State of the art paper

Aspirin in primary prevention of cardiovascular disease in diabetes

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Abstract

It is well established that people with diabetes are at an increased risk of cardiovascular disease compared with those without diabetes. Although the protective role of aspirin in secondary prevention is well documented, its role in primary prevention of cardiovascular disease in people with diabetes, after the results of major clinical trials and meta-analyses, is unclear. The observed discrepancies might be explained in part in terms of the differences between the background cardiovascular risks, follow-up periods, age and gender of the study populations. Recently, the results of the ASCEND trial in people with diabetes documented the cardiovascular benefit of aspirin for primary prevention, but with an increased risk of bleeding that might outweigh the observed cardiovascular benefit. Therefore, current guidelines recommend its use for primary prevention in people with and without diabetes under specific circumstances. The purpose of the present review is to summarize the existing literature data regarding the place that aspirin has in primary prevention of cardiovascular disease in people with diabetes.

Key words: primary cardiovascular prevention, diabetes, aspirin, cardiovascular disease, myocardial infarction, stroke.

Introduction

It is known that diabetes mellitus (DM) has reached epidemic dimensions, affecting 285 million adults worldwide [1], and is associated with increased mortality and morbidity as well as poor quality of life [2]. Furthermore, DM is a major risk factor for cardiovascular disease (CVD) and cardiovascular mortality [3]. The increased risk of CVD in patients with DM has been known since the 1970s when the Rochester Epidemiologic Project and the Framingham Heart Study showed for the first time that people with DM are at increased risk for myocardial infarction (MI), stroke, and peripheral artery disease (PAD) compared to people without DM [4, 5].

The role of aspirin for the secondary prevention of MI, stroke, or transient ischemic attack (TIA) is well established [6]. However, the efficacy and safety of aspirin for primary prevention are under scientific investigation following the results of large randomized clinical trials (RCTs) in the general population, in people with diabetes and in elderly people [7–10]. The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) [7], the ASCEND (A Study of Cardiovascular Events in Diabetes) [8], and the

Table I. Patient characteristics of the included studies, cardiovascular death and any major bleeding with aspirin versus control

Study (year)	Aspirin/control (*n*)	Patient population	Estimated 10-year CV risk	Mean follow-up [years]	Cardiovascular death RR (95% CI)	Number needed to treat	Any major bleeding RR (95% CI)	Number needed to harm
Aspirin primary prevention trials in people with diabetes:								
ETDRS (1992)	1,856/1,855	Age 18–70 years & DM & diabetic retinopathy	40.8	5	0.89 (0.76, 1.04)	50	–	–
JPAD 2 (2017)	7,220/7,224	Age 60–85 years & HTN, DM, or dyslipidemia	7.8	10.3	0.94 (0.44, 1.99)	**	0.74 (0.34, 1.61)*	333
POPADAD (2008)	638/638	Age > 40 years & DM & asymptomatic PAD with ABI ≤ 0.99	25.3	6.7	1.23 (0.80, 1.89)	80	–	–
ASCEND (2018)	7,740/7,740	Age > 40 years & DM	10.2	7.4	0.91 (0.75, 1.10)	400	1.28 (1.09, 1.51)	111
Aspirin primary prevention trials in people without diabetes:								
ARRIVE (2018)	6,270/6,276	Male > 55 years & 2–4 CV risk factors, female > 60 years & 3–4 CV risk factors	6.9	5	0.98 (0.62, 1.52)	**	2.72 (1.14, 6.46)	500
ASPREE (2018)	9,525/9,589	Age ≥ 70 years (≥ 65 years among blacks and Hispanics in U.S.)	8.2	4.7	0.82 (0.62, 1.08)	470	1.37 (1.17, 1.60)	100

**Intracranial bleeding, **cannot be calculated. ABI – ankle brachial index, CI – confidence interval, CV – cardiovascular, DM – diabetes mellitus, HTN – hypertension, PAD – peripheral arterial disease, RR – risk ratio.*

ASPREE (Aspirin in Reducing Events in the Elderly) trials [9, 10] added more data to the existing debate showing a neutral effect in the prevention of CVD, with the exception of people with DM, where a beneficial effect was observed, while there was a high incidence of bleeding adverse events.

Therefore, the purpose of the present review is to summarize the existing literature data regarding the place that aspirin has in primary prevention of CVD in people with DM.

Aspirin primary prevention trials in people with diabetes

There have been several studies evaluating the role of aspirin in primary prevention of CVD in patients with DM before the results of the ASCEND trial that showed conflicting results [11–15]. Despite the lack of a clear beneficial effect, aspirin was used for the primary prevention of CVD in people with DM and only the results of the three recent published trials have placed under consideration aspirin's beneficial and/or harmful effects (Table I).

The Early Treatment of Diabetic Retinopathy Study (ETDRS) examined the effect of aspirin versus placebo in patients with type 1 or type 2 DM and retinopathy [11]. Regarding patients' characteristics at enrollment it must be mentioned that about 49% of study participants had a history of CVD, with less than 10% having a history of a previous MI or stroke. The results of the study showed a beneficial effect of aspirin use; patients on aspirin had a lowered risk of nonfatal or fatal MI (relative risk (RR) = 0.85, 95% confidence interval (CI): 0.73–1.00) compared to placebo users. This study showed promising results of aspirin use in a population, such as people with DM, that is characterized by an increased CVD risk.

In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, 2,539 type 2 DM patients were assigned to low-dose aspirin versus placebo with a mean follow-up of 4.4 years. The study's composite endpoint consisted of serious vascular events, angina, hemorrhagic stroke, aortic and peripheral vascular diseases, and TIA [12]. The JPAD study showed no difference in the primary outcome or mortality between the two study groups; 68 in the aspirin group (1.36 per 100 person-years) and 86 in the non-aspirin group (1.7 per 100 person-years) (RR = 0.80; 95% CI: 0.58–1.10; p = 0.16). In addition, the extension of the JPAD trial, JPAD2, with a mean follow-up of 10.3 years, showed an increased risk of gastrointestinal (GI) bleeding in patients taking aspirin without any favorable effect on CVD events [13]. The JPAD and JPAD2 studies showed no favorable effect of aspirin use in the primary prevention in people

with DM with the cost of an increased risk of GI bleeding events.

The Prevention of Progression of Arterial Disease and Diabetes trials (POPADAD) enrolled 1,276 patients with DM free of established CVD with an ankle brachial index, a biomarker of PAD, below 0.99. The purpose of the study was to evaluate whether 100 mg aspirin and/or antioxidants had any favorable effect on the primary prevention of CVD [14]. However, in accordance with the JPAD and JPAD2 studies, after a mean follow-up of 6 years no significant difference regarding the incidence of CVD or stroke death was observed between the two study groups.

The position statement and meta-analysis of the American College of Cardiology (ACC) [15], based on the results of the above-mentioned clinical trials, clearly stated that aspirin use had no effect on the reduction of CVD (RR = 0.91, 95% CI: 0.79–1.05). Aspirin use might reduce CVD 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.

Most recently, the ASCEND trial, a large prospective RCT, evaluated the effects of aspirin for primary prevention in patients with DM. The ASCEND trial enrolled 15,480 patients from the United Kingdom and randomized them to receive either aspirin at a dose of 100 mg daily or placebo [8]. Patients were included if they had a diagnosis of any type of DM, but no history of CVD. Approximately 63% of participants enrolled in the study were white males, mean age was 63 years and mean hemoglobin A_{1c} was 7.2%. Statin use was identified in about 75% of patients, with 36% of participants reporting aspirin use prior to enrollment in the study. Less than 15% reported proton-pump inhibitor use and over 80% of patients had a low-to-moderate vascular risk score at baseline. The primary efficacy outcome was the first serious vascular event (i.e., MI, stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or other serious bleeding). Secondary outcomes included GI tract cancer.

During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (8.5% versus 9.6%, respectively, RR = 0.88; 95% CI: 0.79–0.97; $p = 0.01$). In contrast, major bleeding events occurred in 4.1% in the aspirin group, as compared with 3.2% in the placebo group (RR = 1.29; 95% CI: 1.09–1.52; $p = 0.003$), with most of the excess being GI bleeding and other extracranial bleeding. There was no significant difference between the aspirin and the placebo group in the incidence of GI tract cancer (2.0% versus 2.0%, respectively) or all cancers (11.6% versus 11.5%). Therefore, the results of the ASCEND trial showed that the absolute benefits of aspirin use were largely counterbalanced by the bleeding risk [8].

There are some major limitations regarding the extrapolation of the findings of the trial. First of all, ASCEND participants had well-controlled DM and were older than 60 years of age, a population that is known to be at increased risk of bleeding. Another limitation is that about one-half of study participants discontinued aspirin before the end of the study, a fact that might partially explain the early benefit of aspirin use [8]. Finally, despite several guideline committees suggesting use of the ACC ASCVD risk score calculator for risk stratification, CVD risk score was calculated using an alternative regression of risk factors that included age, sex, smoking, and duration of DM. Therefore, tools for more accurate risk assessment should be used to identify patients at high CVD risk in order to take part in studies related to preventive strategies such as aspirin. Finally, an important finding in the ASCEND trial was that the majority of deaths in patients with DM were due to non-vascular causes [8]. This finding shows that statins, antihypertensive medication, and possibly newer antidiabetic agents too, protect patients with DM from the deleterious effects of CVD.

In general, the different findings regarding the role of aspirin in primary prevention of CVD might be in part explained by the differences in studies' primary endpoints. Some trials restricted the definition of CV death to a composite of fatal MI and fatal stroke, while others included other causes (e.g., sudden cardiac death, and heart failure), the different characteristics of the study population (differences in age and gender, background cardiovascular risks) and the duration of patients' follow-up (Table I).

Aspirin primary prevention trials in people without diabetes

Not only in people with DM but also in the general population the use of aspirin in the primary prevention of CVD remains controversial. In order to answer the above question two large RCTs, in the general population and in elderly people, were performed and their results were recently published [7, 9, 10] (Table I).

ARRIVE was a randomized, double-blind, placebo-controlled, multicenter study carried out in seven countries that enrolled patients with an average CVD risk. Patients at high risk of GI bleeding or other bleeding disorders or DM were excluded by the study. The primary efficacy endpoint of the

ARRIVE study was a composite outcome of time to first occurrence of CVD death, MI, unstable angina, stroke, or TIA, while safety endpoints were mainly the hemorrhagic events [7].

A total of 12,546 patients were enrolled and randomly assigned to receive aspirin or placebo with a median follow-up of 60 months. In the intention-to-treat analysis, the primary endpoint occurred in 4.29% of patients in the aspirin group versus 4.48% of patients in the placebo group (RR = 0.96; 95% CI: 0.81–1.13; p = 0,6038). GI bleeding events occurred in 0.97% of patients in the aspirin group versus 0.46% in the placebo group (RR = 2.11; 95% CI: 1.36–3.28; p = 0,0007). The overall incidence rate of serious adverse events was similar in both treatment groups (20.19% in the aspirin group versus 20.89% in the placebo group). There were 321 documented deaths in the intention-to-treat population (2.55% of patients in the aspirin group versus 2.57% of patients in the placebo group). The investigators concluded that the event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. Therefore, the role of aspirin in primary prevention among patients at moderate risk could not be addressed [7].

Accordingly, the primary analysis of the Aspirin in Reducing Events in the Elderly (ASPREE) trial reported that daily use of aspirin did not provide any benefit with regard to the primary endpoint of disability-free survival among older adults. On the contrary, a numerically higher rate of the secondary end point of death from any cause was observed with aspirin than with placebo [9, 10].

The ASPREE trial enrolled community-dwelling persons in Australia and the United States who were 70 years of age or older and did not have at baseline CVD, dementia, or disability. Of the 19,114 persons who were enrolled, 9,525 were assigned to receive aspirin and 9,589 to receive placebo. A total of 1,052 deaths occurred during a median of 4.7 years of follow-up. The risk of death from any cause was 12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group (RR = 1.14; 95% CI: 1.01–1.29). Cancer was the major contributor to the higher mortality in the aspirin group, accounting for 1.6 excess deaths per 1000 person-years. Cancer-related death occurred in 3.1% of the participants in the aspirin group and in 2.3% of those in the placebo group (RR = 1.31; 95% CI: 1.10–1.56). The results of the study showed higher all-cause mortality among apparently healthy older adults who received daily aspirin than among those who received placebo. The observed higher all-cause mortality was attributed primarily to cancer-related death [9, 10].

Two systematic review and meta-analyses that included previous studies with the use of aspirin for the primary prevention of CVs as well as ASCEND, ARRIVE and ASPREE trials were recently published, showing conflicting results. The first one, which included RCTs enrolling at least 1,000 participants with no known CVD and a follow-up of at least 12 months, compared aspirin use with no aspirin (placebo or no treatment). A total of 13 trials randomizing 164,225 participants with 1,050,511 participant-years of follow-up were included. The median age of trial participants was 62 years, 47% were men, 19% had DM, and the median baseline risk of the primary CVD outcome was 9.2%. Aspirin use was associated with significant reductions in the composite CVD outcome compared with no aspirin use (RR = 0.89, 95% CI: 0.84–0.95). Absolute risk reduction was 0.38% (95% CI: 0.20–0.55%) and number needed to treat was 265. Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin (RR = 1.43, 95% CI: 1.30–1.56), while the absolute risk increase was 0.47% (95% CI: 0.34–0.62%) and the number needed to harm was 210 [16]. The results of the above-mentioned meta-analysis showed that aspirin use in individuals without CVD was associated with a lower risk of CVD events and an increased risk of major bleeding.

The other meta-analysis included a total of 15 RCTs with 165,502 participants. Compared with the control, aspirin was associated with similar all-cause death (RR = 0.97; 95% CI: 0.93–1.01), CVD death (RR = 0.93; 95% CI: 0.86–1.00), and non-CVD death (RR = 0.98; 95% CI: 0.92–1.05), but a lower risk of nonfatal MI (RR = 0.82; 95% CI: 0.72–0.94), TIA (RR = 0.79; 95% CI: 0.71–0.89), and ischemic stroke (RR = 0.87; 95% CI: 0.79–0.95). Aspirin was associated with a higher risk of major bleeding (RR = 1.5; 95% CI: 1.33–1.69), intracranial bleeding (RR = 1.32; 95% CI: 1.12–1.55), and major GI bleeding (RR = 1.52; 95% CI: 1.34–1.73), with similar rates of fatal bleeding (RR = 1.09; 95% CI: 0.78–1.55) compared with the control subjects. Total cancer and cancer-related deaths were similar in both groups within the follow-up period of the study. The authors concluded that aspirin for primary prevention reduces nonfatal ischemic events but significantly increases nonfatal bleeding events [17].

Clinical implications of the results of the RCTs

The observed modest reduction in CVD events or lack of benefit with aspirin use in recent RCTs [7–10] suggests a potential role for other primary prevention strategies, such as regular exercise and healthy diet patterns, as well as the benefits of strategies against CVD such as statin and an-

tihypertensive treatment. Especially, in people with DM, these conflicting results create uncertainty regarding which patients would benefit from aspirin therapy and not be harmed. Thus, in patients with DM the therapeutic option to use aspirin or not for the primary prevention of CVD is to choose the patient at increased CVD risk with comorbidities such as dyslipidemia, hypertension and microalbuminuria. Another way that is emphasized by current guidelines is to discuss with the patient the potential risks and benefits and make joint decisions. This is reflected in the ACC/AHA and American Diabetes Association (ADA) guidelines [18, 19], which suggest that aspirin might be used in patients at an increased risk of CVD but without an increased risk of bleeding.

According to the AHA guidelines low-dose aspirin is recommended only in those aged 40 to 70 years who are at higher atherosclerotic CVD risk but without an increased bleeding risk. The AHA guidelines do not use the specific risk calculator score in order to reach a decision on aspirin use, since they recognized that the calculator tended to overestimate the actual rates of atherosclerotic CVD [18]. Furthermore, reflecting the results of the ASPREE trial, the AHA guidelines recommend against aspirin use in adults aged above 70 years and in those aged 40–70 years at increased bleeding risk, regardless of atherosclerotic CVD risk. Accordingly, the ADA Standards of Medical Care in Diabetes suggest aspirin use for primary prevention in adults aged above 50 years with DM at high CVD risk with low bleeding risk. ADA Standards of Medical Care in Diabetes do not recommend aspirin use in people with DM older than 70 years as the risk of bleeding appears to be greater than the CVD benefit in this age group [19].

Summarizing the current recommendations for aspirin use for primary prevention of CVD, both ACC/AHA and ADA guidelines emphasize the role of the individual approach to each patient as well as the importance of joint decisions. Both guidelines set an upper limit (70 years) for the use of aspirin while the lower limit is different: 40 years for ACC/AHA guidelines and 50 years for ADA guidelines. Finally, the ACC/AHA guidelines recommend aspirin use, in contrast to the ADA guidelines, regardless of the presence of atherosclerotic CVD risk factors.

Conclusions

The results of the ASCEND trial in people with DM documented the cardiovascular benefit of aspirin for primary prevention, but with an increased risk of bleeding that might outweigh the observed CVD benefit. Therefore, current guidelines recommend its use for primary prevention in people with DM with at least an additional CVD risk factor, such as hypertension and dyslipidemia, under the age of 70 years and without an indication of increased bleeding risk.

Therefore, tools for improved risk stratification in the new era of aspirin use as well as optimal control of risk factors, such as hypertension and dyslipidemia in people with DM, are needed. Finally, according to current guidelines, the best way to use aspirin for the primary prevention of CVD in patients with DM is to discuss individualized risks and benefits and make joint decisions. Consequently, the decision to use aspirin for primary prevention might be made on an individual basis according to the balance of risk versus benefits.

Conflict of interest

The authors declare no conflict of interest.

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