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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Aspirin for Primary Prevention of Cardiovascular Disease in Diabetes: a Review of the Evidence

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Abstract

Purpose of Review People with diabetes are at a higher risk of atherosclerotic cardiovascular disease (ASCVD) compared with those without diabetes. Though aspirin has been shown to have an overall net clinical benefit when used for secondary prevention of ASCVD in people with and without diabetes, the evidence for primary prevention, especially in those with diabetes, remains inconsistent. In this article, we review the latest studies examining the risks and benefits of aspirin use for primary prevention of ASCVD in adults with diabetes, discuss key aspects in assessing the risk-benefit ratio of aspirin use for primary prevention of ASCVD, and summarize current guidelines from professional societies on aspirin use for primary prevention in adults with diabetes.

Recent Findings In the general population, past studies have shown no difference in the beneficial effect of aspirin for primary cardiovascular disease prevention by diabetes status. However, several randomized controlled studies and meta-analyses in adults with diabetes have shown lack of net clinical benefit of aspirin use for primary prevention of ASCVD. The recent ASCEND trial documented cardiovascular benefit of aspirin for primary prevention in adults with diabetes but suggested that the increased risk of bleeding may outweigh the cardiovascular benefit.

Summary The decision to initiate aspirin for primary prevention of ASCVD must be considered carefully on an individual basis to balance the cardiovascular benefit and bleeding risk in all patients, especially those with diabetes. A multifactorial approach that focuses on managing ASCVD risk factors such as hypertension, dyslipidemia, dysglycemia, and smoking is recommended in all patients. More research is needed to identify subgroups of people with diabetes who are more likely to benefit from aspirin use for primary prevention of ASCVD and develop better antithrombotic strategies that shift the risk-benefit balance toward an overall net clinical benefit.

Keywords Primary cardiovascular prevention · Diabetes · Aspirin · Atherosclerotic cardiovascular disease

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Introduction

The risk of atherosclerotic cardiovascular disease (ASCVD) is two- to fourfold higher in people with versus without diabetes [1–3]. The increased risk of ASCVD in people with diabetes has been attributed to several possible mechanisms including endothelial and macrophage dysfunction, higher in vivo and/or in vitro platelet activation, increased platelet turnover, higher plasma fibrinogen, and decreased fibrinolytic activity [4–12]. As the global prevalence of diabetes is projected to rise, the burden of ASCVD, a major cause of morbidity and mortality in people with diabetes, is also predicted to increase [13, 14]. Hence, primary prevention of ASCVD is considered a major goal of therapy when managing people with diabetes. Aspirin has been shown to have an overall net clinical benefit (i.e., cardiovascular benefit exceeds bleeding risk) when used for secondary prevention of ASCVD in people with and

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without diabetes. However, the data remains controversial regarding the net clinical benefit of aspirin for primary prevention in the general population, especially in those with diabetes. Several randomized controlled studies and meta-analyses in adults with diabetes have shown lack of net clinical benefit of aspirin use for primary prevention of ASCVD [15–18]. However, in the general population, past studies have shown no difference in the cardiovascular beneficial effect of aspirin by diabetes status [19••]. This has led to questions about whether the ASCVD risk associated with diabetes only is high enough to justify the use of low-dose aspirin considering the bleeding risk. Others have suggested that people with diabetes may respond less to aspirin for various reasons and, therefore, the risk of bleeding may outweigh the benefit. As a result, there have been inconsistent recommendations from different professional societies around the world regarding the appropriate use of aspirin for primary prevention of ASCVD in adults with diabetes. In this article, we provide a comprehensive review of the latest studies evaluating the risk-benefit ratio of aspirin use for primary prevention of ASCVD in people with diabetes and how the results of these studies appear to differ from those conducted in the general population. We also discuss clinical factors to be considered by providers before prescribing aspirin for primary prevention in people with diabetes and review the recent guideline recommendations from various professional societies.

Platelet Function and Response to Aspirin in People with Diabetes

In general, people with diabetes have a hyperactive platelet phenotype and a higher in vivo platelet activation compared with those without diabetes [20••, 21, 22]. The enhanced platelet aggregation with diabetes is thought to be due to chronic hyperglycemia resulting in nonenzymatic glycation of platelet glycoproteins and oxidative stress; deficient insulin action or insulin resistance resulting in platelet dysfunction and impaired response to prostaglandin I_2 (PGI_2); and other abnormalities such as increased platelet turnover, endothelial dysfunction, or combination of two or more of these mechanisms [23]. Aspirin is one of the oldest antithrombotic agents with a cardiovascular benefit that is believed to be due to its ability to irreversibly inactivate the cyclooxygenase-1 (COX-1) pathway and prevent the conversion of arachidonic acid to thromboxane A2 (TXA2), a potent stimulator of platelet aggregation. Due to the irreversible inactivation of COX-1 activity, the antithrombotic effect of aspirin lasts for the entire lifespan of the platelets (i.e., 7 to 10 days). Nonetheless, low-dose aspirin has no measurable effect on the COX-2 pathway and platelets may still be activated through pathways that are independent of COX-1 in those taking low-dose aspirin. Moreover, there are several factors that can reduce the effectiveness of aspirin in preventing ASCVD and may potentially provide explanations for why some patients are thought to not respond, or benefit less, from aspirin compared with others in reducing cardiovascular events. This phenomenon is sometimes referred to as "aspirin resistance" and will be discussed separately at the end of this article.

Major Aspirin Primary Prevention Trials in the General Population (*People with and Without Diabetes*)

There have been many primary prevention studies conducted evaluating the effect of aspirin on cardiovascular disease outcomes in the general population. The Antithrombotic Trialists' (ATT) Collaboration aggregated the first six of these studies and published a meta-analysis in 2009 [19••]. These studies included 95,000 people, nearly 4000 of whom had diabetes. The dose of aspirin used varied in each trial included, ranging from 75 mg daily to 500 mg daily (Table 1). Aspirin was shown to decrease the risk of vascular events by 12% in both the general population (RR 0.88, 95% CI 0.82–0.94) and in those with diabetes (RR 0.88, 95% CI 0.67–1.15) with no significant interaction by diabetes status ($p = 0.9$). In those with diabetes, this result may not have been statistically significant given the smaller sample size and lower incidence of CVD events. From a safety perspective, aspirin increased the frequency of major GI and extra-cranial bleeds in the general population (0.10% vs 0.07% per year, $p < 0.0001$). Importantly, the main risk factors for coronary disease were also risk factors for bleeding. Additional trials were subsequently completed evaluating the effect of aspirin for primary prevention in the general population, including the Aspirin for Asymptomatic Atherosclerosis (AAA) and the Japanese Primary Prevention Project (JPPP), both in which participants received 100 mg aspirin daily. Neither study found a difference in mortality, MI, or stroke between participants receiving aspirin and those receiving placebo [30, 31]. In 2018, the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial was designed to determine if aspirin 100 mg daily was beneficial to patients at moderate risk of CV disease (excluding those with diabetes), but there was no difference found in the primary outcome between the aspirin group versus placebo group [33]. The Aspirin in Reducing Events in the Elderly (ASPREE) trial evaluated aspirin 100 mg daily compared with placebo among healthy elderly participants (11% with diabetes) and found that aspirin increased the risk of major bleeding without improving disability-free survival or reducing major CV events (see Table 1) [34].

A recent meta-analysis combined 13 RCTs composed of a mix of studies, ten involving general populations and three involving people with diabetes specifically [35]. It found that aspirin, dosed at 100 mg in most of the included studies, reduced the incidence of the composite CV outcome (57.1 events per 10,000 participant-years with aspirin and 61.4 events per 10,000 participant-years with no aspirin) (hazard

Table 1 Major aspirin primary prevention trials in people with and without diabetes

Study	Study population	Percentage (number) and characteristics of participants with diabetes	Study period	Mean follow-up (years)	Aspirin dose	ASCVD endpoint	RR (95% CI) of ASCVD with ASA in participants with diabetes	RR (95% CI) of ASCVD with ASA in participants without diabetes	RR (95% CI) of bleeding with ASA
British Doctors' Study (1988) [24]	Sample size 5139 Age 19–90 Females 0%	2% (103) - Male doctors	1978–1984	5.6	500 mg daily	CV death, nonfatal MI, nonfatal stroke	1.00 (0.42–2.40)	0.98 (0.81–1.18)	Not reported
US Physicians' Health Study (1989) [25]	Sample size 22,071 Age 45–73 Females 0%	2.5% (551) - Male doctors	1982–1988	5.0	325 mg every other day	Fatal and nonfatal MI	0.59 (0.33–1.06)	0.56 (0.45–0.70)	1.32 (1.25–1.40)
ETDRS (1992) [15]	Sample size 3711 Age 18–70 Females 44%	100% (3711) - All had diabetic retinopathy.	1980–1985	5.0	650 mg daily	Fatal and nonfatal MI	0.82 (0.65–1.03)	Not applicable	Not reported
Thrombosis Prevention Trial (1998) [26]	Sample size 5085 Age 45–69 Females 0%	Not recorded - Men with risk factors for CVD	1984–1997	6.7	75 mg daily	Fatal and nonfatal MI	Not recorded	0.90 (0.28–2.89)	Not reported
Hypertension Optimal Treatment Trial (1998) [27]	Sample size 18,790 Age 50–80 Females 47%	8% (1503) - People with HTN	1992–1997	3.8	75 mg daily	Nonfatal MI, nonfatal stroke, and CV death	0.77 (0.44–1.36)	0.85 (0.73–0.99)	Nonfatal major bleeds 1.84
Primary Prevention Project (2001) [28]	Sample size 4495 Age 45–94 Females 58%	17% (764) - People with one or more CVD risk factors	1994–1998	3.7	100 mg daily	Fatal and nonfatal MI	0.85 (0.73–1.00)	0.59 (0.37–0.94)	9.5 (1.9% in aspirin group and 0.2% in non-aspirin group) ($p = 0.007$)
Women's Health Study (2005) [29]	Sample size 39,876 Age older than 45 Females 100%	2.6% (1036) - Female health professionals	1992–2004	10.0	100 mg every other day	Fatal and nonfatal MI	1.34 (0.85–2.12)	0.91 (0.80–1.03)	GI bleeding 1.40 (1.07–1.83) Hemorrhagic stroke 1.24 (0.82–1.87)
POPADAD (2008) [18]	Sample size 1276 Age older than 40 years Females 56%	100% (1276) - All had ABPI < 0.99	1997–2006	6.7	100 mg daily	ASCVD death + nonfatal MI	0.87 (0.40–1.87)	Not applicable	GI bleeding 0.90 (0.53–1.52)
JPAD (2008) [16]	Sample size 2539 Age 30–85 Females 45%	100% (2539) - No known CVD	2002–2008	4.4	81 or 100 mg daily	Fatal or nonfatal MI, fatal or nonfatal stroke, and peripheral arterial disease (PAD)	0.80 (0.58–1.10)	Not applicable	Not reported

Table 1 (continued)

Study	Study population	Percentage (number) and characteristics of participants with diabetes	Study period	Mean follow-up (years)	Aspirin dose	ASCVD endpoint	RR (95% CI) of ASCVD with ASA in participants with diabetes	RR (95% CI) of ASCVD with ASA in participants without diabetes	RR (95% CI) of bleeding with ASA
AAA (2010) [30]	Sample size 3350 Age 50–75 Females 72%	3% (100) - ABPI < 0.95	1998–2008	8.2	100 mg daily	Fatal or nonfatal MI or stroke or revascularization	Not reported	1.03 (0.84–1.27)	Major hemorrhage requiring hospital admission 1.71 (0.99–2.97)
JPPP (2014) [31]	Sample size 14,464 Age 60–85 Females 58%	34% (4917) - Participants had to have either HTN, dyslipidemia, or diabetes	2005–2012	5.02	100 mg daily	Death, nonfatal MI, nonfatal CVA	0.89 (0.66–1.18)	0.94 (0.77–1.15)	Extra-cranial hemorrhage requiring transfusion or hospitalization 1.85 (1.22–2.81)
JPAD2 (2016) [17]	Sample size 2160 Age 30–85 Females 45%	100% (2160) - No known CVD	2008–2015	10.3	81 or 100 mg daily	Sudden death, fatal or nonfatal MI, fatal or nonfatal stroke, and PAD	1.14 (0.91–1.42)	Not applicable	1.22 (0.88–1.69)
ASCEND (2018) [32••]	Sample size 15,480 Age older than 40 Females 37%	100% (15,480) - No known CVD	2005–2011	7.4	100 mg daily	First vascular event (MI, stroke or TIA, or CV death)	0.88 (0.79–0.97)	Not applicable	1.29 (1.09–1.52)
ARRIVE (2018) [33]	Sample size 12,546 Age men ≥ 55 and women ≥ 60 Females 30%	0% - Males with ≥ 2 and females with ≥ 3 CV risk factors	2007–2016	5.0	100 mg daily	Composite outcome of time to first occurrence of CV death, MI, unstable angina, stroke, or TIA	Not applicable	0.96 (0.81–1.13)	GI bleed 2.11 (1.36–3.28)
ASPREE (2018) [34]	Sample size 19,114 Age ≥ 65 in Blacks and Hispanics and ≥ 70 in other individuals Females 56%	11% (2102) - Older adults were the target population	2010–2014	4.7	100 mg daily	Disability-free survival (survival free from dementia or persistent physical disability)	RR of primary outcome not reported Risk of death from any cause in those with diabetes 1.33 (0.97–1.82)	1.01 (0.92–1.11)	Major hemorrhage 8.6 events per 1000 person-years in the aspirin group vs 6.2 events per 1000 person-years in the placebo group ($p < 0.001$)

CV, cardiovascular; *MI*, myocardial infarction; *HTN*, hypertension; *CVD*, cardiovascular disease; *ASCVD*, atherosclerotic cardiovascular disease; *ABPI*, ankle-brachial pressure index

ratio (HR), 0.89 (95% confidence interval, 0.84–0.95); absolute risk reduction, 0.38% (95% CI, 0.20–0.55%); number-needed-to-treat, 265). However, aspirin increased the incidence of major bleeding (23.1 per 10,000 participant-years with aspirin versus 16.4 per 10,000 participant-years with no aspirin) (HR, 1.43 (95% confidence interval, 1.30–1.56); number-needed-to-harm, 210). In participants with diabetes (19% of the trial population), aspirin reduced the composite CV outcome (HR, 0.89 (95% confidence interval, 0.80–1.00); absolute risk reduction, 0.65% (95% CI, 0.1–1.16%), but increased the rates of major bleeding (HR, 1.29 (95% confidence interval, 1.11–1.51).

Major Aspirin Primary Prevention Trials in People with Diabetes

There have been 4 primary prevention studies conducted specifically evaluating the effect of aspirin on cardiovascular disease outcomes in patients with diabetes. The Early Treatment of Diabetic Retinopathy Study (ETDRS) looked at the effect of aspirin versus placebo in patients with type 1 or type 2 diabetes and retinopathy [15]. About 49% of people in this trial had a history of cardiovascular disease, which included patients taking antihypertensive medication. Less than 10% of patients had a previous MI or stroke. Patients assigned to aspirin exhibited a lowered risk of nonfatal or fatal MI (RR 0.85, 95% CI 0.73–1.00). In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, participants were assigned to low-dose ASA versus placebo and followed for an average of 4.4 years [16]. There was no difference in the primary outcome (a composite of fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, or PAD) or mortality between those assigned to aspirin and those to placebo. The JPAD2 study extended the follow-up to 10.3 years, and it found an increased risk of GI bleeding in patients taking aspirin and no decrease in CV events [17]. The Prevention of Progression of Arterial Disease and Diabetes trials (POPADAD) evaluated whether 100 mg aspirin and/or antioxidants were better than placebo at preventing cardiovascular events in patients with diabetes and asymptomatic PAD [18]. There was not a significant difference in the rate of CHD or stroke death between the intervention and placebo groups over a mean follow-up of 6 years. A 2010 position statement jointly issued by the American Diabetes Association, the American Heart Association, and the American College of Cardiology performed a meta-analysis by adding in the data from the 3 trials using aspirin in patients with diabetes alone (ETDRS, JPAD, POPADAD) to the data from the subgroup of patients with diabetes in the ATT meta-analysis [36]. They discovered that aspirin did not significantly reduce the number of CV events (RR 0.91, 95% CI 0.79–1.05). The investigators concluded that aspirin probably reduced CV risk by a modest amount, but the true effect size was difficult to determine given a lack of enough events in the primary prevention trials and the reliance on subgroup analyses from general population studies.

Findings from the recent trial, A Study of Cardiovascular Events in Diabetes (ASCEND), were published in 2018. This trial randomized 15,480 patients with diabetes (62.5% men, 96% White, mean age 63 years) to either 100 mg aspirin daily or placebo and then followed them for an average of 7.4 years [32••]. The primary efficacy outcome was the first serious vascular event, which was a composite of MI, stroke or TIA, or death from any vascular cause. The primary safety outcome was the first major bleeding event (composite of intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or other serious bleeding). 8.5% of those assigned to aspirin had a serious vascular event versus 9.6% of those assigned to placebo (rate ratio 0.88, 95% CI 0.79–0.97) for a NNT of 91. However, 4.1% of participants assigned to aspirin had a major bleeding event versus only 3.2% of those assigned to placebo (rate ratio 1.29, 95% CI 1.09–1.52), for a number-needed-to-harm of 112. GI bleeds accounted for 42.5% of the major bleeding events; notably, only 25% of patients were on PPI's by trial's end. Eighty percent of patients in the trial had a hemoglobin A1c < 8.0%, 75% were on a statin, and < 10% were current smokers.

The overall body of literature suggests that, on a population level, the cardiovascular benefits of aspirin for primary prevention may be outweighed by the increased bleeding risk from taking aspirin in people with diabetes though the net clinical benefit at the individual level may differ.

Aspirin Resistance

The lack of consistent overall net clinical benefit of aspirin in preventing ASCVD in adults with diabetes has raised concerns about "aspirin resistance," a phenomenon that has been largely debated in literature. In this section, we discuss important points related to the platelet response to aspirin in people with and without diabetes and how the inconsistent findings from previous studies can be interpreted. First, it is essential to distinguish between "clinical aspirin resistance" and "physiological aspirin resistance/high on-treatment platelet reactivity" when discussing aspirin resistance. Although these terms refer to different phenomena, they are often used interchangeably and this may explain some of the mixed conclusions from observational studies on aspirin resistance.

Clinical Aspirin Resistance This refers to the ineffectiveness of aspirin in reducing ASCVD events in people who are prescribed daily aspirin. This is a non-specific definition of aspirin resistance but a common one used in literature. Reduced oral bioavailability of aspirin (e.g., enteric-coated aspirin), patient lack of adherence to therapy, or concomitant use of non-

steroidal anti-inflammatory drugs are some of several factors that can lead to "clinical aspirin resistance" and contribute to what many believe is an overestimation of the prevalence of aspirin resistance in literature. Obesity has also been linked to a reduced effectiveness of low-dose aspirin in preventing ASCVD; and a weight-based dose of aspirin has been suggested as a more optimal approach to provide net clinical benefit of aspirin in preventing ASCVD [37]. In addition, sex differences in the effects of aspirin in primary prevention of ASCVD events have been previously suggested in the Antithrombotic Trialists' Collaboration; but at the platelet level, both men and women appear to have a comparable response to low-dose aspirin [19••, 38].

Physiological Aspirin Resistance (High on-Treatment Platelet Reactivity) This refers to the inability of aspirin to fully inhibit the COX-1 activity and platelet aggregation. In contrast to clinical aspirin resistance, this is a more specific definition and considered a more rare phenomenon. We have recently shown that people with diabetes who had no history of ASCVD have a similar in vitro platelet response to aspirin therapy compared with those without diabetes, refuting the notion of physiological aspirin resistance in diabetes [20••]. Those with diabetes have a higher in vivo platelet activation before and after aspirin therapy compared with those without diabetes suggesting that the greater platelet activation in people with diabetes may be due to factors that are extrinsic to the platelets (e.g., endothelial dysfunction). A systematic review of 31 studies showed a higher prevalence of high on-treatment platelet reactivity in people with versus without diabetes; however, the conclusion from this study should be interpreted with caution due to the considerable differences among measures to assess platelet function used across those studies and heterogeneity in clinical characteristics of the participants in those studies (including differences in risk of ASCVD) [39].

Taken together, it appears that the intrinsic (in vitro) platelet response to low-dose aspirin is likely not different in people with versus without diabetes; and any differences observed clinically in the net benefit of aspirin for primary prevention of ASCVD by diabetes status are more likely to be due to "clinical aspirin resistance" or "physiological aspirin resistance" that is due to factors extrinsic to the platelets.

Clinical Considerations

Diabetes has long been categorized as a CVD risk factor and at times a CVD equivalent, though the exact increase in risk has been difficult to quantify and likely varies by the presence of other ASCVD risk factors [40]. Thus, instead of considering diabetes in isolation as a high-risk category, many society guidelines endorse the use of a risk calculator and also consider other variables contributing to CVD. Over 100 risk calculators are present in the literature, with more than 40 specific to those with diabetes [41]. Arguably, the most popular recent calculator is the ACC/AHA ASCVD risk calculator, which is based on the pooled cohort equations (PCE) and includes the presence of diabetes as a risk factor, though no metric of diabetes control or duration is included [42]. The PCE may overestimate or underestimate the ASCVD risk depending on the population studied and, further, validation in people with diabetes has not yet been specifically studied [43]. The Framingham and Systematic Coronary Risk Evaluation (SCORE) risk calculators are also popular, but may underestimate risk in those with diabetes, as their initial cohorts contained relatively small populations with diabetes [44]. The most specific risk engine for people with diabetes is likely the United Kingdom Prospective Diabetes Study (UKPDS) engine, which considers HbA1c and duration of diabetes in its risk calculation [45]. In the real world, this has been shown effective in ranking cardiovascular risk among those with diabetes but may overestimate the actual risk [46].

Regarding current guidelines on aspirin for primary prevention in those with diabetes, a 2015 AHA/ADA joint scientific statement suggested that low-dose aspirin (75–162 mg) is reasonable for those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding, and also reasonable for those with a risk of 5–10%, though they note weaker data for the latter [47]. However, in light of new data, the 2019 ACC/AHA guidelines changed that recommendation to recommending low-dose aspirin only in those "40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk, removing the specific risk calculator score consideration as they recognized that the calculator tended to overestimate the actual rates of ASCVD [48]. This update recommends against aspirin in adults > 70 and in those aged 40–70 at higher bleeding risk, regardless of ASCVD risk. The 2019 ADA Standards of Medical Care in Diabetes suggests considering the use of aspirin for primary prevention in adults aged ≥ 50 years with diabetes at high CVD risk with low bleeding risk; but generally not in adults older than 70 years as the risk of bleeding appears to be greater than the cardiovascular benefit in this age group [49]. Many other societies have tempered their aspirin recommendations as well (see Table 2).

Regarding the risk of overall bleeding, those with diabetes may be at higher risk than those without, though aspirin does not appear to independently exacerbate that risk. A 2012 Italian cohort study of over 300,000 people found that of the approximately 56,000 people with diabetes, those on ASA therapy were not at higher risk of hemorrhagic events compared with those who were not. However, irrespective of aspirin use, diabetes was independently associated with an increased risk of major bleeding episodes (IRR, 1.36; 95% CI, 1.28–1.44) [53]. Increased risk of bleeding in those with diabetes using other forms of anticoagulation (AC) is mixed, with some finding diabetes

Table 2 Summary of guideline recommendations on the use of aspirin for primary prevention of ASCVD in people with diabetes

Society	Populations recommended *for*	Populations recommended *against*
American Diabetes Association [49]	If at increased CV risk, after discussion of benefits versus increased risk of bleeding	- < 50 years with no other major ASCVD risk factors - > 70 years old: carefully consider and may generally not be recommended
American College of Cardiology/American Heart Association [48]*	40–70-year-olds who are at higher ASCVD risk but not at increased bleeding risk	-Age > 70 - Aged 40–70 at higher bleeding risk, regardless of ASCVD risk
USPSTF [50]*	A) 50–59-year-olds with ≥ 10% 10–year CVD risk are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years B) 60–69-year-olds with ≥ 10% 10-year CVD risk—individualize decision based on patient risk of bleeding, life expectancy, and willingness to take low-dose aspirin daily for at least 10 years.	-Insufficient evidence to make recommendations in those ≥ 70 or < 50 years old
European Society of Cardiology and others [51]*¶	In patients with DM at high/very high risk, aspirin may be considered in primary prevention.	-In patients with DM at low/moderate CV risk, aspirin for primary prevention is not recommended
Canadian Cardiovascular Society [52]*	In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk is low	-Men and women without evidence of manifest vascular disease

*Not specific to those with diabetes

¶ *ESC*, European Society of Cardiology; *EASD*, European Association for the Study of Diabetes; EAS, European Atherosclerosis Society; EHN, European Heart Network; *ESH*, European Society of Hypertension; ESO, European Stroke Organization; *IDF Europe*, International Diabetes Federation European Region; *FIMS*, International Federation of Sport Medicine; ISBM, International Society of Behavioural Medicine; WONCA Europe

an independent risk factor for major and non-major bleeding and others seeing no increased risk [54, 55].

To date, no bleeding risk calculators specifically for those with diabetes exist. The major bleeding risk calculators (HAS-BLED; HEMORR(2)HAGES, ATRIA) for patients being considered for starting AC do not include diabetes as a risk factor [56–58].

Summary and Future Direction

Though people with diabetes have an increased risk of ASCVD compared with those without diabetes, several randomized controlled trials and meta-analyses have questioned the overall net clinical benefit of aspirin use for primary prevention of ASCVD in most people with diabetes. The optimal antithrombotic regimen for primary prevention of ASCVD in people with diabetes remains to be established. In clinical practice, balancing the cardiovascular benefit of low-dose aspirin for primary prevention and bleeding risk must be considered in all patients, especially those with diabetes. The persistent higher in vivo platelet activation in people with diabetes after aspirin therapy has raised interest in identifying more effective antithrombotic regimens for primary prevention in this population. Increasing the dose of aspirin to > 150 mg daily or frequency to twice-daily low-dose aspirin has been suggested; however, future studies are needed to assess the long-term CVD outcomes for such strategies [59–61]. Future research is also needed to examine the risk-benefit ratio of aspirin use for primary prevention in adults with diabetes when low-dose aspirin is used concurrently with proton-pump inhibitors (to lower the risk of GI bleeding) and statin or antioxidant therapy (to lower the ASCVD risk) and in those with multiple ASCVD risk factors [62]. Such strategies may shift the risk-benefit balance of aspirin use toward an overall net clinical benefit. For the meantime, it is recommended that the decision to start aspirin for primary prevention of ASCVD in adults with diabetes be considered carefully on an individual basis. In addition, a multifactorial approach that focuses on promoting a healthy lifestyle, smoking cessation, and managing other ASCVD risk factors such as hypertension, dyslipidemia, and dysglycemia is recommended in people with diabetes.

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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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