and in turn enhances platelet inhibition by augmenting the phosphorylated status of vasodilator-stimulated phosphoprotein, a key intraplatelet mediator of $P2Y_{12}$ signaling.[95] Pharmacodynamic studies have shown that, in patients treated with aspirin and clopidogrel, the adjunctive use of cilostazol enhances levels of $P2Y_{12}$ inhibition.[35] Patients with DM have reduced cAMP levels which may explain why the magnitude of platelet inhibitory effects achieved with adjunctive clopidogrel use is greater among patients with DM compared with those without DM.[96,97] The observations may explain why clinical studies, mostly conducted in Asian populations, have shown enhanced benefits of cilostazol therapy in patients with DM.[98,99] Of note, the reduction in ischemic events with cilostazol occurred without any increase in bleeding which has been suggested to be attributed to the protective effects of cilostazol on endothelial cells.[95] However, nonbleeding side effects (ie, headaches, palpitations, and gastrointestinal disturbances) are common with cilostazol therapy.

Thrombin receptor antagonists also represent an attractive class of antiplatelet agents for the treatment of patients with DM with atherosclerotic manifestations.[100] Vorapaxar is an orally active, highly selective, competitive, slowly reversible PAR-1 inhibitor that exerts potent inhibition of thrombin-mediated platelet aggregation,[101] without affecting clot kinetics. In a large-scale clinical trial, vorapaxar in adjunct to standard-of-care antiplatelet therapy (mostly aspirin and clopidogrel) significantly reduced recurrent thrombotic events in patients with previous atherothrombosis, particularly those with previous MI or peripheral arterial disease, albeit at the cost of increased bleeding.[102] Notably, the absolute risk reduction of thrombotic complications associated with the adjunctive use of vorapaxar was greater among patients with, versus without, DM.[103] These observations appeared to be attributable to the enhanced baseline risk of patients with DM given that pharmacodynamic data have shown that the effects of vorapaxar was associated with reduced platelet-mediated thrombogenicity irrespective of DM status on a background of aspirin and clopidogrel therapy.[36] Moreover, after aspirin withdrawal, platelet-mediated thrombogenicity increased, particularly among patients with DM, an observation that was not seen with the use of more potent $P2Y_{12}$ inhibitors, supporting the importance of having adequate alternative antithrombotic regimens if an aspirin-free approach is being considered in patients with DM.[36,52,58,104]

CONCLUSIONS

Despite remarkable progresses in recent years, the rates of atherothrombotic events remain substantial in patients with DM. Those without established CAD have marginal benefit from administration of low-dose aspirin that comes at the expense of increased rates of bleeding if given on a routine basis. Alternative administration modalities based on presumptive circadian effects of aspirin are under investigation, aiming at improving the net benefit of aspirin in this setting. Studies investigating antithrombotic agents other than aspirin for primary ASCVD prevention are lacking. On the other hand, patients with DM and established CAD strongly benefit from antithrombotic treatment in several scenarios, including ACS, PCI, and CCS. After an ACS, DAPT consisting of the adjunctive use of a $P2Y_{12}$ inhibitor to aspirin and, preferably, prasugrel (in patients managed by PCI) or ticagrelor (in patients invasively and noninvasively managed), is the standard of care for at least 12 months. In CCS patients undergoing PCI, DAPT with the combination of aspirin and clopidogrel is the accepted standard for at least 6 months. However, shorter durations of DAPT (1–3 months in CCS and 3–6 months in ACS) may be considered in selected patients to reduce the risk of bleeding. Dropping of a $P2Y_{12}$ inhibitor (eg, at 3 months post-PCI) has recently emerged as a bleeding reduction strategy without compromising efficacy. In patients with CCS at increased ischemic risk, there is emerging evidence on the net benefit of prolonging DAPT, consisting in the combination of aspirin with any of the $P2Y_{12}$ inhibitors (although the best evidence is with low dose ticagrelor in previous MI patients), or using DPI, consisting in the combination of aspirin with a vascular dose of rivaroxaban. Because the risk of bleeding with these strategies remains as a

counterargument to their adoption, patient selection must be carefully considered.

ARTICLE INFORMATION

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