

Is Aspirin Beneficial for Primary Prevention of Cardiac Events in Diabetes?

Sacco M, Pellegrini F, Roncaglioni MC, et al. 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* 2003;26:3264-72.

Study Overview

Objective. To determine if aspirin or vitamin E reduces cardiovascular death, stroke, or myocardial infarction in patients with type 2 diabetes mellitus.

Design. Multicenter, randomized, open-label, controlled trial with a 2-by-2 factorial design and an intention-to-treat analysis.

Setting and participants. Diabetic patients from 316 general practitioners and 14 diabetic outpatient clinics in Italy. Patients were eligible if they had been diagnosed with diabetes, had a venous plasma glucose concentration ≥ 125 mg/dL on at least 2 separate occasions or were treated with antidiabetic drugs, were aged ≥ 50 years, and had no history of major cardiovascular events. Exclusion criteria included diabetes with severe pathology, treatment with antiplatelet drugs, chronic use of anticoagulants, chronic use of aspirin or vitamin E, contraindications to aspirin, poor short-term prognosis, and difficulties with compliance.

Intervention. Patients were randomly allocated to receive 1 tablet of enteric-coated aspirin (100 mg) per day or no aspirin or 1 tablet of vitamin E (300 mg synthetic α -tocopherol) per day or no vitamin E.

Main outcome measures. The primary outcome was a major cardiovascular event. Major cardiovascular events were defined as cardiovascular deaths, nonfatal myocardial infarction, and nonfatal cerebrovascular events. Other cardiovascular events identified included angina pectoris, transient ischemic attack, peripheral artery disease, and revascularization procedures. Outcomes were assessed yearly.

Main results. The study was initially designed with a 5-year mean follow-up. The study was prematurely stopped by an independent data safety and monitoring committee based on emerging evidence that suggested a consistent benefit of aspirin therapy for the primary prevention of cardiovascular events in nondiabetics. The results presented included data from a mean follow-up of 3.7 years. 1031 diabetic patients were recruited for participation. 519 patients were randomly

assigned to receive aspirin and 509 patients were assigned to receive vitamin E. After randomization, patients assigned to the aspirin group were more likely to have hypercholesterolemia and hypertension than the control group (35.7% versus 26.3% [$P < 0.01$] and 66.7% versus 59.4% [$P < 0.05$], respectively). At the end of the study, no differences were found between the groups with respect to use of angiotensin-converting enzyme inhibitors or HMG-CoA reductase inhibitors, and values for glycosylated hemoglobin, lipids, and blood pressure also were similar. Kaplan-Meier survival curves were estimated for the time-to-major cardiovascular event, and no differences were seen in either the group receiving aspirin versus control or the group receiving vitamin E versus control (log-rank test $\chi^2 = 0.13$ [$P = 0.71$] and $\chi^2 = 0.16$ [$P = 0.69$], respectively). Multivariate analysis was performed and hazard ratios (HRs) were calculated for both the aspirin and vitamin E treated groups. As demonstrated by the Kaplan-Meier curves, there were no statistically significant differences in either the aspirin group (HR, 0.90 [95% confidence interval (CI), 0.49-1.67]) or the vitamin E group (HR, 1.21 [95% CI, 0.65-2.23]) when compared with controls. Bleeding complications were more common in the aspirin-treated group than in the control group (1.9% versus 0.2%; $P = 0.007$), and no intracranial hemorrhages were reported.

Conclusion. In diabetic patients, aspirin and vitamin E do not appear to be effective for primary prevention of cardiovascular events.

Commentary

Cardiovascular disease is the leading cause of mortality in diabetics [1]. Several randomized trials have demonstrated a beneficial effect of aspirin in primary prevention of cardiovascular events [2]; however, little data have exclusively evaluated aspirin's effects in a diabetic population. The Primary Prevention Project (PPP) trial was a large, ($n = 4495$) randomized trial evaluating the effects of aspirin for primary prevention of cardiovascular events in a general practice setting [3]. As a substudy to this trial, Sacco et al investigated the effects of aspirin on diabetics.

Unfortunately Sacco et al's results were less than impressive. Diabetics randomized to the aspirin group did not have fewer events than control patients. When compared with the nondiabetic patients on aspirin therapy in the larger trial, the diabetic patients on aspirin therapy had a statistically significant increase in cardiovascular deaths ($P = 0.03$). The trial was prematurely stopped and perhaps this resulted in an inadequate power to detect a difference between the diabetic aspirin and diabetic nonaspirin study groups. However, in light of a statistically significant increase in bleeding events in the aspirin group, the clinician should be cautious about the routine use of aspirin therapy for primary prevention in this group. Because this study was underpowered and there were significant differences in important baseline characteristics after randomization, further larger trials are necessary to definitively answer this question.

Applications for Clinical Practice

Despite strong evidence that suggests a protective effect of aspirin for the primary prevention of cardiovascular events,

in the subgroup of patients with diabetes aspirin appears less efficacious. This lack of benefit, along with the known toxicities of aspirin, would argue against the routine use of aspirin for primary prevention in diabetes. Further studies will be required to definitively answer this question.

—Review by Harvey J. Murff, MD, MPH

References

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3. de Gaetano G; Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Collaborative Group of the Primary Prevention Project [published erratum in *Lancet* 2001;357:1134]. *Lancet* 2001;357:89–95.

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