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COMMENTARY

Aspirin for primary prevention of cardiovascular disease in diabetes

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in people with diabetes. Aspirin is commonly used in the treatment and prevention of CVD, and the effectiveness of aspirin for the secondary prevention of CVD is well established in people with or without diabetes. In contrast, the role of aspirin in primary prevention is still controversial, as the cardiovascular benefit of aspirin might not outweigh the risk of hemorrhage. Even though diabetes raises cardiovascular risk, which would suggest that aspirin could have a greater benefit, it remains uncertain whether there is a clear net benefit of aspirin for the primary prevention of CVD in people with diabetes.

A number of randomized clinical trials have investigated the impact of aspirin for primary prevention in healthy men and women, in individuals with cardiovascular risk factors, and in individuals with documented subclinical atherosclerosis. People with diabetes were included in some of these primary prevention trials. However, the diabetes subgroups were usually small and therefore most of these studies did not have adequate power to evaluate the cardiovascular effect of aspirin in people with diabetes. To date, just three primary prevention trials of aspirin specifically involving people with diabetes have been carried out (Table 1). The Early Treatment of Diabetic Retinopathy Study carried out back in the 1980s investigated the effect of aspirin in people with diabetes and retinopathy, and suggested that aspirin might have cardiovascular benefits[1]. However, that study was in fact a combination of primary and secondary prevention, as nearly half of the randomized participants had prior CVD. The other two trials were carried out at the turn of this century. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes showed that aspirin did not have any significant effect on cardiovascular outcome[2], and a subsequent 10-year follow up reported an increased risk for gastrointestinal hemorrhage. The Prevention of Progression of Arterial Disease and Diabetes also did not find any cardiovascular benefit of aspirin in people with diabetes and asymptomatic peripheral artery disease[3]. These early prevention trials of aspirin in people with diabetes had limited power, and a number of meta-analyses have been carried out over the years to evaluate the use of aspirin in the primary prevention of CVD in people with diabetes. The latest meta-analysis combining the data of people with diabetes from 10 randomized trials of primary prevention suggested that there was a significant reduction in the risk of major adverse cardiovascular events with a relative risk of 0.90 (95% confidence interval 0.81–0.99; $P = 0.03$) in the aspirin-treated group. The increase in the risk of major or gastrointestinal bleeding events was not statistically significant, but the estimates were imprecise due to insufficient detailed information on bleeding events[4].

Two large randomized trials have been designed to address this important issue of primary prevention with aspirin in people with diabetes: A Study of Cardiovascular Events in Diabetes (ASCEND) trial and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes. The ASCEND trial has been completed and the results have been released[5]. Table 1 summarizes the salient features of all the completed and ongoing primary prevention trials with aspirin in people with diabetes. ASCEND was a large, randomized, placebo-controlled trial of aspirin involving 15,480 participants with diabetes (94% with type 2 diabetes). The average duration of follow up was approximately 7 years, and at the end of the study, there was a significant 12% reduction in the rate of serious vascular events in the aspirin group compared with the placebo group. This was accompanied by a 29% increase in the rate of major bleeding episodes, which were predominantly gastrointestinal or extracranial hemorrhage. There were no significant differences in all-cause mortality and in the incidence of gastrointestinal tract cancer or all cancers between the two groups.

Compared with the previous prevention trials of aspirin in people with diabetes, the ASCEND trial was a much larger study, and had the statistical power to identify a 15% difference in the primary cardiovascular outcome between the aspirin and placebo group. The earlier aspirin prevention trials in people with diabetes were carried out at a time when modifiable risk factors were treated less aggressively. The management of cardiovascular risk factors has since improved, and the contemporary approach in risk factor control might potentially reduce the benefits of aspirin and/or decrease the overall risk and change the benefit-to-harm ratio. In the ASCEND trial, cardiovascular risk factors were managed according to the current standard of care. A large proportion of the participants were taking statins and antihypertensive drugs, and only a small proportion were current smokers. Hence, the ASCEND trial is able to address the balance of the benefits and risks of aspirin within the setting of current preventive practice of CVD. The trial has shown that aspirin is beneficial in

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Table 1 | Primary prevention trials with aspirin in diabetes

Trial	ETDRS	POPADAD	JPAD	ASCEND	ACCEPT-D
Participants	Type 1 or type 2 diabetes mellitus aged 18–70 years with retinopathy, n = 3,711 (49% with prior CVD)	Type 1 or type 2 diabetes mellitus aged ≥40 years, ABI ≤0.99 but no symptomatic CVD, n = 1,276	Type 2 diabetes mellitus aged 30–85 years, no prior CVD, n = 2,539	Type 1 or type 2 diabetes mellitus aged ≥40, no prior CVD, n = 15,480	Type 1 or type 2 diabetes mellitus aged ≥50, no prior CVD, n = 5,170
Mean age (years)	52% aged ≥50	60	65	63	–
Mean duration of follow up (years)	5.0	6.7	4.4	7.4	–
Intervention	650 mg aspirin vs placebo	Low dose aspirin vs placebo	Low dose aspirin vs placebo	Low dose aspirin vs placebo	Simvastatin + low dose aspirin vs simvastatin
Main cardiovascular end-point	Cardiovascular death, non-fatal MI or stroke 0.90 (95% CI 0.74–1.09)	Death from CHD or stroke, non-fatal MI or stroke, or above ankle amputation 0.98 (95% CI 0.76–1.26)	Total atherosclerotic events 0.80 (95% CI 0.58–1.10)	MI, stroke or TIA, or death from any vascular cause 0.88 (95% CI 0.79–0.97), P = 0.01	Cardiovascular death, non-fatal MI, non-fatal stroke, and hospital admission for cardiovascular causes
Bleeding risk	No significant difference	0.90 (95% CI 0.53–1.52)	No significant difference	1.29 (95% CI 1.09–1.52), P = 0.003	–

95% CI, 95% confidence interval; ABI, ankle brachial index; ACCEPT-D, Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; ASCEND, A Study of Cardiovascular Events in Diabetes; CHD, coronary heart disease; CVD, cardiovascular disease; ETDRS, Early Treatment Diabetic Retinopathy Study; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI, myocardial infarction; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; TIA, transient ischemic attack.

reducing cardiovascular events, but it also adversely increases the risk of major bleeding. Based on the results of ASCEND, it has been estimated that the numbers needed to treat to avoid a serious cardiovascular event and to induce a major bleeding episode are 91 and 112, respectively. The absolute benefits from avoiding major cardiovascular events are therefore mostly negated by the increased risk of hemorrhage. Even when participants were stratified according to their baseline cardiovascular risk, there was no group in which the benefits of aspirin clearly outweighed the hazards in ASCEND.

In addition to ASCEND, the recently published Aspirin in Reducing Events in the Elderly trial provided further insight into the role of aspirin in primary prevention[6]. In the Aspirin in Reducing Events in the Elderly trial, 19,114 elderly participants (aged ≥70 years) free from CVD, dementia and disability were enrolled. A total of 11% of the participants had diabetes at baseline, and the presence of diabetes was a pre-specified subgroup analysis. Cardiovascular outcome was a secondary end-point of the study. The trial showed that in healthy elderly participants, the use of aspirin conferred no cardiovascular benefits, but the risk of major bleeding was significantly increased by 38% ($P < 0.001$). No differential effect of aspirin on CVD was seen in the pre-specified diabetes subgroup analysis.

Current recommendations on the use of aspirin in people with diabetes are based on data derived from other high-risk populations and diabetes subgroup analysis of primary prevention trials. The United States Preventive Services Task Force advocates initiating low-dose aspirin for primary prevention based on age regardless of the presence or absence of diabetes[7]. Aspirin is recommended to prevent CVD in adults aged 50–59 years with 10-year cardiovascular risk ≥10% and not at increased risk of bleeding. For adults aged 60–69 years with 10-year risk ≥10% and not at increased risk of bleeding, the decision to use aspirin is individual-based. The

2018 guidelines from the American Diabetes Association recommend aspirin therapy for primary prevention in those with diabetes and high cardiovascular risk; that is, those aged ≥50 years who have one additional major risk factor (family history, hypertension, dyslipidemia, smoking or chronic kidney disease/albuminuria) and do not have any susceptibility to bleeding[8]. In light of the new evidence from the recent contemporary aspirin trials, how should physicians approach the use of aspirin for primary prevention in people with diabetes? It is clear that although people with diabetes have increased cardiovascular risk, the mere presence of diabetes is insufficient to bestow a distinct advantage for cardiovascular protection using aspirin with respect to bleeding. There is a fine balance between the risks and benefits of aspirin, and the overall magnitude of the net benefit of aspirin in primary prevention is likely to be small. For adults with diabetes aged >70 years, aspirin therapy is not indicated for primary prevention, as the risk outweighs the benefit. Similarly, for those aged <50 years with no major risk factors and low cardiovascular risk, aspirin is also not recommended, as the benefit is small. For those aged >50 years, an approach based on cardiovascular risk is still reasonable. Assessment of the benefit-to-risk profile should be made on an individual basis in those individuals with major cardiovascular risk factor(s), and aspirin might be offered as an additional risk-reducing therapy after maximizing cardiovascular risk control with smoking cessation, statins and blood pressure control. Shared decision-making taking into account the individual's values, preferences and willingness to undergo long-term aspirin therapy is necessary.

DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. *JAMA* 1992;268:1292–1300.
2. Ogawa H, Nakayama M, Morimoto T, *et al*. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; 300: 2134–2141.
3. Belch J, MacCuish A, Campbell I, *et al*. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; 337: a1840.
4. Kunutsor SK, Seidu S, Khunti K. Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials. *Diabet Med* 2017; 34: 316–327.
5. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018; 379: 1529–1539.
6. McNeil JJ, Wolfe R, Woods RL, *et al*. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; 379: 1509–1518.
7. Bibbins-Domingo K, U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2016;164:836–845
8. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes 2018. *Diabetes Care* 2018; 41(Suppl 1): S86–S104.

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