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DIABETES AND CARDIOVASCULAR DISEASE (N WONG, SECTION EDITOR)

Role of and Recent Evidence for Antiplatelet Therapy in Prevention of Cardiovascular Disease in Diabetes

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Abstract

Purpose of Review When treating patients with diabetes mellitus (DM), the benefits of antiplatelet therapy in preventing cardiovascular disease must be weighed against an increased risk of bleeding. Recent trials have sought to determine both the optimal anti-platelet regimen for patients with DM, and who specifically requires medication among the DM population. This paper will review recent trials and evidence recommending the use of antiplatelet therapy in the prevention of cardiovascular disease in patients with diabetes.

Recent Findings Seven notable trials assessed the effectiveness of antiplatelet therapy in the DM population. The ASCEND trial concluded 100 mg aspirin/day reduced rates of serious vascular events (OR 0.88, $p < 0.01$) but also increased rates of major bleeding events (OR 1.29, $p < 0.01$). The DAPT study revealed a longer dual antiplatelet regimen (30 months vs. 18 months) after coronary stent placement was more effective in reducing rates of stent thrombosis (0.5% vs. 1.1%, $p = 0.06$) and rates of myocardial infarction (3.5% vs. 4.8%, $p = 0.06$). DECLARE DIABETES showed that adding cilostazol to dual antiplatelet therapy after a coronary stent procedure reduced rates of in-stent and in-segment late loss and increased rates of revascularization ($p < 0.04$). In PEGASUS-TIMI, daily ticagrelor demonstrated reduced rates of major adverse cardiovascular and cerebrovascular events (OR 0.84, $p < 0.04$). The DAVID trial compared daily picotamide with daily aspirin therapy, finding reduced mortality rates in the picotamide group (OR 0.55, $p < 0.05$). Lastly, ACUITY found bivalirudin monotherapy resulted in lower rates of major bleeding events when compared to a glycoprotein IIb/IIa inhibitor and heparin or bivalirudin combination regimen ($p < 0.01$).

Summary Dual antiplatelet therapy guidelines still typically revolve around aspirin, but an increasing number of studies have demonstrated other drugs that may have a role in preventing atherosclerotic cardiovascular disease while decreasing the risk of major bleeding. Overall, it is wise to weigh the cardiovascular risk of a DM patient before prescribing antiplatelet medication. More research is necessary to determine a universal drug or combination of drugs that is safe and effective for DM patients.

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Introduction

Diabetes Mellitus (DM) is one of the most prevalent diseases in the world. Researchers project that from 2000 to 2050, DM will increase 165% in prevalence, from 4.0 to 7.4% of the American population [1]. Currently, an estimated 25.8 million Americans are affected by type 2 DM (25.2% of seniors ≥ age of 65) [2]. DM remains an incurable disease to date, but there are treatment options that can help to control the disease and mitigate its negative effects. However, even with treatment options that are currently available, DM remains the seventh most common cause of death in the USA [3].

DM patients are faced with a two- to three-times greater risk of developing atherosclerotic cardiovascular disease [4]. In a study comparing the hearts of individuals (aged 15–34 years old) with hyperglycemia, fatty streaks were found covering a significantly greater percentage of the right coronary artery intimal surface in hyperglycemic individuals. Hyperglycemic individuals were also three times more likely to have macroscopic raised lesions on the right coronary artery, demonstrating the greater risk DM patients face in developing cardiovascular disease [5].

Pathogenically, DM patients are in a constant prothrombotic state, where platelets are more subject to aggregation as blood vessel walls experience constant microtraumatic disruption. Metabolic changes induced by DM (i.e., hyperglycemia, free fatty acid excess) contribute to endothelial changes by way of oxidative stress and protein kinase C activation. Subsequently, these endothelial changes eventually manifest as clinically significant vasoconstriction, thrombosis, and inflammation [6].

In addition to existing in a prothrombotic state, individuals with DM also experience autonomic nervous system dysfunction, with a decrease in parasympathetic control and an increase in sympathetic control. It is proposed that in insulin-resistant DM individuals, hyperinsulinemia leads to increased sympathetic tone, which in turn leads to increased heart rate and blood pressure and a greater risk for hypertension [6]. Thus, not only are individuals with DM at a greater risk to sustain cardiovascular and atherosclerotic disease, but they are also at risk for poorer clinical outcomes following a cardiovascular event. A study by Tajik et al. found that individuals with DM had significantly increased 2-year morbidity and mortality following a myocardial infarction. In addition, the risk for all-cause death in these DM individuals rose by around 40% [7].

The necessity of antiplatelet therapy in this population has been a point of great contention and research. While these medications lower the risk of plaque buildup in arteries, they may also result in a significant bleeding risk. Different classes of anti-platelet medications have previously been associated with varying levels of bleeding risk, but a review of antiplatelet medications in the context of individuals with DM is lacking in the literature [8]. Much of the current discussion on the topic revolves around two issues: (a) determining the optimal anti-platelet regimen and (b) among the DM population, who specifically requires medication (i.e., all DM patients or only individuals meeting high-risk criteria). This review serves to provide the information that will allow for educated answers to both questions.

Current Guidelines (Table 1)

Current guidelines regarding the use of antiplatelet therapy in the diabetic population reflects the debated efficacy of these medications. The American Diabetes Association (ADA) currently maintains four recommendations. For secondary prevention, they advise 75–162 mg aspirin/day in those with diabetes and a history of atherosclerotic cardiovascular disease (ASCVD). For primary prevention, they only advise 75–162 mg aspirin/day in those with type 1 or type 2 diabetes who are at increased cardiovascular risk. They define increased cardiovascular risk as patients aged ≥ 50 years who are not at increased risk of bleeding and have at least one of the following additional risk factors: family history of ASCVD, hypertension, dyslipidemia, smoking, and albuminuria. Their last two recommendations include 75 mg clopidogrel/day in those with a documented aspirin allergy and dual antiplatelet therapy (aspirin and a P2Y12 inhibitor) for 1 year after an acute coronary syndrome. Of these recommendations, only the first and last mentioned have earned a grade A recommendation [9••]. The American College of Cardiology and American Heart Association have endorsed these standards set forth by the ADA [10].

The US Preventive Services Task Force (USPSTF) has similar recommendations, though none reach a grade A recommendation. For primary prevention, the USPSTF recommends low-dose aspirin for those aged 50–59 years who have a 10% or greater 10-year ASCVD risk and are not at increased risk for bleeding. They hold the same recommendation for those aged 60–69 years, but at a lower grade of confidence.

The American Association of Clinical Endocrinologists maintains one grade A recommendation, promoting the use of aspirin therapy for secondary prevention in those with diabetes. They do refer to a role of aspirin as primary therapy in those with high cardiovascular risk, but apply only a grade D recommendation [11]. Recently, the Endocrine Society has supported the use of aspirin therapy for secondary prevention in those with diabetes, but specifies the population to only those greater than 65 years [12].

Review of Studies (Table 2)

A Study of Cardiovascular Events in Diabetes (ASCEND) Trial [13••]

The ASCEND trial was an approximately 7-year project studying the efficacy and safety of aspirin use in patients with DM. Fifteen thousand four hundred-eighty adults over the age of 40 that had been diagnosed with DM but had no apparent history of cardiovascular disease were randomized into two groups. The experimental group received 100 mg tablets of aspirin daily, while the control group consumed an identical placebo pill daily. The primary outcome was defined as a patient's first serious vascular event, such as nonfatal and fatal myocardial infarctions and strokes. The study also tracked major bleeding events (i.e., intracranial hemorrhage,

Table 1 Current guidelines regarding antiplatelet therapy in diabetic patients

Organization (year of recommendation)	Recommendations (Grade)
American Diabetes Association (2019) (endorsed by the American College of Cardiology, American Heart Association)	1. Use of aspirin therapy (75–162 mg/day) for secondary prevention in those with diabetes and a history of ASCVD (A)
	2. Use of clopidogrel (75 mg/day) for those with documented aspirin allergy and ASCVD (B)
	3. Use of dual antiplatelet therapy (low-dose aspirin and P2Y12 inhibitor) for a year after an acute coronary syndrome (A)
	4. Use of aspirin therapy (75–162 mg/day) for primary prevention in those with diabetes who are at increased cardiovascular risk (C)
Endocrine Society (2019)	1. Use of aspirin therapy (75–162 mg/day) for secondary prevention of cardiovascular disease in patients ≥ 65 years old with diabetes
US Preventive Services Task Force (2016)*	1. Use of low-dose aspirin for those aged 50–59 years who have a 10% or greater 10-year ASCVD risk and are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take aspirin for at least 10 years (B)
	2. Use of low-dose aspirin for those aged 60–69 years who have a 10% or greater 10-year ASCVD risk and are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take aspirin for at least 10 years (C)
American Association of Clinical Endocrinologists (2015)	1. Use of aspirin therapy (75–162 mg/day) for secondary prevention of cardiovascular disease in those with diabetes (A)
	2. Use of aspirin therapy (75–162 mg/day) for primary prevention of cardiovascular disease in those with diabetes at high cardiovascular risk (10-year risk > 10%) (D)

*These recommendations are not specific to those with diabetes

gastrointestinal bleeding, or other serious bleeding) as the primary safety outcome. Over the follow-up period of 7.4 years, a significantly lower percentage of participants in the experimental group (aspirin) experienced a serious vascular event (odds ratio, 0.88; 95% CI, 0.79 to 0.97; $p = 0.01$) than the control group. However, a significant percentage of the participants in the experimental group experienced a major bleeding event (odds ratio, 1.29; 95% CI, 1.09 to 1.52; $p = 0.003$). Further analysis of the 7.4-year trial showed that the significant risk differences between the experimental and control groups occurred in the first 5 years of the study, with no improved reduction of risk after this time. Overall, this clinical study asserted that the benefits of aspirin therapy were "largely counterbalanced" by the risk of major bleeding. This conclusion remained true when examining different types of participants, including patients of low, moderate, and high vascular risk (based on a predicted 5-year risk of a serious vascular event). Various guidelines have recommended the use of aspirin for DM patients of high risk specifically (i.e., ≥ 10% of atherosclerotic cardiovascular disease risk (ASCVD)) [14, 15]. However, the ASCEND trial revealed nearly no difference between the number of serious vascular events between the aspirin and placebo participants in their high-risk population subgroup (270 patients with events vs. 297 patients, $p = 0.47$). These statistics perhaps support a revisiting of guidelines calling for precautionary aspirin use in DM patients who meet criteria for high ASCVD risk, given the lack of benefit seen in the ASCEND trial.

Dual Antiplatelet Therapy (DAPT) Study [16, 17]

The DAPT study investigated the safety and efficacy of extended dual antiplatelet therapy on DM patients following placement of a coronary stent. The specific dual antiplatelet therapy regimen consisted of thienopyridine therapy (clopidogrel or prasugrel) plus aspirin. Prior to this study, standard of care included only 6–12 months of dual antiplatelet therapy post-stent placement [18]. In this study, the effect of dual antiplatelet therapy for 30 months vs. 12 months post stenting was assessed. 3391 patients with DM were randomized into two groups. The experimental group would continue the dual antiplatelet therapy for 18 additional months after a year of treatment, and the control group would take a placebo for only 18 months. The primary efficacy endpoint of the DAPT study included stent thrombosis and major adverse cardiovascular or cerebrovascular events (MACCE). The

Table 2 Clinical trials investigating antiplatelet therapy in diabetic patients

Trial	Length of study	Number of patients	Major enrollment criteria	Experimental group	Control group	Statistically significant results in DM populations
ASCEND (2018)	7 years	15,480	-Diagnosed with DM	100 mg aspirin/day	Placebo pill/day	-Reduced rates of serious vascular events (OR 0.88, $p < 0.01$) -Increased rates of major bleeding events (OR 1.29, $p < 0.01$)
DAPT (2014)	12 months	11,648 (3391 with DM)	-Undergone coronary stent procedure	Clopidogrel/prasugrel + aspirin for 30 months post-stent placement	Clopidogrel/prasugrel + aspirin for 12 months, placebo pill for 18 months post-stent placement	-Reduced rates of stent thrombosis (0.5% vs. 1.1%, $p = 0.06$) -Reduced rates of myocardial infarction (3.5% vs. 4.8%, $p = 0.06$)
DECLARE DIABETES (2008)	6 months	400	-Diagnosed with DM -Undergone coronary stent procedure	Clopidogrel + aspirin + cilostazol for 6-month post-stent placement	Clopidogrel + aspirin for 6-month post-stent placement	-Reduced rates of in-stent and in-segment late loss ($p < 0.04$) -Increased rate of target lesion revascularization ($p < 0.04$)
PEGASUS-TIMI 54 (2016)	33 months (median)	21,162 (6806 with DM)	-Prior myocardial infarction	60 mg or 90 mg of ticagrelor/day	Placebo pill/day	-Reduced rates of MACCE (OR 0.84, $p < 0.04$) -Reduced rates of cardiovascular death (OR 0.78, $p < 0.05$) -Increased rate of major bleeding events (OR 2.56, $p < 0.01$)
THEMIS (2019)	58 months	19,271	-≥ 50 years old -Diagnosed with DM -Documented CAD or previous coronary artery revascularization - History of glucose lowering medication for ≥ 6 months	60 mg ticagrelor twice/day + aspirin	Aspirin monotherapy	-Reduced rates of MACCE (primary endpoint; full results not yet released)
DAVID (2004)	24 months	1209	-Diagnosed with DM for ≥ 5 years -Diagnosed with peripheral artery disease	600 mg picotamide twice/day	320 mg aspirin/day	-Reduced rate of mortality (OR 0.55, $p < 0.05$)
ACUITY (2006)	12 months	3852	-Diagnosed with DM -History of moderate- to high-risk acute coronary syndromes	Bivalirudin monotherapy	Heparin + glycoprotein IIb/IIIa inhibition, or bivalirudin + glycoprotein IIb/IIIa inhibition	-Reduced rate of composite ischemia or major bleeding ($p = 0.02$) -Decreased rate of major bleeding events ($p < 0.01$)

DM diabetes mellitus, *OR* odds ratio, *p p* value, *MACCE* major adverse cardiovascular or cerebrovascular events

primary safety endpoint of the study was moderate or severe bleeding, classified according to the criteria of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Trial and the Bleeding Academic Research Consortium [19, 20]. Researchers determined that, while not powered to detect statistical significance, the reaction of DM patients to the continued treatment was heterogenous, with reduction of MACCE increasing only from 6.6 to 7.0% with the extended 18 months of treatment. However, there was a relative decrease in incidence of myocardial infarction in the DM patients, with a reduction of 19% (27 to 56%). There was no reported increased incidence in bleeding events. The study concluded that DM patients had less of a positive response to continued treatment compared to non-DM patients, but there was still minor treatment benefit. Overall, extended DAPT in DM patients did not appear to have a clinically significant benefit.

Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus (DECLARE-DIABETES Study) [21]

The DECLARE-DIABETES trial studied the efficacy and safety of using cilostazol as a treatment to reduce restenosis in DM patients after bare-metal stent implantation. This prospective study included 400 DM patients over the age of 18 that presented with angina pectoris or a positive stress test and native coronary lesion. The patient cohort was divided into two groups: (a) one was given triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) and (b) the other was given dual antiplatelet therapy (aspirin and clopidogrel). All patients were studied for 6 months after receiving a drug-eluting stent (DES) implant. The primary endpoint of the study was in-stent late loss, defined as the difference between minimum lumen diameter immediately after stent implantation and that obtained at angiographic follow-up [22]. In-segment (stented segment and margins 5 mm proximal and distal to stent), late loss and MACE were two of several secondary end points. Safety was monitored with major and minor bleeding occurrences. The results showed that the patients receiving the triple antiplatelet therapy had significantly reduced in-stent late loss (0.25 ± 0.53 mm vs. 0.38 ± 0.54 mm; $p < 0.05$) and reduced in-segment late loss (0.53 ± 0.49 mm vs. 0.42 ± 0.50 mm; $p < 0.05$), demonstrating a benefit when adding cilostazol. Though not statistically significant, there was a reduction in MACE in the patients receiving triple antiplatelet platelet therapy (3.0% vs. 7.0%; $p = 0.066$). The study reported no major bleeding events or any other adverse effects of the drugs in either group throughout the study. The DECLARE-DIABETES study shows that triple antiplatelet therapy was effective in improving the efficacy of DES implants in terms of patient outcomes, without increasing the risk of major bleeding incidents.

Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) Study [23, 24•]

This study examined a subset of DM patients that were enrolled in the PEGASUS-TIMI 54 trial. Specifically, this study assessed the safety and efficacy of ticagrelor in DM patients who had a history of myocardial infarction in the past 3 years. Six thousand eight hundred-six DM patients were randomized into two groups: (a) an experimental group taking either 60 or 90 mg of ticagrelor (randomly assorted) and (b) a control group taking a placebo pill. The populations with two different doses of ticagrelor were analyzed as a pooled group and as separate groups. DM patients taking ticagrelor (pooled group) experienced a significant reduction in MACCE (odds ratio 0.84; 95% CI, 0.72–0.99; ARR 1.5%; $p = 0.03$) and cardiovascular death (odds ratio 0.78; 95% CI, 0.61–0.99; ARR 1.1%; $p = 0.0495$). However, there was a significant increase in major bleeding events for DM patients taking ticagrelor (2.56% vs. 0.98%; odds ratio 2.56; 95% CI, 1.52 to 4.33; $p = 0.0004$). There was no statistically significant difference within the DM subgroup in terms of fatal or intracranial bleeding between patients taking different dosages of ticagrelor (0.62% vs. 0.63%; odds ratio 0.90; 95% CI, 0.42 to 1.90; $p = 0.78$). The PEGASUS-TIMI 54 trial concluded that participants taking ticagrelor had significant reduction in cardiovascular events, but experienced a significant increase in major bleeding events. Furthermore, further research by the same group with the Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) will aid in the decision of whether to clinically prescribe ticagrelor by conducting an analysis on lower-risk patients without a history of myocardial infarction (study completion date: Jan. 25th, 2019). Although full results from the phase III trial have not yet been released, this study has met its primary endpoint and demonstrated that individuals taking ticagrelor and aspirin experienced a significant reduction in MACCE compared to those taking aspirin only [25].

Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics (DAVID) Study [26]

The DAVID study aimed to study the safety and efficacy of the use of picotamide versus aspirin. The study included participants between 40 and 75 years old who had a positive history of type 2 DM (T2DM) for at least 5 years and peripheral artery disease (PAD). The primary endpoint of the study was mortality, while the secondary endpoint included non-

fatal vascular events. A total of 1209 patients were enrolled in the study and randomized into two different groups: (a) one that would take picotamide and (b) one that would receive aspirin. Patients were followed up after a median of 2 years. While combined mortality and morbidity did not show significant conclusions, data showed that for morbidity, the incidence of non-fatal vascular events was significant, with 7.1% in the picotamide group and 8.7% in the aspirin group. The occurrence of major bleeding events (leading to hospitalization) was 0.2% for the picotamide group and 1.2% for the aspirin group. The greatest reported advantage of picotamide over aspirin was the amount of gastrointestinal discomfort (10.9% vs. 18.3%; $p < 0.0001$). While picotamide did not prove to be more effective in preventing death than aspirin, picotamide showed promise in its reduction of significant side effects.

Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial [27]

The ACUITY trial studied the efficacy and safety of bivalirudin monotherapy in DM patients who had a history of moderate- to high-risk acute coronary syndromes, defined as any patients who underwent an invasive management strategy. The study analyzed the subset of a larger trial, looking only at the patients who had DM. A total of 3852 patients of the randomized 13,819 patients had DM. Patients were randomized into three groups: (a) heparin plus glycoprotein IIb/IIIa inhibition (GPI), (b) bivalirudin plus GPI, or (c) bivalirudin monotherapy. The primary end points for the 30-day follow-up were composite ischemia and major bleeding, evaluated separately and together as net averse clinical outcomes. DM patients who were treated with bivalirudin monotherapy experienced a significantly lower rate of net adverse clinical outcomes (composite ischemia or major bleeding) compared with the heparin plus GPI group (10.9% vs. 13.8%; $p = 0.02$. Major bleeding events occurred in a significantly lower number of patients being treated with bivalirudin as opposed to heparin plus GPI (3.7% vs. 6.3%; $p < 0.001$). There was no significant difference in the occurrence of composite ischemia. The study showed that bivalirudin monotherapy was more effective than the other studied drug combinations in reducing net adverse outcomes while also lowering major bleeding event occurrence.

Review of Antiplatelet Treatments

COX Inhibitors

Cyclooxygenase (COX) inhibitors act by directly binding to and inhibiting COX-1 or COX-2. Aspirin, the most widely used antiplatelet medication, is a COX-1 inhibitor that binds irreversibly to COX-1, preventing arachidonic acid from being converted to prostaglandin H_2, and ultimately preventing thromboxane A2 from being formed. Aspirin has been shown many times to be effective in reducing the risk of major adverse cardiac events, despite its potential increase in risk of bleeding events. In the Anti-Thrombotic Trialists' Collaboration (ATCC) study, aspirin was shown to reduce occlusive vascular events (95% CI, 6%–18%), but was also shown to increase bleeding events by approximately 50% [28]. Although only 4% of participants in this trial had DM, researchers noted augmented effects of aspirin in the DM population, with both an increase in effectiveness and an increase in bleeding events. The ASCEND trial showed similar results, with reduced vascular events at the expense of increased bleeding. Other studies have shown no effect of aspirin, including the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, in which aspirin had no effect on vascular events in patients with DM and reduced ankle-brachial index [29]. The variety of results in these studies emphasizes the continued need for further research.

ADP Receptor Inhibitors

Clopidogrel is the most commonly used ADP receptor inhibitor and is a thienopyridine that is a $P2Y_{12}$ inhibitor. Several studies have demonstrated its effectiveness in reducing cardiovascular events (CURE and CAPRIE Trials); however, clopidogrel has been shown to have a delayed therapeutic onset and may cause variable degrees of anti-coagulation in different patient populations [30–32]. Ticagrelor, while also an ADP receptor inhibitor, is different in its mechanism of action as it does not require metabolic conversion to take effect in the body. Ticagrelor was shown to significantly reduce occurrence of death from vascular causes, MI, or stroke when compared with clopidogrel [33]. Ticagrelor exhibited these advantages without an increase in overall major bleeding. Ticagrelor is also a reversible binder, losing its ability to inhibit platelets upon clearance from the body. The effects of ticagrelor were found to be about 50% platelet inhibition after 24 h and 20% platelet inhibition after 3 days [32]. Specifically, in the DM population, the PEGASUS-MITI trial demonstrated a significant reduction in MACCE with ticagrelor compared to placebo, but also documented a significant increase in major bleeding events. The THEMIS study by the same group will provide further insight into ticagrelor by studying its cardiovascular benefits and risks in a low-risk DM population. Prasugrel is another member of the thienopyridine drug class and acts as an irreversible antagonist of P2Y12 ADP receptors. Compared to clopidogrel, prasugrel inhibits platelet aggregation more rapidly and can be used in patients taking proton pump

inhibitors [34, 35]. Recent clinical trials investigating antiplatelet effects in patients with DM have concluded that prasugrel is associated with greater platelet inhibition when compared to both clopidogrel and ticagrelor, though final decision on which therapy to administer should be made on a patient specific basis [36, 37].

Phosphodiesterase Inhibitors [38]

Cilostazol is a phosphodiesterase III inhibitor that is most commonly prescribed in patients who undergo stenting. Cilostazol suppresses intimal proliferation, thereby causing a significant reduction of narrowing of coronary arteries. Participants at major risk for restenosis experienced benefits from cilostazol in the Cilostazol for Restenosis Trial (CREST). Minimal luminal diameter was significantly increased, and binary restenosis rate was significantly decreased in the experimental group receiving treatment with cilostazol compared to the placebo group. Cilostazol has also been shown to significantly reduce bleeding time when compared with ticlopidine and aspirin [39]. In clinical practice, cilostazol often has a more limited role confined to the treatment of claudication symptoms. Though the aforementioned studies do imply a potential application of cilostazol in dual antiplatelet therapy for coronary stents, current standard of care has not adapted this conclusion. Researchers have also studied the synergistic effect of cilostazol and dipyridamole, another phosphodiesterase inhibitor, showing that when the two drugs are used together, there is a significant reduction in platelet aggregation [40]. In the DM population in particular, the DECLARE DIABETES trial demonstrates significant reduction in in-state late loss and in-segment late loss, with no reported no major bleeding events.

Thromboxane Synthase Inhibitors [41]

Picotamide is an antiplatelet medication that inhibits both thromboxane receptors and thromboxane synthesis. An initial study of picotamide in the Atherosclerotic Disease Evolution by Picotamide (ADEP) study showed no significant effect on vascular events in patients with peripheral obstructive arterial disease. However, a post-hoc analysis of the ADEP study that analyzed the diabetic subgroup revealed that picotamide had a significant reduction in vascular events in the experimental group as compared to the control group (RR 48%; 95% CI, 26 to76; $p = 0.022$) [42]. Results from this analysis prompted the DAVID trial, which showed that picotamide caused a significant reduction in MACCE as well as major bleeding risk when compared with aspirin in DM patients. In addition, other studies have shown that extended use of picotamide leads to diminished risk of microalbuminuria and cessation of carotid plaque growth [23].

Direct Thrombin Inhibitor

Bivalirudin is a direct thrombin inhi0bitor primarily indicated in unstable angina patients that are undergoing percutaneous transluminal coronary angioplasty. It is a synthetic polypeptide that binds directly to the catalytic and substrate recognition sites. In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, individuals with ST-elevation MI undergoing percutaneous coronary intervention were shown to have significantly reduced rates of major bleeding and net adverse clinical outcomes following the 30-day trial when taking bivalirudin alone as opposed to heparin plus glycoprotein IIb/IIIa inhibitors [43]. A similar conclusion was found in DM patients in the ACUITY trial. Compared with other common heparin therapies, DM patients treated with bivalirudin monotherapy experienced significantly lower cardiovascular events, as well as a decrease in major bleeding events. Further work comparing bivalirudin with aspirin and ADP receptor inhibitors should be conducted to see if it could be incorporated into a mainstay antiplatelet therapy regimen.

Conclusion

Individuals with DM have a greater risk of developing cardiovascular disease, but within the DM population, there also exists varying levels of risk. Dual antiplatelet therapy guidelines still typically revolve around aspirin, but an increasing number of studies have demonstrated other drugs that may have a role in preventing atherosclerotic cardiovascular disease while decreasing the risk of major bleeding. Overall, it is wise to weigh the cardiovascular risk of a DM patient before prescribing antiplatelet medication. More research is necessary to determine a universal drug or combination of drugs that is safe and effective for DM patients. With these future studies, many of which are already underway, the current guidelines for antiplatelet use in DM patients will be markedly improved.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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