Aspirin for Primary Cardiovascular Prevention in Patients with Diabetes: Uncertainties and Opportunities

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Abstract

The use of the antiplatelet agent aspirin (acetylsalicylic acid) was previously routinely recommended for the primary prevention of cardiovascular (CV) events in patients with diabetes, but recent large-scale randomized trials have failed to demonstrate a sizeable net clinical benefit with a once-daily, low-dose (81–100 mg) regimen in this population. Previous pharmacokinetic and pharmacodynamic studies have suggested that the aspirin formulation (enteric-coated) and dosing schedule (once daily) studied in randomized trials for primary prevention of CV events defining contemporary clinical practice may not leverage the full potential of the drug, particularly in patients with diabetes. Indeed, the diabetic platelets bear characteristics that increase their thrombotic potential and alter their pharmacologic response to the drug. Consequently, the appropriateness of studying a uniform aspirin regimen in landmark primary prevention trials needs to be revisited. In this review, we present the evidence showing that diabetes not only increases baseline platelet reactivity, but also alters platelet response to aspirin through different mechanisms including a faster platelet turnover rate. Obesity, which is frequently associated with diabetes, also impacts its pharmacokinetics via an increase in distribution volume. Small-scale pharmacokinetic and pharmacodynamic studies have suggested that the relative aspirin resistance phenotype observed in patients with diabetes may be reversed with a twice-daily dosing schedule, and with nonenteric-coated aspirin formulations. Properly powered randomized controlled trials investigating the efficacy and safety of aspirin dosing schedules and formulations tailored to the population of patients with diabetes are urgently required to optimize patient care.

Keywords
► diabetes mellitus
► aspirin resistance
► aspirin
► antiplatelet agent
► platelet

Introduction

Patients with diabetes present a disproportionally higher risk of cardiovascular (CV) disease compared with nondiabetic individuals with otherwise similar characteristics.[1,2] For this reason, pharmacological and healthy lifestyle interventions beyond glycemic control are recommended to improve CV outcomes in this high-risk population.[3,4] The use of the antiplatelet agent aspirin (acetylsalicylic acid) was previously routinely recommended for the primary prevention of CV events in patients with diabetes, but recent large-scale randomized trials have failed to demonstrate a sizeable net clinical benefit with a once-daily, low-dose (81–100 mg) regimen in this population.[5–8] Given the lack of evidence in favor of aspirin, international guidelines currently recommend against its routine use in patients with diabetes without established atherosclerotic CV disease (ASCVD), and favor an individualized approach weighing both expected protection against ischemic events and potential bleeding risk conferred by the drug.[1,3,4,7,9]

Previous pharmacokinetic and pharmacodynamic studies have suggested that the aspirin formulation (enteric-coated [EC]) and dosing schedule (once daily) studied in randomized trials for primary prevention of CV events defining contemporary clinical practice may not leverage the full potential of the drug, particularly in patients with diabetes. Indeed, the diabetic platelets bear characteristics that increase their thrombotic potential and alter their pharmacologic response to the drug.[10–12] Consequently, the appropriateness of studying a uniform aspirin regimen in landmark primary prevention trials needs to be revisited.[5,13,14] In this review, the evidence underlying the clinical use of aspirin in primary prevention of CV disease in patients with diabetes will be summarized, the pharmacokinetic and pharmacodynamic particularities of aspirin in this population will be examined, and the impact of EC formulations and of body weight on clinical outcomes will be discussed.

Aspirin in Primary Prevention of Cardiovascular Events in Patients with Diabetes

Current clinical practice guidelines advocate against the routine use of aspirin for the primary prevention of CV disease.[1,2,4,9,15] The 2019 American College of Cardiology/American Heart Association guidelines on the primary prevention of CV disease provide a low-grade recommendation for consideration of low-dose aspirin for patients 40 to 70 years old at high risk of ASCVD and at low risk of bleeding (class IIb), but not among adults >70 years or bearing a high bleeding risk (class III).[4] Similarly, the 2019 European Society of Cardiology (ESC) guidelines on diabetes, prediabetes, and CV diseases recommend against the use of aspirin in primary prevention in general (class III), except in patients with diabetes at high or very high CV risk, in which aspirin may be considered in the absence of clear contraindications (class IIb).[9,15] This recommendation was reiterated in the more recent 2021 ESC guidelines on CV disease

prevention in clinical practice.[16] The 2021 American Diabetes Association guidelines also mention that aspirin may be considered in primary prevention in patients who have diabetes and who are at increased CV risk (level A).[3]

Four major randomized trials contributed to the evidence underlying current clinical practice regarding the use of aspirin in primary prevention in patients with diabetes, summarized in ►Table 1. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial studied the efficacy of low-dose aspirin (81–100 mg daily) to prevent CV events over a median follow-up of 4.4 years in patients with type 2 diabetes without history of CV disease.[6] Among the 2,539 participants, aspirin was not associated with a significantly lower risk of events (hazard ratio [HR]: 0.80; 95% confidence interval [CI]: 0.58–1.10; $p = 0.16$).[6] A follow-up extension of the JPAD trial, in which 1,621 of the original participants were followed for a median of 10.3 years, yielded consistent findings with a neutral effect of low-dose aspirin and no difference in total bleeding events or in hemorrhagic strokes.[8] In the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) randomized trial, 1,276 patients with type 1 or type 2 diabetes and asymptomatic peripheral arterial disease were randomized to receive aspirin 100 mg daily or placebo. Aspirin was not associated with a significant reduction in the primary ischemic endpoint at 6.7 years (HR: 0.98; 95% CI: 0.76–1.26; $p = 0.86$).[17] More recently, the larger A Study of Cardiovascular Events iN Diabetes (ASCEND) trial randomized 15,480 patients with diabetes (94.1% type 2), without CV disease, to EC low-dose aspirin (100 mg daily) or placebo, and followed them for a mean of 7.4 years.[5] Aspirin reduced the occurrence of a first serious vascular event (composite of nonfatal myocardial infarction [MI], nonfatal stroke, transient ischemic attack (TIA), and death from any vascular cause) compared with placebo (8.5 vs. 9.6%, respectively; HR: 0.88; 95% CI: 0.79–0.97; $p = 0.01$). This 1.1% absolute reduction in serious vascular events was counterbalanced by a significant increase in the risk of major bleeding of a similar magnitude (4.1 vs. 3.2%, respectively; relative risk [RR]: 1.29; 95% CI: 1.09–1.52; $p = 0.003$), of which most (41.3%) were from the gastrointestinal (GI) system. Of note, TIA was added to the original composite primary endpoint while recruitment was ongoing to increase the statistical power of the trial. Aspirin was not associated with a significant reduction in the rate of the original primary endpoint excluding TIA (HR: 0.92; 95% CI: 0.82–1.03).[18] Finally, in the Polypill with or without Aspirin in Persons without Cardiovascular Disease (TIPS3) trial, in which 5,713 participants at high CV risk were randomized to EC aspirin 75 mg daily or placebo, aspirin was not associated with a significant reduction of the composite of CV death, MI, or stroke (HR: 0.86; 95% CI: 0.67–1.10) after a mean follow-up of 4.6 years, and this finding was consistent in patients with diabetes ($n = 2,095$) or without diabetes ($n = 3,618$) in a prespecified subgroup analysis, although the study was not powered to detect a significant difference in subgroups.[19]

In a recent meta-analysis of 12 randomized trials evaluating the role of aspirin in primary prevention of ASCVD,

Table 1 Major randomized trials evaluating the role of aspirin in primary prevention of atherosclerotic cardiovascular disease in patients with diabetes

	JPAD[6] (2008)	POPADAD[17] (2008)	ASCEND[5] (2018)	TIPS-3[19] (2021)
Country	Japan	United Kingdom	United Kingdom	International
Participants	Type 2 diabetes	Type 1 or type 2 diabetes with asymptomatic PAD	Type 1 or type 2 diabetes	Elevated INTERHEART Risk Score
Sample size	2,539	1,276	15,480	5,713 (2,095 with diabetes)
Study interventions	Low-dose aspirin (81 mg or 100 mg daily) vs. no aspirin	Aspirin 100 mg daily vs. placebo	Enteric-coated aspirin 100 mg daily vs. placebo	Enteric-coated aspirin 75 mg daily vs. placebo
Follow-up time	Median: 4.37 years	Median: 6.7 years	Median: 7.4 years	Mean: 4.6 years
Primary endpoint	Nonfatal ischemic heart disease, fatal or nonfatal stroke, or peripheral arterial disease Aspirin: 13.6 per 1,000 person-years No aspirin: 17.0 per 1,000 person-years (HR: 0.80; 95% CI: 0.58–1.10; $p = 0.16$)	Death from coronary heart disease or stroke, nonfatal myocardial infarction or stroke, or above ankle amputation for critical limb ischemia Aspirin: 18.2% Placebo: 18.3% (HR: 0.98; 95% CI: 0.76–1.26; $p = 0.86$)	Nonfatal myocardial infarction, nonfatal stroke or transient ischemic attack, or death from any vascular cause Aspirin: 8.5% Placebo: 9.6% (HR: 0.88; 95% CI: 0.79–0.97; $p = 0.01$)	Death from cardiovascular causes, myocardial infarction, or stroke Aspirin: 4.1% Placebo: 4.7% (HR: 0.86; 95% CI: 0.67–1.10) No heterogeneity of treatment according to diabetes status
Safety	No significant difference in the composite of severe GI bleeding or hemorrhagic stroke (*p*-value not available)	GI bleeding Aspirin: 4.4% Placebo: 4.9% (OR: 0.90; 95% CI: 0.53–1.52; $p = 0.69$)	Major bleeding events Aspirin: 4.1%; Placebo: 3.2% (RR: 1.29; 95% CI: 1.09–1.52; $p = 0.003$)	Similar number of patients with major bleeding (no *p*-value provided)

Abbreviations: CI, confidence interval; HR, hazards ratio; OR, odds ratio; PAD, peripheral arterial disease; RR, relative risk.

Seidu et al pooled 34,227 participants with diabetes, and showed that aspirin was associated with a significant reduction in the risk of major adverse CV event (RR: 0.89; 95% CI: 0.83–0.95), but not all-cause or CV death, MI, stroke, and coronary heart disease taken individually.[20] These results were consistent in a smaller meta-analysis of five trials ($n = 24,037$ participants with diabetes) by Fortuni et al.[21]

Long-term dual antiplatelet therapy and the combination of aspirin with low-dose rivaroxaban (2.5 mg twice daily) are associated with a significant reduction of CV events, but with a significant increase in the risk of bleeding in secondary prevention of ASCVD.[22,23] Patients with diabetes in primary prevention have a high risk of incident ASCVD, but whether these strategies are associated with net clinical benefits in this population remain speculative.

Aspirin Pharmacology and Response in Patients with Diabetes

Overview of Aspirin Pharmacology

Aspirin induces irreversible acetylation of the cyclooxygenase (COX)-1 enzyme, thus inhibiting thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) biosynthesis from arachidonic acid (AA), resulting in inhibition of platelet activation and aggregation.[24–28] Given the putative incapacity of anucleate platelets to synthesize new, active COX-1 enzymes, aspirin's antiplatelet effect lasts for the entire platelets' lifespan (7–10 days).[24,26] Since aspirin's half-life is short (20 minutes),[29] regular administration is required to inhibit newly released platelets that progressively replace the pool of inactivated ones. Low-dose aspirin has a higher selectivity for COX-1 than COX-2, and complete COX-1 inhibition can be achieved with doses as low as 30 mg.[28] On the other hand, COX-1 selectivity is lost and COX-2 inhibition is enhanced at higher doses of aspirin, promoting vasoconstriction and a paradoxical proaggregation state.[28] The clinical impact of this shift in COX selectivity based on dosing is currently unknown, but the Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term (ADAPTABLE) trial has examined the efficacy of aspirin 81 mg versus 325 mg in secondary prevention in 15,076 patients to answer this question.[30,31] In ADAPTABLE, there was no significant difference in the composite of death from any cause, hospitalization for MI, or hospitalization for stroke after a median follow-up of 26.2 months (HR: 1.02; 95% CI: 0.91–1.14).[31] However, 41.6% of those assigned to the 325 mg dose switched dose during the course of the trial, compared with 7.1% of those assigned to the 81 mg dose, which may have diluted a potential treatment effect with the higher dose. In ADAPTABLE, the treatment effect was similar in subgroups based on diabetes status (diabetes: HR: 0.99;

95% CI: 0.84–1.17; no diabetes: HR: 1.06; 95% CI: 0.89–1.25), although interaction between treatment assignment and diabetes was not formally reported.

When administered orally, plain aspirin is almost exclusively absorbed in the stomach and in the upper small intestine where the local lower pH promotes the diffusion of the unionized and lipophilic form of the drug.[24–28] Its absorption is almost complete, with maximal plasma concentrations being observed approximately 2 hours after administration. Many factors can influence the bioavailability of the drug, such as the presence of food, higher gastric pH, gastric emptying time, tablet disintegration and solubility, particle size, and the pharmaceutical formulation used.[27] The EC formulation of aspirin resists the disintegration in the stomach and is mostly absorbed in the small intestine, thus reducing the bioavailability down to 50%.[24–27,32,33] Following absorption, aspirin is rapidly hydrolyzed to inactive metabolites by esterases in numerous tissues (GI mucosa, plasma, liver, etc.). Therefore, platelet COX-1 inhibition takes place mostly within the presystemic portal circulation.[24–26,28]

The definition of aspirin resistance varies considerably in the literature, describing alternatively pharmacological failure (inability to completely inhibit COX-1), biological failure (inability to inhibit platelet activation and aggregation), or clinical failure (inability to prevent atherothrombotic events).[24–26,34] Numerous assays can measure the antiplatelet effect of aspirin; however, not all are specific to COX-1 activity.[24–26,35] Therefore, the reported prevalence estimates of aspirin resistance are not standardized, heterogeneous, and variable depending on the type of assays, the agonists used, and the selected study populations. Patients with diabetes appear to express a suboptimal response to aspirin, related to higher platelet reactivity, to a faster platelet turnover rate, as well as to some extrinsic factors affecting aspirin pharmacokinetics.[24–26,36,37]

High-dose aspirin (>1 g) has established anti-inflammatory effects, but mechanistic studies suggest that even low doses can exert an anti-inflammatory action by facilitating endothelial nitric oxide release through 15-epi-lipoxin A_4 synthesis, platelet NOS acetylation increasing its activity, and an overall inhibition of innate immune-mediated responses to inflammatory stress.[38,39] Atherosclerosis is an inflammatory disorder and its clinical manifestations can be prevented by anti-inflammatory therapy,[40,41] but the extent to which the anti-inflammatory component of the mechanism of action of low-dose aspirin contributes to atherothrombotic prevention is unknown. Daily doses of 325 mg (vs. 81 mg) are not associated with better clinical outcomes among patients with established ASCVD,[31] and increasing the dose further significantly increases GI bleeding risk rendering these doses clinically not appropriate. It is interesting that there is some controversy as to the anti-inflammatory nature of low-dose aspirin. For example, in a randomized study including 40 healthy participants, aspirin increased the circulation of inflammatory cytokines in experimentally induced systemic inflammation with administration of *Escherichia coli* endotoxin, but how this observation translates in patients with diabetes without systemic sterile inflammation remains speculative.[42] The inflammation balancing effect of low-dose aspirin in diabetes thus merits further evaluation.

The Diabetic Platelet

Diabetes mellitus contributes to systemic inflammation, endothelial dysfunction, oxidative stress, increased catecholamine levels, and consequently platelet hyperreactivity through a TxA_2-independent pathway implicating α_2-adrenoreceptors.[26,43] In addition, COX-2 activation, normally induced in inflammatory states, is favored in diabetes, thereby increasing TxA_2 production independently from COX-1 activity.[25,26,36,43] Also, endothelial dysfunction induced by diabetes downregulates nitric oxide (NO) synthesis, and the diabetic platelet is desensitized to NO. As NO inhibits AA liberation and TxA_2 production, an impaired release may thus contribute to upregulation of platelet activation.[24,26,36,37,43] Dyslipidemia, often concomitantly observed in patients with diabetes, also contributes to endothelial dysfunction and perpetuates this phenomenon.[37] Oxidative stress induced by diabetes also causes lipid peroxidation, leading to an increase in isoprostane production that binds TxA_2 receptors, thus modulating platelet activation.[24,26,36,43] Also, an upregulated expression of glycoproteins IIb/IIIa and $P2Y_{12}$ adenosine diphosphate (ADP) receptors has also been documented in diabetic patients, resulting in hypersensitivity to other agonists (collagen and ADP), independently of the COX-1 pathway targeted by aspirin.[24,26,37,44] Finally, hyperglycemia by itself increases platelet reactivity.[45]

Altered Response to Aspirin in Patients with Diabetes

In addition to the impact of diabetes on increased platelet reactivity, platelet response to aspirin is altered in poorly controlled diabetes because hyperglycemia induces structural alterations of the COX-1 enzyme, thereby reducing its aspirin-binding capacity[36,43,46–48] (►**Fig. 1**). Chronic hyperglycemia also leads to albumin glycation, resulting in a 50% higher fraction of unbound aspirin in patients with diabetes compared with nondiabetic individuals.[10,11,36,43,46]

Platelet function recovery after exposure to aspirin may be more rapid in patients with diabetes, a phenomenon that is at least partly due to an increased platelet turnover rate, and to a faster incorporation of new functional platelets in the circulation once aspirin has been eliminated (►**Fig. 2**).[49–51] Nonsustained aspirin response in the diabetic population may also be related to de novo synthesis of COX-1 by platelet messenger RNA in certain individuals.[52,53] Consequently, chronopharmacology of aspirin may matter in patients with diabetes, with more frequent administration potentially leading to more sustained platelet inhibition than an equivalent dose administered once daily. Of note, platelet aggregation follows a circadian rhythm, with peaks observed in the morning after patients arise and until noon, which may explain the increased frequency of MI in the morning.[54,55] As such, the advantage of twice-daily dosing might also be associated to the timing of aspirin administration.
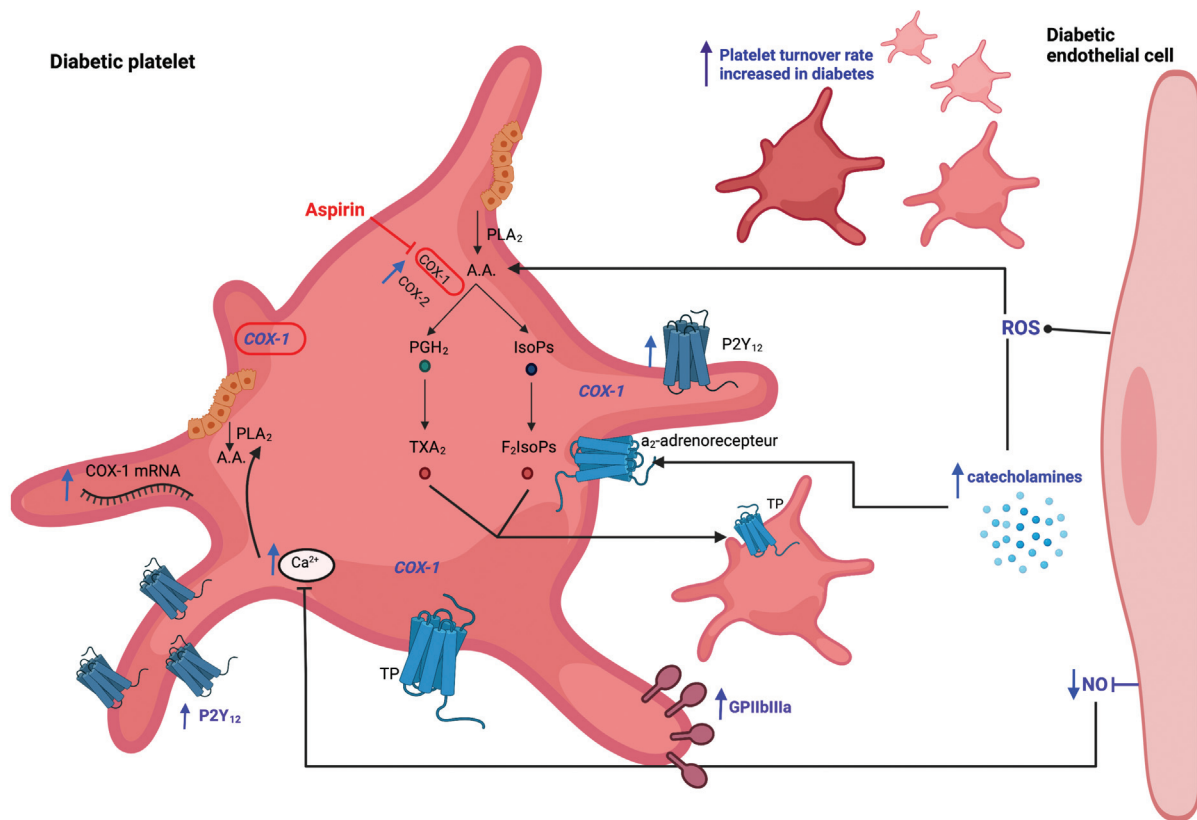
Fig. 1 The diabetic platelet presents several differences as opposed to the healthy platelet. *Dotted arrows* and text in the figure designate altered characteristics within the diabetic and endothelial cell. Hyperglycemia induces structural alterations to COX-1, limiting aspirin's capacity to bind it and reducing its efficiency. Furthermore, an increase in COX-2 concentrations is observed in diabetes, allowing for TXA_2 production independently of COX-1. TXA_2 will then in turn activate the surrounding platelets through its prostanoid receptor (TP). Furthermore, the endothelial inflammation observed in diabetes causes an increase in free radical release which in turn increases the release of isoprostanes that also activate the TP receptor. The increase in free radicals can also increase platelet activation through the α_2-adrenoreceptor. Other differences observed in diabetes include an increased platelet turnover rate, an increase in COX-1 mRNA, and an increase in the expression of GPIIb/IIIa and ADP $P2Y_{12}$ receptors, as well as a decrease in endothelial NO production resulting in an increase in the release of Ca^{2+} increasing TXA_2 release. (Created with BioRender.com.)

In a randomized, double-blind, crossover study evaluating the optimal dose of aspirin for secondary prevention, DiChiara et al evaluated the impact of various doses in both diabetic and nondiabetic individuals with established CV disease.[56] A total of 120 patients (30 with diabetes) were administered various doses of aspirin (81, 162, and 325 mg daily). Inadequate platelet inhibition with aspirin 81 mg was more frequent in diabetics compared with nondiabetics. Platelet resistance, measured with collagen-induced light transmission aggregometry (LTA), was significantly higher in diabetic patients treated with 81 mg daily versus 162 mg daily and 325 mg daily.[56] Similarly, Rosiak et al observed in a study of 254 patients with type 2 diabetes treated chronically with low-dose (75 mg once daily) aspirin that 35.4% of participants had high platelet reactivity despite therapy. Among them, doubling the dose of aspirin to 150 mg once daily was associated with a significant collagen/epinephrine-induced closure time prolongation, and reduction in serum TxB2 levels.[57]

In a three-way crossover randomized controlled trial comparing the impact of aspirin 100 mg once daily, 100 mg twice daily, and 200 mg once daily in 24 patients with type 2

diabetes, Bethel et al found a statistically significant reduction in platelet function measured with VerifyNow with the 100 mg twice-daily regimen as compared with the 100 mg once-daily regimen, but not compared with the 200 mg once-daily dose.[58] The aspirin 200 mg once-daily regimen did not significantly improve platelet inhibition compared with 100 mg once daily, suggesting that time between doses may matter more than total daily dose, lending credence to the importance of chronopharmacology. However, there was no difference between the three doses when using the LTA test with AA. These findings were validated by another study by Capodanno et al, where 20 patients with diabetes and stable coronary artery disease were assigned to different aspirin regimens: 81 mg once daily, 81 mg twice daily, 162 mg once daily, 162 mg twice daily, and 325 mg once daily. Using collagen-induced aggregation and the Verify-Now assay, the authors found that increasing the dose of a once-daily regimen had no impact on platelet reactivity whereas adding an extra daily dose (i.e., twice-daily administration) was associated with a significant reduction in platelet reactivity.[12] Similarly, Rocca et al recruited 100 patients with diabetes and 73 patients without diabetes on
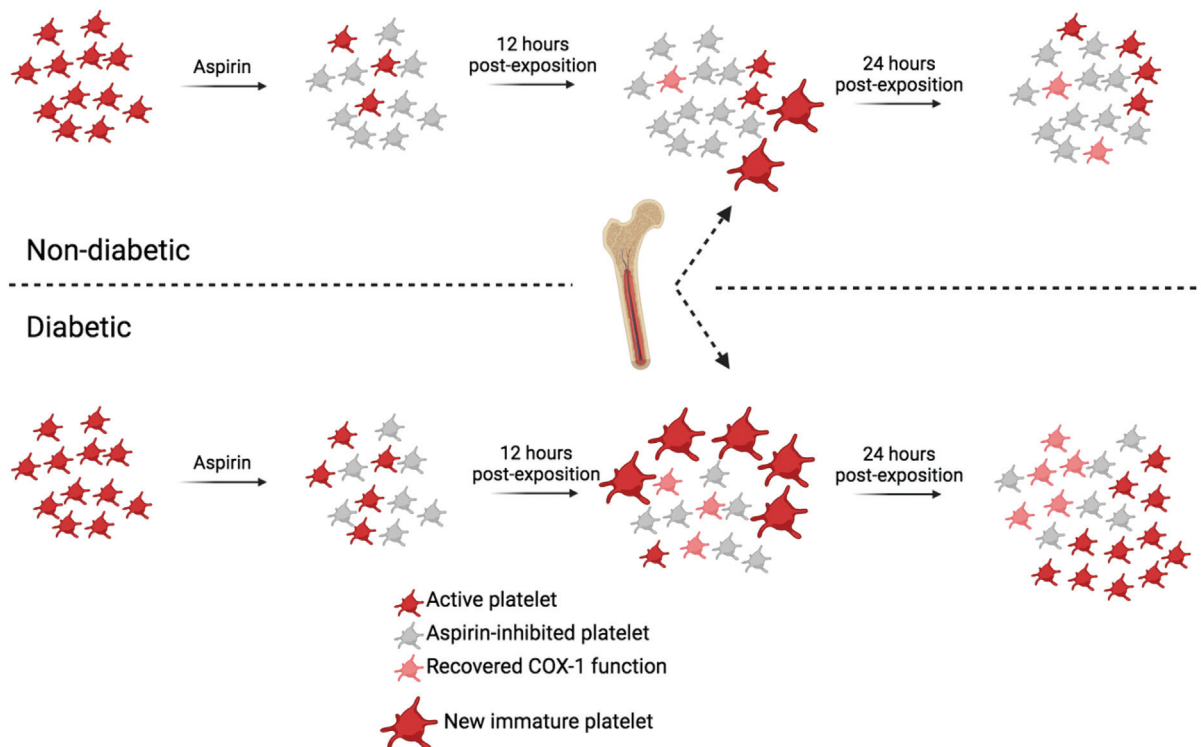
Fig. 2 Proposed conceptual model underlying faster platelet function recovery in patients with diabetes. Platelet function recovery after exposure to aspirin may be more rapid in patients with diabetes, a phenomenon that is at least partly due to an increased platelet turnover rate, and to a faster incorporation of new functional platelets in the circulation once aspirin has been eliminated. Nonsustained aspirin response in the diabetic population may also be related to de novo synthesis of COX-1 by platelet mRNA in certain individuals. (Created with BioRender.com.)

chronic aspirin therapy. Among their cohort, 33 diabetic patients and 18 nondiabetic patients expressed a rapid COX-1 recovery phenotype, as measured by serum TxB_2 levels. This subgroup was then randomized to aspirin 100 mg once daily, 200 mg once daily, or 100 mg twice daily, for 28 days. The investigators found that a twice-daily regimen completely reversed the abnormal COX-1 recovery kinetic, whereas the 200 mg daily regimen only partially improved it.[59] In a randomized crossover study of 25 participants with diabetes comparing aspirin 75 mg once daily, 75 mg twice daily, and 320 mg once daily, Spectre et al also found that platelet response assessed by AA-induced impedance aggregometry was significantly lower with a twice-daily regimen as compared with once-daily standard dosing (75 mg) or increased dosing (320 mg) administered once daily.[60] Finally, in a small study ($n = 20$) of acute coronary syndrome (ACS) patients treated with ticagrelor, among which three had diabetes, aspirin 20 mg twice daily was associated with similar predosing TxB2 levels and AA-induced platelet aggregation after 14 days of treatment[61] Compared with 75 mg once daily.

In brief, these studies all have relatively small sample sizes, but they are consistent in suggesting that patients with diabetes may experience incomplete and nonsustained platelet inhibition with the once-daily administration schedule, a phenomenon that may be completely reversed by twice-daily administration. Nevertheless, the benefits of a twice-daily aspirin regimen on the long-term CV event rate in patients with diabetes remain to be determined in a

properly powered randomized controlled trial. The ongoing Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome (ANDAMAN) randomized trial will shed light on this question (NCT02520921).[62] It is currently evaluating the impact of administering EC aspirin 100 mg twice daily versus once daily on ischemic endpoints in 2,574 patients with diabetes, obesity, large waist circumference, or who had a coronary event while on aspirin, and who present for an ACS. In addition, based on preliminary data suggesting that the circadian rhythm impacts the efficacy of aspirin, the ongoing Chronotherapy With Low-dose Aspirin for Primary Prevention (CARING) randomized trial (NCT00725127) compares bedtime versus morning administration of 100 mg of daily aspirin in 3,200 participants with diabetes or impaired fasting glucose.[63] The primary endpoint is a composite of CV, cerebrovascular and renal fatal and nonfatal events.

Modifying Effect of Body Weight on Aspirin Pharmacodynamics

Obesity is frequently associated with diabetes, whether contributing as a cause of the disease, or secondary to oral antihyperglycemic agents/insulin, psychological factors, or physical factors.[64] Since aspirin is a hydrophobic drug, obesity alters its pharmacokinetics via an increase in distribution volume, but the impact of this phenomenon on platelet inhibition is limited given that the antiplatelet effect of aspirin occurs before acetylsalicylic acid is detectable in the peripheral blood, owing to the exposure of platelets to aspirin in the portal circulation where platelets are exposed

to a higher drug level.[65,66] In a meta-analysis examining the impact of body weight and of body mass index (BMI) on aspirin efficacy in the reduction of CV outcomes, low-dose aspirin (total daily dose $\leq$ 100 mg) was associated with a significant reduction in CV events in patients weighing <70 kg (HR: 0.77; 95% CI: 0.68–0.87; $p < 0.0001$), but not in individuals weighing $\geq$70 kg.[67] The beneficial effect of low-dose aspirin decreased as weight increased, whereas a body weight $\geq$90 kg appeared to be protective against bleeding while on therapy.[67] While these results suggest the presence of an interaction between body weight and aspirin, the interpretation of these data is limited since none of the nine studies included in the meta-analysis directly evaluated the interplay between weight and aspirin dosing. A subgroup analysis of the ASCEND trial identified a significant interaction between weight and the clinical impact of low-dose aspirin (100 mg daily), although in the opposite direction than the meta-analysis.[5] Indeed, low-dose aspirin was associated with a lower risk of CV events only in patients with a BMI $\geq$30 kg/m^2 or weighing $\geq$70 kg (p for interaction: 0.01 and 0.02, respectively). Based on the limited evidence available, a recent expert consensus statement recommends considering administering aspirin on a twice-daily basis in morbidly obese patients (BMI $\geq$40 kg/m^2) to address relative aspirin resistance in this subpopulation.[68] The large randomized trials evaluating aspirin in primary prevention of CV outcomes did not adjust dosing according to participant's body weight, and doing so is currently generally not advised until weight-based dose-tailoring strategies are studied in CV outcomes trials.

Impact of Enteric-Coated Formulations

EC aspirin is the most commonly used formulation of the drug studied in large-scale primary prevention trials.[5,13,14] In the ASCEND randomized trial, which currently drives clinical practice for the use of aspirin in primary prevention in patients with diabetes, all participants randomized to aspirin received an EC formulation.[5] Absorption of the EC formulation is however erratic because of inconsistent disintegration of the coating in the stomach, leading to heterogeneous drug exposure to esterases in the small intestine and fluctuating bioavailability between doses, a phenomenon that is amplified by disorganized gastric emptying observed in diabetes-associated gastroparesis.[24–27] In a randomized crossover study evaluating the impact of five formulations of aspirin on platelet reactivity in 71 healthy volunteers, incomplete platelet inhibition, defined as <99% inhibition of serum TXB2 formation, was significantly higher in the EC group (54.3%) than in the dispersible aspirin group (8.0%).[33]

Grimaldi et al also compared the prevalence of poor response to aspirin between three different formulations in 163 patients with diabetes.[69] Patients expressing an aspirin resistance phenotype with EC aspirin 100 mg daily ($n = 30$), defined as either collagen/epinephrine-induced closure time <160 seconds with the PFA-100 assay or aspirin reaction units >550 with the VerifyNow assay, were switched to an infusion treatment of 288 mg of lysine

acetylsalicylate (equivalent to 160 mg of oral aspirin). Only three patients (10%) demonstrated refractory platelet activity with that later formulation, indicating that initial aspirin resistance was, in part, mediated by the suboptimal bioavailability of the EC formulation. To confirm this hypothesis, the 27 patients whose resistance was reversed after the infusion dose were then switched to a 30-day treatment of 288 mg of oral soluble salt of lysine acetylsalicylate (non-EC formulation), and were retested after 1 month, and only two participants (7.4%) presented persistent aspirin resistance.

In a randomized crossover study, Bhatt et al evaluated the impact of aspirin formulation on platelet function and its pharmacokinetic parameters in 40 obese patients with type 2 diabetes.[32] Patients were exposed to three different formulations of 325 mg of aspirin for 3 consecutive days each: immediate-release aspirin, PL2200 aspirin (modified-release lipid-based), and EC aspirin. The area under the curve and the maximum plasma concentration (C_{max}) were 4.3- and 2.6-fold higher with plain aspirin and PL2200 than with EC aspirin, respectively. EC aspirin also had a higher incidence of nonresponsiveness (52.8%) compared with plain aspirin (15.8%), defined as <99% inhibition of TxB_2 formation or a TxB_2 minimum concentration (C_{min}) of >3.1 ng/mL. Peace et al further assessed the relationship between weight and EC formulation on aspirin response in 236 patients (148 on EC aspirin, and 88 on dispersible aspirin) for secondary prevention of CV disease. Upon recruitment, platelet function was tested and 44 participants (19%) were found to express aspirin resistance. After direct supervision of aspirin intake, the resistance rate dropped to 4.2% (10 patients). All 10 participants were significantly heavier (mean body weight 105 kg vs. 80 kg for the whole cohort), and all were taking EC aspirin. After switching these participants to 75 mg of dispersible aspirin, only three remained resistant (mean body weight of these participants was 120 kg). Finally, all three patients were given 150 mg of dispersible aspirin and none were found to be resistant. The authors highlighted that heavier patients appeared to be at increased risk of EC-aspirin resistance and that overall, high dose of aspirin may need to be used in patients weighing >120 kg.[70]

The abovementioned studies indicate that EC formulations of aspirin have an unfavorable bioavailability profile and are associated with a significant increase in treatment failure compared with plain aspirin. While these findings raise some concerns on the appropriateness of using EC-coated aspirin formulations in patients with or without diabetes, the small sample and the nonrandomized design of some of these studies call for larger, properly powered randomized trials to evaluate the impact of EC formulation on CV outcomes compared with plain aspirin.

Is There True Gastroprotective Benefit with Enteric Coating?

A common side effect of chronic aspirin therapy is GI toxicity, occurring in up to 15% of patients taking low-dose aspirin and ranging from simple dyspepsia to GI bleeding.[71] COX inhibition indirectly promotes a decrease in prostaglandin synthesis, subsequently lowering local gastric mucus

production, bicarbonate secretion, and mucosal cell proliferation. The gastric mucosa is thus exposed to the acidic content of the stomach, causing damages ranging from local irritation to the formation of a peptic ulcer. To a lesser extent, direct injury is caused by local cellular absorption of aspirin, which then dissociates into its ionized form intracellularly, leading to trapping of hydrogen ions.[72] In the aim of minimizing the latter mechanism of GI toxicity, EC formulations were designed, with a coating that can resist disintegration in the stomach and thus prevent local irritation of the stomach mucosa.[73] Contrary to widespread belief, however, quality evidence to confirm that the use of EC aspirin is effective in preventing GI side effects is lacking.

Kelly et al evaluated the RR of GI bleeding in a case–control study of three formulations: plain, EC, and buffered aspirin. A total of 550 patients who suffered from a GI bleeding were identified and matched to 1,202 controls.[74] The RRs of gastric and duodenal bleeding were similar across the types of formulations.[74] In another case–control study of 2,105 patients who suffered GI bleeding and 11,500 matched controls, De Abajo and García Rodríguez found that there were no significant differences in RRs between EC and plain aspirin.[75]

In a review of the efficacy of EC aspirin to prevent GI complications, Walker et al identified five randomized controlled trials of healthy volunteers who were randomized to either plain aspirin or EC aspirin with subsequent endoscopic control to detect potential mucosal irritation.[76] Most trials showed significantly less gastric irritation with EC aspirin. However, the authors highlighted that these trials enrolled a very small number of healthy individuals, were using high doses of aspirin, and that endoscopic control was performed only after a short course of aspirin use. Therefore, these results cannot be extrapolated to long-term, low-dose aspirin use in an older population taking chronic aspirin for CV prevention, and no data on actual clinical outcomes were provided.[76] Finally, in a systematic review evaluating serious upper GI complications with aspirin, García Rodríguez et al identified four studies examining different aspirin formulations. They found that the pooled RR of GI events for EC aspirin (compared with no aspirin) was 2.4 (95% CI: 1.9–2.9) compared with 2.6 (95% CI: 2.3–2.9) for plain formulation.[77]

Alternative Aspirin Formulations

A pharmaceutical lipid-aspirin (PL-ASA) complex liquid formulation has recently been developed to minimize drug-related gastric toxicity by protecting the integrity of the epithelial mucosa.[78] In a randomized study of 204 healthy volunteers, immediate release aspirin was associated with a significantly higher rate of upper GI erosions and/or ulcers compared with the new PL-ASA formulation at a dose of 325 mg daily for 7 days (42.2 vs. 22.2%; $p = 0.0027$).[79] The bioequivalence of the PL-ASA formulation compared with the immediate-release aspirin formulation 24 hours after one oral dose was demonstrated in a crossover randomized trial including 32 healthy volunteers.[80] In this trial, all participants were responders to both aspirin formulations. In a crossover trial including 40 obese patients with diabetes

treated with aspirin 325 mg for 3 days, the PL-ASA formulation was shown to be associated with a 8.1% nonresponse rate, which was similar to plain aspirin (15.8%; $p = 0.30$), but lower to EC aspirin (52.8%; $p < 0.001$).[32] PL-ASA may thus retain the bioavailability of plain aspirin, while minimizing the risk of GI toxicity.

In addition, a Food and Drug Administration-approved extended-release aspirin formulation (Durlaza, New Haven Pharmaceuticals, North Haven, Connecticut, United States) leveraging microcapsule technology has also been developed to address the diurnal variability in platelet inhibition observed with standard one-daily administration, particularly in patients with diabetes and high platelet turnover rates. In a single-arm study including 40 patients with diabetes, platelet inhibition was consistent during the whole 24-hour period after administration.[81] Larger studies are required to determine the safety and efficacy of these new formulations on clinical outcomes in patients with diabetes in primary prevention of ASCVD.

Conclusion

Aspirin is the cornerstone of antithrombotic secondary prevention of CV diseases, but its role in primary prevention remains uncertain, especially in patients with diabetes. While the contemporary evidence suggests a small magnitude of reduction in CV events with aspirin in this population, a similar increase in the risk of bleeding has been documented.[5] Patients with diabetes express platelet hyperreactivity, a higher platelet turnover rate, and pharmacokinetic changes leading to pharmacological resistance to aspirin. Small-scale pharmacokinetic and pharmacodynamic studies have suggested that the relative aspirin resistance phenotype observed in patients with diabetes may be reversed with a twice-daily dosing schedule, and with non-EC aspirin formulations. Properly powered randomized controlled trials investigating the efficacy and safety of aspirin dosing schedules and formulations tailored to the population of patients with diabetes are urgently required to optimize patient care.

from AstraZeneca, DalCor Pharmaceuticals, HLS Pharmaceuticals, Pendopharm, and Sanofi; minor equity interest in DalCor Pharmaceuticals; and patents were submitted on pharmacogenomics-guided CETP inhibition and use of colchicine after myocardial infarction in which he is mentioned as an author. There are no other conflicts of interest to disclose.

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