Aspirin and Primary Prevention in Patients with Diabetes—A Critical Evaluation of Available Randomized Trials and Meta-Analyses

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Abstract

Primary prevention of cardiovascular events with aspirin in patients with elevated cardiovascular risk, including diabetics, is currently under intense discussion. Data from meta-analyses suggests that the efficacy of aspirin in these patients is low, whereas there is a significantly increased bleeding tendency. However, meta-analyses are based on trials that differ in many important aspects, including study selection. Fresh insights were expected from the ASCEND trial, by far the largest primary, randomized, placebo-controlled prevention trial in diabetics without known cardiovascular disease. There was a small but significant reduction in serious cardiovascular events by aspirin (8.6% vs. 9.6%) but also a significant increase in major bleeding: 4.1% versus 3.2%. Unfortunately, this trial did not meet the desired annual rate of elevated vascular risk of $\geq$ 2%. It was only 1.2 to 1.3%, and thus in the range of other primary prevention trials in low-risk patients. Apart from potential compliance problems, possible explanations for the small cardioprotective effect of antiplatelet treatment include a healthy lifestyle as well as improved vascular protection by comedication with vasoactive and anti-inflammatory drugs, such as statins or antihypertensive agents, as well as proton-pump inhibitors that might modify bleeding, specifically in the upper gastrointestinal tract—the most frequently affected site. Also, the introduction of new antidiabetic drugs with more favorable cardiovascular effects may in part explain the low event rate. ASCEND, similar to ARRIVE, did not study patients at elevated (as planned) but only at low vascular risk and, therefore, was largely confirmatory of earlier primary prevention trials.

Keywords
- diabetes
- aspirin
- primary prevention
- myocardial infarction
- bleeding

Introduction

Diabetes mellitus is a systemic disease, associated with low-grade inflammation. There is high on-treatment platelet reactivity (HTPR) with some antiplatelet drugs, as seen from elevated levels of inflammatory and platelet activation markers.[1] Diabetes is related to risk of death from both vascular and nonvascular reasons. There is a strong linear correlation between vascular and nonvascular death and fasting glucose levels above 6 mmol/L (ca. 110 mg/dL)[2] (►**Fig. 1**). The prevalence of diabetes is continuously increasing, by a remarkable 50 to 100% during the past 20 years in some European countries,

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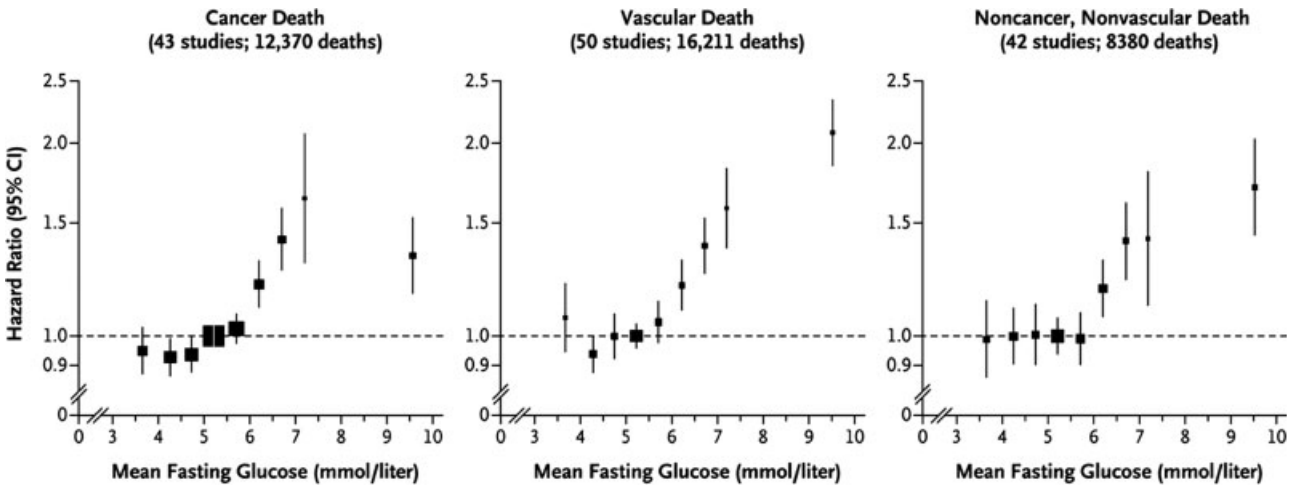

Fig. 1 Hazard ratios for major causes of death, according to baseline levels of fasting glucose. Glucose levels for participants without a known history of diabetes at baseline were classified as less than 4.0, 4.0 to less than 4.5, 4.5 to less than 5.0, 5.0 to less than 5.5, 5.5 to less than 6.0, 6.0 to less than 6.5, 6.5 to less than 7.0, 7.0 to less than 7.5, and 7.5 mmol per liter or higher. Hazard ratios were plotted against the mean fasting glucose level in each group (reference category, 5.0 to < 5.5 mmol per liter). The sizes of the data markers are proportional to the inverse of the variance of the log hazard ratios. All analyses were stratified or adjusted for sex and adjusted for baseline age, smoking status (current smoker vs. any other status), and body mass index. Participants with known preexisting cardiovascular disease at baseline were excluded from all analyses. (Reprinted with permission from Rao Kondapally Seshasai et al.[2]

including Finland and the United Kingdom.[3] A frequently cited Finnish diabetes trial, published 20 years ago, showed an annual myocardial infarct risk of patients with noninsulin-dependent diabetes of 3.2% as opposed to 0.5% in nondiabetics. The cardiovascular (CV) mortality per 100 person-years was 2.5% as opposed to 0.3% in nondiabetics.[4] This was equivalent to a six- to eightfold increased vascular risk in diabetic persons and led to the conclusion that diabetic patients without previous myocardial infarction (MI) have the same high risk of a MI as nondiabetic patients with previous MI.[4]

The present report focuses on the importance of adequate thrombosis prophylaxis in diabetics in addition to control of hyperglycemia and insulin resistance. Aspirin is the best-studied compound in this respect. Interestingly, more recent studies and meta-analyses could not confirm the beneficial effects seen in early trials. They rather found that aspirin in diabetics has only a small, if any, effect on major CV outcome parameters, but constantly increases the risk of bleeding.[5–9] It is, however, questionable whether the current thrombotic risk of diabetics is still the same as in studies published 20 years ago when, with the exception of metformin, no effective antidiabetics were available for treatment of noninsulin-dependent diabetes mellitus. In addition, there were only few, if any, drugs to retard or even prevent the typical vascular changes in diabetes, notably the progression of diabetic macro- and microangiopathy. A bulk of compounds is available meanwhile, including statins, angiotensin-converting enzyme (ACE) inhibitors, sartans, and others for concomitant treatment of modifiable vascular risk factors, such as hypercholesterolemia or hypertension. In addition, there is now a significant number of new oral antidiabetics with established vasoprotective activities that are associated with decreased CV mortality, such as empagliflozin and other inhibitors of sodium glucose cotransporter-2,[10] dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists.[11] This raises the question whether the improved antidiabetic treatment and comedications, such as statins, have an impact on the efficacy of antithrombotic drugs such as aspirin. This is particularly relevant for primary prevention. There is no question on secondary prevention, where aspirin received a grade A recommendation for prevention of vascular events in diabetics according to the 2018 recommendations of the American Diabetes Association (ADA).[11]

This article discusses the current position of aspirin as the most intensively studied antiplatelet drug in primary prevention of CV events in diabetics. This review also tries to explain the different outcome data, specifically with respect to early and more recent clinical studies. The role of different inclusion and exclusion criteria of trials, efficacy parameters, study duration, aspirin galenics, dosing, and dosing intervals are also discussed, as is the possible role of comedications. Initially, the multiple diabetes-related alterations of the clotting system that determine the overall diabetic vascular and nonvascular risk are summarized. The risk profile of diabetics differs in different trials along with the severity and duration of diabetes and this may altogether determine the clinical outcomes and the efficacy and risk of aspirin use.

Pathophysiology of Elevated Thrombotic Risk in Diabetics

There are multiple reasons for an elevated thrombotic risk in diabetes patients. These include not only most components of the clotting system but also other soluble mediators and secretory functions of the vessel wall. Hyperglycemia may play an independent role in the abnormalities of platelets of diabetic patients.[12] Most important determinants are hyperreactive platelets and an enhanced platelet turnover rate[13] with an increased proportion of reticulated platelets.[14] These immature platelets are known to be more reactive than mature platelets. They also bear significant amounts of

cyclooxygenase-2 (COX-2) protein, due to carryover from the bone marrow megakaryocytes.[15] Reticulated platelets are considered an independent predictor of major adverse CV events, including mortality, in diabetics.[16] In addition, there are multiple proinflammatory transformations of the vessel wall, predominantly in context with an enhanced oxidative stress and increased levels of inflammatory mediators. At the same time, antioxidative defense is reduced, resulting in the formation of advanced glycation end products[17–19] as well as platelet-activating isoprostanes and lipid peroxides.[19]

Targets of Aspirin

In 1991, the first evidence for an association between platelet number and reactivity with long-term incidence (13.5 years) of fatal coronary heart disease in apparently healthy, middle-aged men was provided. Interestingly, there was no association between platelets and the development of angina pectoris. This suggested that the role of blood platelets was rather to precipitate acute complications of coronary artery narrowing than to change the progression of the atherosclerotic disease itself.[20] A similar conclusion was drawn from the data of the Physicians' Health study,[21,22] suggesting that the cardioprotective actions of aspirin are limited to the prevention of platelet-mediated vessel occlusion.

The major target of thrombosis prevention by antiplatelet drugs such as aspirin in diabetics is, by definition, the blood platelet and the megakaryocyte, respectively.[23,24] The outstanding position of platelets is also evident from their priming function in tissue factor-dependent thrombin formation that occurs mainly at the surface of activated platelets and then starts the "bulk" thrombin formation.[25,26] Another reason is that platelets are the dominant source of thromboxane A_2, the major platelet-related stimulus for aggregate formation, stimulation of white cells and platelet-white cell aggregates, and thrombin formation. Inhibition of platelet-COX-1,[27] and thus the COX-1-dependent thromboxane formation and its multiple autocrine and paracrine functions, is the generally accepted mode of antiplatelet action of aspirin.[28]

The more rapid platelet turnover rate in diabetics is also associated with a lower sensitivity to and shorter duration of antiplatelet actions of aspirin in vivo. This pharmacological action is determined by the survival of acetylated, that is COX-1-inactivated, platelets in the systemic circulation.[23,29–31] Shortened survival will contribute to a reduced efficacy of aspirin as a coronary preventive in diabetics[32] as well as a suboptimal inhibition by antiplatelet agents after platelet stimulation by oxidative stress-related mechanisms.[19] This eventually results in clinical aspirin "resistance," that is, a too rapid recovery of the reduced platelet-dependent thromboxane formation[33] with its multiple procoagulant consequences, including platelet stimulation by nonaspirin-sensitive mechanisms.

Meta-Analyses

The older data from the Antiplatelet Trialists Collaboration obtained from studies finished until 1997, with aspirin as the most frequently used antiplatelet drug, indicate a reduction of vascular events from 22.3 to 18.5% in diabetics ($p < 0.002$) and from 16.4 to 12.8% in nondiabetics with antiplatelet therapy ($p < 0.0001$).[34,35] This confirms a higher incidence of vascular events in diabetics but also a consistent benefit of aspirin treatment, which reduced the event rate by 17 and 22%, respectively. However, these data were mainly derived from secondary prevention trials.

The odds ratio (OR) for aspirin in primary prevention of serious vascular events in 6 primary prevention trials was: 0.88 (95% confidence interval [CI]: 0.67–1.15) in diabetics and 0.87 (95% CI: 0.79–0.96) in nondiabetics, corresponding to a total OR in all 6 primary prevention trials of 0.88 (95% CI: 0.82–0.94; $p = 0.0001$).[36] Similar data were obtained in the meta-analysis of De Berardis et al,[37] showing a trend for reduced CV events in favor of aspirin in 6 selected prospective randomized trials (relative risk [RR] for aspirin vs. placebo or no treatment: 0.90; 95% CI: 0.81–1.00), which was not significant. No effect was seen in other more recent meta-analyses.[7,38] Interestingly, there was a considerable heterogeneity in the incidence of MIs ($p = 0.02$) and stroke ($p = 0.08$). Aspirin significantly reduced MI in men (RR: 0.57, 95% CI: 0.34–0.94) but not in women (RR: 1.08; 95% CI: 1.08–1.65), but this effect was no longer evident when limiting the analysis to the more recent trials.[38] There was also some inconsistent evidence of harm.[37] Another review of 5 meta-analyses on aspirin in primary prevention, published between 2008 and 2013, came to similar results and concluded that the available data on aspirin in primary prevention suggests a modest benefit for patients at high risk of CV disease, and a promising benefit for those at risk of cancer. However, there was an increased risk of bleeding and future studies should help to elucidate whether the benefit of aspirin outweighs risk in appropriate patient groups.

Meta-analyses are useful tools in evidence-based medicine and allow more reliable estimates of the effect of drug treatment than individual studies. Major benefits are the large number of cases resulting in a higher statistical power, allowing hypothesis generation also for more random events. In addition, they have the advantage of generalization to a larger population. However, the investigator must make choices. Study selection and careful editing of data and the weight of individual studies, that is, quality and size, of included data are essential to make different studies intercomparable. Only methodological sound studies should be included with the possible negative consequence of causing selection bias. In the CV field, it was recently shown that among 56 meta-analyses reporting relationships between biomarkers and CV events, there was considerable heterogeneity and only 13 were not affected by selection bias.[39] In addition, publication bias may arise in favor of the drug being tested if not all negative trials with this drug have been published. Thus, meta-analyses are secondary sources of information. They are hypothesis-generating but do not define causality and their messages need to be confirmed in prospective randomized trials.

According to a recent review of randomized, placbo-controlled primary prevention trials with aspirin that also included diabetics, there were considerable differences in the composition of the study populations. These included differences in numbers of men and women and the proportion of diabetics,

differences in primary study endpoints, often insufficient sample size to allow statistical analysis of clinical outcome, and differences in treatment duration as well as inclusion and exclusion criteria.[7] In addition, comedications and, in particular, patients' compliance are two other independent but quite important variables that might be different between different trials. Finally, heterogeneities in trial baseline risk of the included studies might also influence the results of meta-analyses by selection bias.

The Primary Prevention Trials in Diabetes

A clear pathophysiological connection between diabetes and CV thrombotic events was shown by a Finnish population-based nonrandomized trial. This study investigated the relationship between noninsulin-dependent diabetes mellitus and MI and was the first trial to document a remarkably increased vascular atherothrombotic risk in diabetic subjects: 3.2% per year versus 0.5% per year in nondiabetics. This was associated with a seven- to eightfold higher vascular mortality.[4] There was not much information about medical treatment except the note that only 9 out of the 1,059 diabetic and 1,373 nondiabetic subjects received treatment with "hypolipidemic drugs" (not specified). Treatment with antiplatelet or antithrombotic drugs was not reported and there was also no data about the severity of diabetes, metabolic control, and/or progression of the disease, for example, in terms of hemoglobin A_{1c} (HbA_{1c}) values or blood glucose levels. Total serum cholesterol was around 250 to 270 mg/dL and not different between the groups of patients.[4] Thus, there was a significant thrombotic risk in diabetics that should be treated adequately.

A few randomized, placebo-controlled primary prevention trials with aspirin in diabetics are also available. The first was the "Early Treatment Diabetic Retinopathy Study" (ETDRS) including both type 1 and type 2 diabetics. The RR for the occurrence of fatal and nonfatal MIs did not differ between the aspirin- and placebo-treated patients (RR: 0.83 [99% CI: 0.66–1.04]). There was no evidence of harmful effects of aspirin, and the primary endpoint total mortality remained unchanged.[40] The authors concluded that use of aspirin in diabetics at elevated CV risk was supported by their results.[40] However, the aspirin dose was high (325 mg twice daily) and is not representative of today's CV prevention with aspirin.

Two other randomized prospective trials using low antiplatelet doses of aspirin have had impact on the discussion of the usefulness of aspirin in primary CV prevention in diabetics for a long time: The "Prevention of Progression of Arterial Disease and Diabetes" (POPADAD) trial and the "Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes" (JPAD) trial.

The POPADAD study was a randomized, double-blind, placebo-controlled trial in 1,276 adults ($\geq$ 40 years), suffering from type 1 or 2 diabetes and asymptomatic peripheral arterial disease (ankle-brachial index [ABI] $\leq$ 0.99) but no symptomatic CV disease. Patients were treated with aspirin (100 mg/day), placebo, and/or an antioxidant using a 2×2 factorial design. Primary endpoint was the composite of CV ischemic events, stroke, CV death, or amputation. After an average observation period of 6.7 years, there were no significant differences between aspirin and placebo with respect to the incidence of MI and death. There were 18.2% primary vascular events in the aspirin group as opposed to 18.3% in the patients receiving placebo (hazard ratio [HR]: 0.98; 95% CI: 0.76–1.26). There was no increased incidence of bleeding or other adverse effects in the aspirin group. The conclusion was that aspirin is not useful for prevention of CV events in diabetics with asymptomatic peripheral arterial disease.[41]

Inconclusive results were also obtained in the JPAD trial, again a prospective, randomized but open-label study including 2,539 Japanese patients with type 2 diabetes and no known CV disease. Patients in the active-treatment group were treated with aspirin (81 or 100 mg/day). For patients of the nonaspirin group, other not well controlled medications including aspirin and antithrombotics were allowed "if needed." Any other concurrent treatment was allowed, including statins (26% in both groups) and ACE inhibitors/angiotensin receptor blockers (ARBs) (35% in both groups). The use of proton-pump inhibitors (PPIs) was not specified. The combined primary endpoint was complex and included all types of atherosclerotic vascular events, newly diagnosed angina, aortic dissection, and peripheral vascular disease. After an average observation period of 4.4 years, there was a nonsignificant overall absolute risk reduction from 6.7 to 5.4%, that is, by 20% (HR: 0.80; 95% CI: 0.58–1.10, $p = 0.16$) in the aspirin group. There were 12 gastrointestinal (GI) bleeding events in the aspirin group and 4 in the control group and 6 versus 7 hemorrhagic strokes in both groups. Interestingly, there was only one fatal ischemic event (stroke) in the aspirin group as opposed to 10 events (MI and strokes) in the control group (HR: 0.10; 95% CI: 0.01–0.79, $p = 0.0037$). The overall conclusion was that aspirin did not reduce the risk of CV events in type 2 diabetics.[42] This conclusion was confirmed at 10-year follow-up.[43]

These studies had several weaknesses.[44] Both the POPADAD and JPAD trials appear to be underpowered. There was an 1.70% annual event rate of the primary endpoint in the control and 1.36% in the aspirin group in the JPAD trial. In POPADAD, the annual vascular event rate amounted to 2.9%; however, the sample size calculation was made with an ambitious estimated annual vascular event rate of 8.0%.[44,45] In addition, a considerably higher threshold value for the ABI (< 0.90) than used here (≤ 0.99, with only half of peripheral artery disease patients $\leq$ 0.90) is currently thought to indicate an increased CV risk.[46,47] Another explanation for the unexpectedly low event rate was the beneficial effects of frequent cotreatment[45] that has been shown to markedly reduce the absolute thrombotic risk in primary prevention.[36] Statins also markedly enhance antiplatelet effects of aspirin in diabetics.[48]

In the JPAD trial, problems were the open design as well as the poorly controlled medications in the comparator group. Furthermore, events, such as the development of angina pectoris, were also considered as primary study endpoint although it is known from other primary prevention trials that they are not aspirin-sensitive[22] and might have diluted the statistical power.[22,49] Consequently, it has been suggested that

the 20% risk reduction in the primary endpoint could have become significant if only aspirin-sensitive endpoints would have been included.[44]

The most recent, and by far the largest, study on antithrombotic effects of aspirin in primary prevention of diabetics was "A Study of Cardiovascular Events in Diabetes" (ASCEND).[50] The study included 15,480 diabetics (94% type 2) without known CV disease and an average duration of known diabetes for 6 to 7 years prior to randomization. The vascular risk score was low (5 years' risk of < 5%) in 40% of both groups. Only 8% of patients in both groups had an estimated glomerular filtration rate below 60 mL/min/1.73 m^2. A total of 8% of participants were current smokers, a remarkable 46% in both groups had stopped smoking, and 45% did never smoke. Diabetes was well controlled according to a HbA_{1c} value of < 8 in 80% of patients. Participants were treated with aspirin (100 mg/day enteric coated [EC]) or placebo in a randomized prospective manner. A total of 75% of patients in both groups received cotreatment with statins, 58 to 59% received ACE inhibitors or ARBs. The major oral antidiabetic in both groups was metformin in 65% of patients, while insulin was given to 25%. Only approximately 15% of patients received a PPI on randomization and 24% at the end of the study. The combined primary efficacy endpoint was the first serious vascular event (i.e., MI, stroke [excluding intracranial hemorrhage], transient ischemic attack, and vascular death). This combined endpoint was significantly reduced after an average duration of the study of 7.4 years: The incidence of the primary endpoint was 9.6% in the placebo group as opposed to 8.5% in the aspirin group ($p = 0.01$). This corresponded to an annual event rate of 1.2 and 1.3%, respectively, in both groups or a significant CV risk reduction by 12% in the aspirin group (►**Fig. 2**). This effect was rather small and in the range of the previous meta-analyses of the Antiplatelet Trialists for primary prevention.[36] The number needed to treat was 91 and the number needed to harm was 112. All-cause mortality was unchanged (RR: 0.94; 95% CI: 0.85–1.04). Thus, there was no evidence for a specific diabetes-related enhanced vascular risk, opposite to the original diabetes-vascular risk studies of Haffner et al mentioned above with an annual incidence rate of MIs of around 3%.[4] At the same time, there was a significant increase of severe bleedings: 3.2% in the placebo versus 4.1% in the aspirin group ($p = 0.003$) (►**Fig. 2**). There were no statistical evaluations of vascular risk in particular subgroups, such as patients with MI.

How to explain these variable findings? Sufficient adherence to study medications is a most relevant point that always has to be considered as an explanation for variable study outcome. Compliance in the diabetes trials varied between 50% (POPADAD) and > 90% (ETDRS).[37] These numbers, in most cases, rely on patient information and there are very few objective validations of these numbers, for example, by measuring appropriate biomarkers. Reduced adherence to aspirin has previously been shown to significantly reduce aspirin's efficacy in primary prevention in the Physicians' Health study

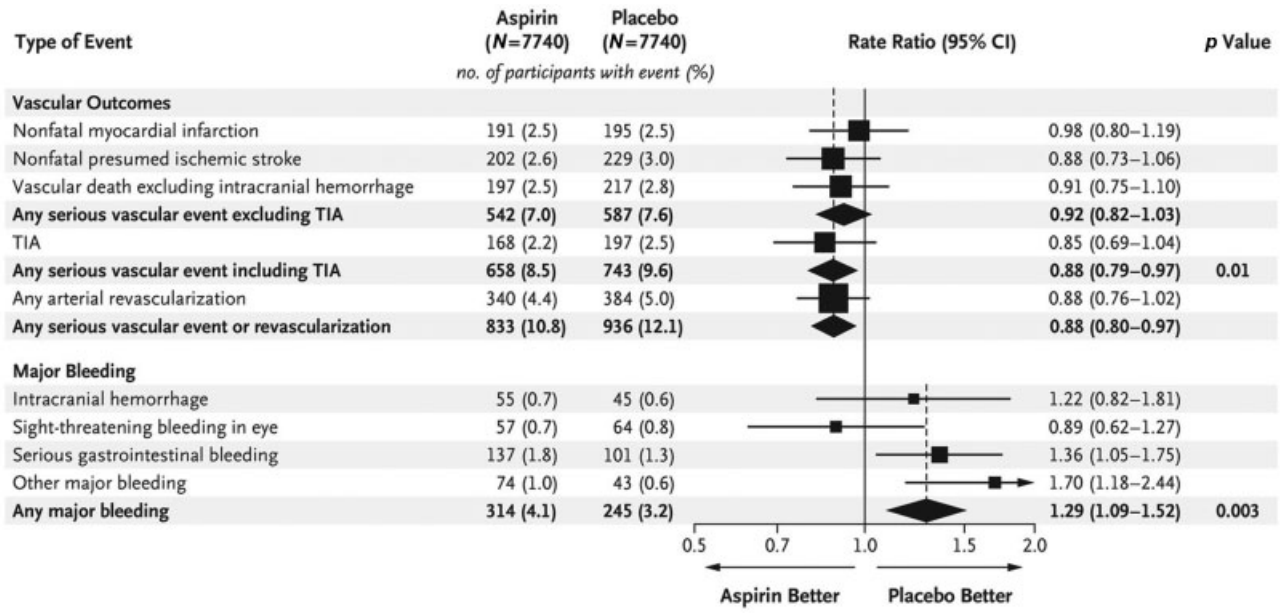

Fig. 2 First serious vascular event (nonfatal myocardial infarction [MI], ischemic stroke or transient ischemic attack [TIA], vascular death without intracranial cerebral hemorrhage [ICH], as well as major bleeding and its components). The ASCEND study.[50] The primary outcome was a serious vascular event (a composite of nonfatal myocardial infarction, nonfatal ischemic stroke or transient ischemic attack [TIA], or death from any vascular cause, excluding confirmed intracranial hemorrhage). Secondary outcomes were a serious vascular event or any coronary or noncoronary revascularization procedure. A single participant may have had multiple events and therefore may contribute information to more than one row. The size of each square for the rate ratio is proportional to the amount of statistical information that was available, the horizontal lines represent 95% confidence intervals, and the dashed vertical line indicates the overall rate ratio for the effect of aspirin use on the first serious vascular event. An arrow on the horizontal line indicates that the confidence interval exceeds the graph area. For composite outcomes, rate ratios and their corresponding 95% confidence intervals are represented by diamonds. Bold entries with diamonds show totals for all data listed above them. The effect of aspirin use on the components of the primary safety outcome of major bleeding event (a composite of intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other major bleeding event) is shown with the use of the same graphic conventions. Reprinted with permission from ASCEND Study Collaborative Group.[50]

where 325 mg aspirin each other day was compared with placebo or β-carotene.[51] According to information by the patient (tablet counting), compliance was estimated as 70% in both groups of ASCEND. This was validated by determination of a nonplatelet-specific thromboxane metabolite (11-DH-TXB_2) in urine. However, this measurement was done only once during the total study duration of more than 7 years and only in 1% of aspirin-treated patients. In these patients, there was a 86% suppression of thromboxane metabolite excretion (11-DH-TXB_2) in aspirin-compliant participants. It was not reported whether these patients were also on statin treatment.[52] This might have had an impact on compliance and could explain the decrease in MIs in a subgroup analysis of the subjects treated "per protocol" with an HR of 0.53 ($p = 0.0014$) compared with placebo in contrast to the conventional intention-to-treat analysis.[53]

Adjunctive Treatments

Diabetic macro- and microangiopathy are progressive diseases, characterized by early endothelial dysfunction, oxidative stress, and vascular inflammation. Several mechanisms are involved, including glycation of platelet surface proteins that decreases membrane fluidity, activation of protein kinase C, and others.[54] Consequently, glucose-lowering treatment by new oral antidiabetics has been shown to reduce the incidence of atherothrombotic events in diabetics in both primary and secondary prevention.[10,55,56] In addition, inadequate insulin secretion and/or diminished tissue responses are not only the key event for the development of diabetes but also for diabetes-associated platelet dysfunction.[57] Insulin "resistance," that is, higher circulating levels of insulin, also stimulates platelet reactivity by a variety of mechanisms.[58]

Another point is the introduction of new vasoprotective and antiatherosclerotic agents, such as statins, ACE inhibitors/ARBs, and new oral antidiabetics, within the last two decades in long-term primary prevention of patients with type 2 diabetes and high CV risk.[10,55,56] Less than 1% of diabetics received treatment with "hypolipidemic drugs" in the historical Haffner et al study,[4] whereas a considerable percentage, for example, 75% of diabetics in ASCEND, were on statins. It has been shown previously that statin cotreatment is associated with an approximately 50% decrease in urinary excretion of the thromboxane metabolite: 25% versus 57% ($p = 0.01$).[48] Statins will retard the progression of the macroangiopathy in diabetics and, therefore, also reduce the atherothrombotic risk.[9] A recent Danish population-based cohort study for a real-world scenario in diabetic patients with high rates of statins, aspirin, and other cotreatments found only small increase in mortality for diabetics but no change in the incidence of MIs in the absence of angiographically significant coronary artery disease, suggesting that diabetics without CV disease had the same risk of MI as patients without diabetes.[59] All diabetic patients of this study received a high rate of cotreatment, most notably statins (75–88%), ACE inhibitors (42–50%), or ARBs (19–20%) as opposed to aspirin which was given to 66% of the diabetics without and to 84% of the diabetics with coronary heart disease.[59]

Statins also interfere directly with the clotting system. Most notable is their inhibition of platelet function and thromboxane formation, specifically in hyperreactive platelets, such as those from patients with hypercholesterolemia.[60] It has also been shown that several statins significantly inhibit the expression of platelet protease-activated receptor 1 (PAR-1) thrombin receptors and PAR-1-mediated signaling in aspirin-naive patients with metabolic syndrome.[61] Consequently, aspirin and statins acted synergistically to reduce C-reactive protein in the REGARDS cohort.[62] In ASCEND, most patients were on statins (75%) or received antihypertensives (ACE, ARB) (60%).

Bleeding

In contrast to the variable findings with aspirin regarding its efficacy in preventing vascular thrombotic events in primary prevention of diabetics, an increased number of aspirin-induced harmful effects, such as increased bleeding, mainly from the GI tract, was a regular finding in most but not all (POPADAD) CV prevention trials with aspirin.[9] This raises the question whether the (small) absolute benefits of aspirin in terms of thrombosis prevention might be counterbalanced by the bleeding hazard. One should realize that ischemic events are usually irreversible, whereas bleeding is mostly reversible. It might be largely reduced by PPIs as seen, for example, in the COGENT trial[63] and confirmed in a recent large meta-analysis.[64] In this context, it should be noted that inhibition of platelet-dependent thromboxane formation by aspirin—the suggested mode of its antiplatelet/antithrombotic action—is only one factor for increased bleeding. Another might be the inhibition of thrombin formation and/or fibrin clot dynamics, which was seen in some[65,66] but not all studies[67] with low-dose aspirin. As a consequence, aspirin-associated changes in (capillary) bleeding time are not equivalents for the efficacy of antiplatelet treatment with aspirin[68] and also do not predict the risk of thrombotic vessel occlusion.[69] Interestingly, there is a linear correlation between bleeding time and platelet count only in thrombocytopenia, that is, circulating platelet numbers between 10,000 and 100,000 per microliter, but not with higher, that is, normal platelet counts.[70] In other words, prolongation of bleeding time and antiplatelet/antithrombotic actions of aspirin are not necessarily parallel phenomena.[71]

Any increased bleeding with aspirin, although numerically highly significant, should also be counterbalanced against prevention of thrombotic vascular events with respect to its clinical impact. In case of GI bleeding, comedication with PPIs will have an impact as well as eradication of *Helicobacter pylori* prior to long-term aspirin treatment of the elderly.[72] A recent meta-analysis of 7,599 publications showed that the risk of upper GI bleeding in persons taking low-dose aspirin is about twice as high in those who are infected with *H. pylori*.[72] Testing for and treatment of infections as well as other appropriate measures, such as eradication of *H. pylori*, is therefore strongly recommended. It should also be noted that generation of protective prostaglandins inside the stomach mucosa is age-dependent, and becomes reduced by more than 50% in the elderly. This reduced prostaglandin formation is probably related to the doubling in basal acid output in this

population[73,74] and will reduce the resistance of the stomach mucosa against noxious stimuli, including aspirin.

There was no increased bleeding in the POPADAD trial. In the JPAD study, there were 12 GI bleedings in the aspirin group as opposed to only 4 in the control and another 13 minor bleedings in the aspirin group. However, there were no significant differences in the composite of hemorrhagic stroke and severe GI bleeding.[75] In ASCEND, there was a 29% higher risk of major bleeding in the aspirin group, specifically in the GI tract. In this study, only 14% of patients of the aspirin group at the beginning and 24% at the end of the trial were on PPIs. A recent large meta-analysis clearly demonstrated that PPIs are effective in preventing GI symptoms without increasing adverse events, cardiac risks, or mortality in long-term aspirin users.[64] PPIs are particularly recommended in the elderly because of an age-dependent increased risk of (GI) bleeding.[76] In addition, protection by PPIs appears to be independent of the aspirin dose.[77] Data from a phase III clinical trial on PA32540 (a coordinated-delivery tablet containing 325 mg EC-aspirin and 40 mg omeprazole) versus 325 mg EC aspirin alone showed improved gastric protection in subjects at risk for aspirin-associated gastric ulcers, a similar CV event profile, and markedly improved adherence to drug treatment because of less upper GI tract adverse effects.[78]

Current Situation

The recent guideline of ADA recommends low-dose aspirin (75–162 mg/day) as a first choice antiplatelet treatment in secondary prevention of individuals with diabetes and a history of atherosclerotic CV disease (grade A). Clopidogrel is an alternative in persons with aspirin intolerance (grade B). For primary prevention, however, aspirin according to ADA may be considered in diabetic subjects at increased CV risk and no increased risk of bleeding; however, only with a grade C recommendation.[11] According to the U.S. Preventive Services Task Force, evidence for aspirin in primary prevention is heterogeneous and limited by rare events and few credible subgroup analyses. In general, the beneficial effect of aspirin for the primary prevention of CV disease is modest and occurs at doses of 100 mg or less per day. Older adults seem to achieve a greater relative CV benefit.[79]

These recommendations were made on the background of available studies that had several limitations, as discussed above, and were given prior to the publication of ARRIVE,[80] ASCEND,[50] and ASPREE.[81] Similar to ASCEND, these studies aimed to address the benefit/risk ratio of primary prevention with low-dose aspirin in persons at elevated vascular risk, due to risk factors, such as hypercholesterolemia and/or hypertension (ARRIVE) or older age ($\geq$ 70 years at study entry; ASPREE). Both studies were negative in the conventional "intention-to-treat" analysis with respect to the triple CV efficacy endpoint, but also showed increased bleeding for the aspirin-treated groups. Interestingly, in both studies, the incidence of vascular events, similar to ASCEND, was also only about half of the predicted incidence. Thus, these studies did not investigate a population at moderate (as suggested) but only at low vascular risk and ARRIVE was considered as confirmatory of previous aspirin primary prevention trials in low-risk populations by the investigators. As a consequence, the 2019 edition of the American College of Cardiology/American Heart Association guideline on the primary prevention of CV diseases has reduced the level of recommendation for aspirin in primary prevention in patients at elevated CV risk to level IIb, with evidence level A.[82] In a discussion forum of the European Society of Cardiology, Aimo and De Caterina concluded that any sensible recommendation on aspirin use should be based on the consideration that primary prevention is an extremely heterogeneous conundrum and do not feel that significant new information has been added by the new trials, including also ASPREE in the apparently healthy elderly.[83] What is urgently needed are randomized prospective studies in high-risk groups with a 2 to 3% annual vascular risk rate. It has also been recently suggested that new risk parameters might be introduced that reflect the CV risk more accurately than tables that are based on risk calculations half a century ago. This includes coronary artery calcification and extent of coronary artery disease as well as a longer duration of CV prevention trials.[84] It would also be interesting to have a direct comparison of aspirin with other antiplatelet drugs as well as against statin monotherapy to check whether the findings of Hennekens et al with aspirin and pravastatin in 5 trials on secondary prevention also apply to primary prevention.[85] The latest available meta-analysis on statins in primary prevention showed significant reductions in composite vascular outcomes overall, but mixed results when these were stratified by baseline risk.[86] In this context, the ACCEPT-D trial will assess the effects of low-dose aspirin on the incidence of major vascular events in $>$ 5,000 diabetics with no clinical evidence of vascular disease and receiving statin therapy.[87] The results will show whether aspirin, on top of another prevention strategy, will further improve clinical outcomes. In any case, discontinuing aspirin prophylaxis, as part of a primary prevention strategy, might not be a good idea because this was found to be associated with an absolute risk increase by 6.9 events per 1,000 patient-years or one additional CV event per year in every 146 patients.[88] Interestingly, this increased risk was not observed if aspirin was replaced by another antiplatelet or an anticoagulant drug although those patients were likely at higher absolute risk of such an event.[88] Similar findings were reported by others, including the possible loss of cancer protection and perhaps other off-target effects.[89] In this context, one should remember that a significant proportion of deaths in diabetics without known vascular disease (40%) is from nonvascular origin, including cancer (►**Fig. 1**).

Regarding the future role of aspirin, pharmacodynamic investigations indicate that no other antithrombotic agent can replace the COX-1-selective, platelet-inhibitory effects of the compound.[89] A recent review indicated that 1 in 4 patients with diabetes had HTPR with doses commonly used and that this may have a significant impact on overall efficacy of aspirin in diabetics.[90] In this context, not only efficacy but also toxicity could be improved by new galenic preparations and/or by twice-daily administration.[91] Twice-daily administration of

aspirin has been shown to be associated with more sufficient inhibition of thromboxane recovery[23] and platelet aggregation[91] and this dosing regimen is currently investigated in ongoing clinical randomized trials, for example, CARING –"Chronotherapy with low-dose aspirin for primary prevention."

Alternatively, aspirin might be given in a retarded-release EC formulation. This might result in lower systemic aspirin plasma levels (less acetylation of megakaryocytes) and less inhibition of thromboxane formation in diabetics.[92] Whether this reduced systemic bioavailability of nonmetabolized aspirin is due to incomplete absorption of EC preparations in diabetics[92] or a more complete deacetylation prior to reaching the systemic circulation and the bone marrow, remains to be determined. However, this could have had an impact on ARRIVE, ASCEND, and ASPREE, the three recently published aspirin prevention trials, which were all done with low-dose (100 mg/day) EC aspirin preparations. A new extended-release aspirin (ER-ASA; Durlaza) formulation at 162.5 mg daily dose provided sustained antiplatelet effects over 24 hours in patients with type 2 diabetes and multiple CV risk factors and had a favorable tolerability profile.[93]

In conclusion, the ASCEND trial has added some information on the benefit/risk ratio with aspirin in primary prevention. It was the first large primary prevention trial in diabetics without known CV disease that demonstrated a reduced vascular risk after long-term, 7.4 years, treatment with aspirin. There was a 12% reduction in the triple vascular efficacy endpoint, which was identical with the 12% reduction in other primary prevention trials in mainly nondiabetic subjects.[36] However, the basic vascular risk of these patients was low as was the absolute number of events and did not change over the study period. This suggests that the metabolic changes in diabetes per se might be a smaller prothrombotic risk factor than secondary, diabetes-related alterations of the vessel wall and the clotting system that become more relevant in diabetics with more advanced disease. In addition, the frequent cotreatment with antiatherosclerotic/anti-inflammatory agents has to be considered in the study interpretation as also mentioned in an actual review.[84] In general, it will be difficult to reduce fatal CV events by any kind of preventive measures in a low-risk population with a low event rate. However, the prevention of a nonfatal vascular event, such as a first MI, is certainly a positive outcome, if the price to pay, that is, induction of bleeding, is not too high. In this respect, the low rate of PPI cotreatment has to be mentioned. We feel that a higher than 24% rate of PPI cotreament might have markedly reduced the GI bleeding risk and, perhaps, also, that eradication of *H. pylori*, particularly in the elderly. Both measures could have improved the benefit/risk ratio. The ASCEND study did not provide new insights into the thrombotic risk of individuals at moderately elevated vascular risk as intended, but largely confirmed previous primary prevention trials in low-risk individuals.

Conflict of Interest

K.S. reports personal fees from Bayer; S.D.K. reports personal fees from Bayer and Bristol-Myers Squibb/Pfizer, grants, personal fees, and other from AstraZeneca, outside the submitted work. R.F.S. reports grants and personal fees from PlaqueTec and AstraZeneca, personal fees from Bayer, Bristol-Myers Squibb/Pfizer, Avacta, Novartis, Idorsia, Thromboserin, Haemonetics, outside the submitted work. In addition, R.F.S. has a patent PCT/GB2017/050692 pending. F.W.A.V. has nothing to disclose.

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