possible efficacy of low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes. This was a multicenter, prospective, randomized, open labeled, blinded end point trial conducted from December 2002 through April 2008 in 163 Japanese institutions. The study enrolled 2539 patients with type 2 diabetes who did not have a history of atherosclerotic disease. The median follow-up was 4.4 years. Patients in the aspirin group were treated with 81 or 100 mg daily. Primary end points included fatal or nonfatal stroke, fatal or nonfatal ischemic heart disease, and peripheral arterial disease. Secondary end points were each component of the primary end point, combinations of primary end points, and death from any cause.

There were 154 atherosclerotic events comprising 68 events in the aspirin group (13.6 per 1000 person-years) and 86 events in the nonaspirin group (17.0 per 1000 person-years; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; $P = .16$). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in one patient in the aspirin group and in 10 patients in the nonaspirin group (HR, 1.10; 95% CI, 0.01-0.79; $P = .0037$). Death from any cause occurred in 34 patients in the aspirin group and 38 patients in the nonaspirin group (HR, 0.90; 95% CI, 0.57-1.14; $P = .67$). There was no difference in the aspirin and nonaspirin groups for the composite of hemorrhagic stroke and significant gastrointestinal bleeding.

Comment: It is becoming frustrating to demonstrate any means of decreasing atherosclerotic events in patients with diabetes. Recent trials have suggested that strictly controlling plasma glucose levels is also ineffective in reducing cardiovascular events in patients with type 2 diabetes. Because of the low event rate in this trial and that it was conducted on an entirely Japanese population, it is probably too early to conclude that aspirin is ineffective as primary preventative therapy in patients with type 2 diabetes. Evidence is accumulating to that effect, however. See also the abstract "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" in this month's abstract section of *Journal of Vascular Surgery*.

Determinants and Time Course of the Postthrombotic Syndrome after Acute Deep Venous Thrombosis

Kahn SR, Shrier I, Julian JA, et al. Ann Intern Med 2008;149:698-707.

Conclusion: The Villalta score at 1 month after an episode of acute deep venous thrombosis (DVT) predicts late symptoms of the post-thrombotic syndrome.

Summary: Post-thrombotic syndrome occurs as a consequence of DVT and occurs despite optimal anticoagulation therapy. The authors note that many studies have addressed the risk of recurrent thromboembolism after DVT, but few studies identify which patients with DVT develop post-thrombotic syndrome. In this study they attempted to determine the frequency, time course, and predictors of post-thrombotic syndrome after acute DVT. This was a prospective, multicenter, cohort study involving eight Canadian hospital centers. From 2001 to 2004, 387 outpatients and inpatients with an objective diagnosis of symptomatic DVT were recruited.

The Villalta score was used to assess patients for post-thrombotic syndrome at 1, 4, 8, and 12 months after enrollment. The Villalta scale is a clinical measurement of post-thrombotic syndrome that grades severity from 0 (absent) to 3 (severe) of five patient-related symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six clinician-related clinical signs (edema, redness, skin induration, hyperpigmentation, venous ectasia, and pain on calf compression). A score of ≥ 5 indicates the presence of post-thrombotic syndrome. The scale has been validated when measured against quality of life instruments as well as anatomic and physiologic markers of post-thrombotic syndrome. It appears to have good to excellent inter-observer reproducibility and responds to clinical change. Mean post-thrombotic syndrome scores and severity categories were calculated at each interval.

At all study intervals, about 30% of patients had mild (5 to 9), 10% had moderate (10 to 14), and 3% had severe (score >14, or ulcer) post-thrombotic syndrome. The greater the category of post-thrombotic syndrome at 1 month, the stronger the predicted higher mean post-thrombotic syndrome scores were throughout 24 months of follow-up. Additional predictors of higher scores over time were thrombosis of the common femoral or iliac vein (2.23 increase in score vs distal [calf] venous thrombosis; $P < .001$), higher body mass index (0.14 increase in score per kg/m^2; $P < .001$), previous ipsilateral venous thrombosis (1.78 increase in score, $P = .001$), older age (0.30 increase in score per 10-year age increase, $P = .011$), and female sex (0.79 increase in score; $P = .020$).

Comment: All the risk factors identified by the authors for an increase in the severity of post-thrombotic syndrome and the development of post-thrombotic syndrome, with the possible exception of female sex, are well recognized. Unfortunately, the risk factors identified by the authors are not likely to be modifiable. Therefore, the information presented here allows the physician to inform the patient about his or her fate, but does not help much in guiding treatment of the acute DVT with the hope of preventing future post-thrombotic syndrome.

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

Belch J, MacCuish A, Campbell I, and the Prevention of Progression of Arterial Disease and Diabetes Study Group. BMJ 2008;337:1030-3.

Conclusion: Neither aspirin, antioxidant therapy, nor the combination of aspirin and antioxidant therapy is useful in the primary prevention of cardiovascular events and mortality in patients with diabetes and asymptomatic peripheral arterial disease (PAD).

Summary: Patients with asymptomatic PAD are six times more likely to die from cardiovascular disease ≤ 10 years than patients without PAD (N Engl J Med 1992;326:381-6). Aspirin as a secondary preventative measure in patients with diabetes and cardiovascular disease is well established. This has led to recommendations for use of aspirin as primary preventative therapy as well; however, a meta-analysis has demonstrated no efficacy for aspirin as a primary preventative therapy in patients with diabetes (BMJ 2002;324:71-86). Some evidence also indicates that there is increase in oxidative stress in patients with diabetes, with free radicals increasing platelet aggregation and antioxidants decreasing platelet aggregation.

Based on the strength of the data for secondary prevention of cardiovascular events with aspirin therapy, the lack of data investigating aspirin as primary preventative therapy, and potential effects of antioxidants in patients with diabetes, the authors sought to study these agents in a group of patients with diabetes and asymptomatic PAD. The objective was to determine whether aspirin and antioxidant therapy, combined or alone, was more effective than placebo in reducing cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease.

This was a multicenter, randomized, double-blind, two by two, factorial, placebo-controlled trial, It was conducted in 16 hospitals in Scotland and involved 188 primary care groups. Entered into the trial were 1276 adults (aged ≥ 40 years) with type 1 or type 2 diabetes and an ankle-brachial index <0.99, and no symptoms of cardiovascular disease. The daily regimen was 100 mg of aspirin plus antioxidant capsule in 320 patients, or aspirin plus placebo in 318, or antioxidant plus placebo in 320, or two placebo capsules in 318). The main outcome measures consisted of two composite primary end points: (1) death from coronary heart disease or stroke, nonfatal myocardial infarction or stroke, or amputation above the ankle, and (2) and death from coronary heart disease or stroke.

There was no evidence of any benefit of aspirin or antioxidant therapy. There were 638 primary events, of which 116 occurred in the aspirin groups compared with 117 in the no-aspirin group (18.2% vs 18.3%; hazard ratio [HR] 0.98, 95% confidence interval [CI], 0.76-1.26). There were 43 deaths from coronary heart disease or stroke in the aspirin groups compared with 35 deaths in the no-aspirin groups (6.7% vs 5.5%; HR, 1.23, 95% CI, 0.79-1.93). In the antioxidant groups, 117 primary events (18.3%) occurred; whereas in the no-antioxidant therapy groups, 116 (18.2%) occurred (HR, 1.03; 95% CI, 0.79-1.33). There were 42 deaths from coronary heart disease or stroke in the antioxidant groups compared with 36 deaths from coronary heart disease or stroke in the no-antioxidant groups (6.6% vs 5.7%, respectively; HR, 1.21; 95% CI, 0.78-1.89).

Comment: Once again, aspirin fails as primary preventative therapy in patients with diabetes. This study extended that conclusion to patients with asymptomatic PAD. The study, however, should not be construed as justification for failure to use aspirin as secondary preventative therapy in patients with cardiovascular disease and diabetes. Aspirin may be a so-called wonder drug, but it does not seem to be good for everything.

A Randomized Controlled Trial of Financial Incentives for Smoking Cessation

Volpp KG, Troxel AB, Pauly MV, et al. N Engl J Med 2009;360:699-709.

Conclusions: Financial incentives for smoking cessation increase rates of smoking cessation.

Summary: In the United States, there are 438,000 deaths each year attributed to smoking. About 70% of smokers desire to quit, but only about 2% to 3% are able to succeed each year. Pharmacologic therapies and smoking-cessation programs can produce higher rates of cessation of tobacco use; however, rates of participation in such programs are low. Previous studies have evaluated financial incentives to induce smoking cessation but have not shown significant increases in long-term cessation rates. The authors postulate that the previous studies were limited by small sample sizes and relatively weak financial incentives.

This trial recruited employees from a large multinational company based in the United States. Financial incentives of up to $750 were tested for their ability to improve long-term smoking cessation. A total of 878 employees received information about smoking-cessation programs. Of these, 436 were randomized to receive this information with financial incentives, and 442 received no financial incentives. The financial incentives offered were $100 for completion of a smoking-cessation program, and $250 for cessation of smoking ≤ 6 months after study enrollment, with smoking cessation confirmed by a biochemical test. Finally, $400 was offered for abstinence for an additional 6 months after the initial cessation, again with