

No Benefit of Daily Low-Dose Aspirin in Diabetic Patients with Peripheral Arterial Disease

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.

Study Overview

Objective. To measure the effect of daily low-dose aspirin, with or without concomitant antioxidant therapy, on the incidence of cardiovascular events in diabetic patients with asymptomatic peripheral arterial disease (PAD).

Design. Multicenter, randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design.

Setting and participants. 1276 adults aged ≥ 40 years with type 1 or type 2 diabetes mellitus, PAD (detected by ankle brachial index ≤ 0.99), and no symptoms of cardiovascular disease were recruited from 16 hospital centers and 188 primary care groups in Scotland. Patients were excluded if they were already using aspirin or antioxidant therapy or had peptic ulcers, severe dyspepsia, bleeding disorders, serious physical illness expected to shorten life expectancy (eg, cancer), psychiatric conditions, or congenital heart disease. Patients were randomized to receive either (1) daily aspirin (100 mg) and a daily antioxidant, (2) daily aspirin and placebo, (3) placebo and daily antioxidant, or (4) double placebo. After randomization, patients were followed for a median of 6.7 years (range, 4.5–8.6 years).

Main outcome measures. There were 2 primary composite outcome measures: (1) death from coronary heart disease (CHD) or stroke; and (2) fatal or nonfatal CHD, myocardial

infarction (MI), or stroke or above-ankle amputation for critical limb ischemia. Secondary outcomes included all-cause mortality, nonfatal MI, and occurrence of other vascular events, such as stroke, transient ischemic attack, coronary or peripheral bypass surgery or arterial angioplasty, and development of angina, claudication, or critical limb ischemia.

Main results. There were 43 (6.7%) deaths from CHD or stroke among patients taking aspirin and 35 (5.5%) among patients not taking aspirin ($P = 0.36$). For the second primary composite outcome, there were 116 events (18.2%) among patients taking aspirin and 117 (18.3%) among patients not taking aspirin ($P = 0.86$). Antioxidant therapy had no significant effects on either primary outcome. Among patients taking antioxidants, 42 (6.6%) died from CHD or stroke as compared with 36 (5.7%) patients not taking antioxidants ($P = 0.40$). For the composite primary outcome, the number of total events was similar between patients taking and not taking antioxidants (117 vs. 116 events; $P = 0.85$). No significant interactions were found between antioxidant and aspirin administration for either primary outcome. No significant differences were found between patients taking aspirin and those not taking aspirin for any of the secondary outcomes, including all-cause mortality (94 vs. 101 deaths; $P = 0.63$). However, all-cause mortality was significantly higher among patients taking antioxidant therapy than among patients not taking antioxidant therapy (115 vs. 80 deaths; $P = 0.006$).

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Conclusion. Low-dose daily aspirin may not benefit diabetic patients without symptomatic cardiovascular disease, even in the presence of asymptomatic PAD. This finding has implications for potential quality measures and incentive programs that include daily aspirin administration to patients with diabetes.

Commentary

Diabetes mellitus and PAD are both associated with an elevated risk of cardiovascular events, and use of daily antiplatelet medications has been associated with a reduction in the magnitude of risk elevation [1]. In PAD, nonaspirin antiplatelet medication (eg, clopidogrel) has shown a stronger benefit than aspirin for reducing the risk of ischemic events [2]. Randomized trials of aspirin use for primary prevention of cardiovascular events among patients with diabetes have produced mixed results [3,4]. Nonetheless, international guidelines have encouraged the use of daily aspirin for both patients with diabetes and those with asymptomatic PAD [5–7].

The study by Belch and colleagues is the first multicenter, randomized, placebo-controlled trial to assess the impact of daily low-dose aspirin as primary prevention for cardiovascular events among diabetic patients with concomitant asymptomatic PAD. Over approximately 7 years of follow-up, patients taking aspirin experienced no significant risk reductions in composite cardiovascular events or all-cause mortality. Adverse events that might be expected with aspirin use (eg, gastrointestinal bleeding) were not significantly more likely among patients receiving aspirin. The addition of antioxidant therapy had no impact on the relationship between aspirin and occurrence of cardiovascular events.

Although this study provides valuable evidence regarding the effectiveness of aspirin for the primary prevention of cardiovascular events in diabetics with asymptomatic PAD, there are some important limitations. First, the trial was underpowered to detect a beneficial effect of aspirin because the number of patients enrolled was lower than expected (slightly over 1200 compared with 1600 expected), and the observed event rate was less than half of the rate expected by the study authors. Second, the dose of aspirin used was not varied among participants (100 mg daily for all participants). It is possible that higher doses of aspirin could have

a different effect on cardiovascular outcomes. Third, the degree of PAD used to enroll patients (ankle brachial index ≤ 0.99) may have included patients with disease too mild to appreciably benefit from aspirin therapy.

Applications for Clinical Practice

Widespread guideline-based use of aspirin for the primary prevention of cardiovascular events in patients with diabetes and PAD should be questioned. Payers and health systems managers should be hesitant to base quality measures and external incentive programs on the use of aspirin in such patients.

—Review by Mark W. Friedberg, MD, MPP

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