

# Aspirin for Cardiovascular Prevention in Patients With Diabetes

Reviewed by Michael Pignone, MD, MPH

## STUDY 1

Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators: Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 300:2134–2141, 2008

## SUMMARY

**Design.** A multicenter, randomized trial.

**Subjects.** A total of 2,539 Japanese patients aged 30–85 years with type 2 diabetes and no previous history of atherosclerotic disease. Mean age was 65 years, and ~45% of participants were female.

**Methods.** Participants were randomized to receive low-dose aspirin or no aspirin in an open-label design. The primary outcome was any atherosclerotic event, defined as cardiovascular death, nonfatal myocardial infarction, unstable angina, new-onset stable angina, stroke (ischemic or hemorrhagic), transient ischemic attack, or new peripheral vascular disease. All outcomes were adjudicated by an independent committee blinded to intervention status. Median follow-up was 4.37 years (193 of 2,539 were lost to follow-up).

**Results.** Aspirin use was associated with a nonstatistically significant reduction in the incidence rate of the primary outcome (13.6/1,000 patient-years in the aspirin group and 17.0/1,000 patient years in the control group (hazard ratio [HR] 0.80, 95% CI 0.58–1.10,  $P = 0.16$ ). Fatal events were lower with aspirin use (HR 0.10, 95% CI 0.01–0.79), but these outcomes were uncommon. Hemorrhagic stroke, gastrointestinal bleeding, and ulcers were more common in the aspirin group, but the differences were not statistically significant.

**Conclusions.** Low-dose aspirin use was associated with a non-statistically significant 20% reduction in atherosclerotic events among Japanese adults with type 2 diabetes. Further study with a larger sample size is required to determine whether this is a real effect or simply a chance finding.

## STUDY 2

Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh: 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* 337:a1840, 2008

## SUMMARY

**Design.** A multicenter, randomized trial

**Subjects.** A total of 1,276 Scottish adults  $\geq 40$  years of age with diabetes and an ankle-brachial index of  $\leq 0.99$  and no previous history of symptomatic cardiovascular disease. Mean age was 60 years, and more than half of the participants were female.

**Methods.** Participants were randomized in a double-blind manner to either receive aspirin, 100 mg daily, or placebo as part of a factorial trial that also evaluated the effect of an antioxidant combination. The primary outcome was a composite of cardiovascular disease death, nonfatal myocardial infarction, stroke, or above-the-ankle amputation. Median follow-up was 6.7 years. Attrition was 14% in the first year and 50% after 5 years.

**Results.** Aspirin did not reduce the incidence of the primary outcome; 18.2% had an event in the aspirin group versus 18.3% in the placebo group (HR 0.98, 95% CI 0.76–1.26). Aspirin was not associated with increased gastrointestinal symptoms (HR 0.77, 95% CI 0.55–1.08) or gastrointestinal bleeding (HR 0.90, 95% CI 0.53–1.52). There was no effect with antioxidants, and there was no

interaction between the aspirin and antioxidants.

**Conclusions.** In middle-aged Scottish adults with diabetes, low-dose aspirin did not reduce cardiovascular events.

## COMMENTARY

These two new trials provide additional evidence about the effect of aspirin in adults with diabetes and no previous history of cardiovascular events (primary prevention). Taken into consideration along with previous trials that either focused on patients with diabetes<sup>1</sup> or performed subgroup analyses of patients with diabetes,<sup>2-5</sup> it appears possible that the relative risk reduction from aspirin for prevention of cardiovascular events may be attenuated in patients with diabetes compared to those without diabetes.

There are several possible explanations for these findings. First, it is possible that the differences in effect observed are simply the result of chance, and the actual effects do not differ. Although a large number of patients have been studied, the actual number of events available to generate estimates of effect is modest across the trials. Second, aspirin may actually be less effective (or require a higher dose to be effective) in patients with diabetes because of the inflammatory, thrombotic, or

platelet-associated effects of diabetes. Third, it is possible that some of the studies that suggest attenuation may have biases. For example, if the level of nonadherence in both groups is particularly high (as may be the case over time in POPADAD), then the estimates of benefit and harm will be biased toward showing no effect. Finally, differences in study populations (e.g., underlying risk, sex, and use of effective co-interventions such as statins) may also lead to different estimates of effect.

Although the JPAD and POPADAD trials add important information, two additional larger trials are in progress and will provide additional insight within the next 1–2 years.<sup>6,7</sup> These additional trials will help clarify whether the benefit of low-dose aspirin for reduction of cardiovascular disease events in patients with diabetes is large enough to support its routine use among patients with diabetes but no previous history of cardiovascular disease.

## REFERENCES

- <sup>1</sup>Early Treatment Diabetic Retinopathy Study Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA* 268:1292–1300, 1992
- <sup>2</sup>Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A: Primary prevention of cardiovascular events

with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26:3264–3272, 2003

<sup>3</sup>Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755–1762, 1998

<sup>4</sup>Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352:1293–1304, 2005

<sup>5</sup>Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321:129–135, 1989

<sup>6</sup>De Berardis G, Sacco M, Evangelista V, Filippi A, Giorda CB, Tognoni G, Valentini U, Nicolucci A; ACCEPT-D Study Group: Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* 28:21, 2007

<sup>7</sup>ASCEND: A Study of Cardiovascular Events in Diabetes [article online]. Available from <http://www.ctsu.ox.ac.uk/ascend/>

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