MINDFUL PRACTICE

Dual Antiplatelet Therapy: Is More Better?

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 63-year-old male with hyperlipidemia, hypertension, and impaired fasting glucose presents to your office for follow-up. He has a history of stable angina for which he takes nitrates, β-blockers, and aspirin. A previous angiogram showed diffuse disease with no stentable lesions. His LDL cholesterol level is under 70 mg/dL with a statin and ezetimibe, and his blood pressure is well controlled with lisinopril. You realize he is at high risk for cardiovascular events, and you wonder if adding clopidogrel to his aspirin will provide additional protection against cardiovascular events.

The Question

In patients with established coronary artery disease, is antiplatelet therapy with aspirin and clopidogrel more efficacious for reducing cardiovascular events than aspirin alone?

The Search

We used PubMed (www.pubmed.gov) and entered "clopidogrel" AND "aspirin," limiting the search to randomized, controlled trials.

Our Critique

There was no observed difference in the combined end point, which included MI, stroke, or death from cardiovascular causes. When evaluating combined end points in general, it is important to consider these questions: a) are the component end points of similar importance, b) did the more important and less important end points occur with similar frequency, c) do the component end points have similar risk reductions, d) is the underlying biology of the component end points similar, and e) are the point estimates of the risk reduction similar with narrow confidence intervals? The underlying biology for all three component end points relates to diseased vascular endothelium and atherothrombotic events. Notably, clopidogrel and aspirin significantly reduced the risk of nonfatal stroke, compared with aspirin alone (relative risk [RR] 0.79, *P* less than .03), but did not reduce MI or death from cardiovascular causes. This finding, in combination with those of previous studies, supports the role of clopidogrel for the prevention of cerebrovascular events. However, clopidogrel plus aspirin may pose too great a bleeding risk for the broad population of patients included in this study.

Patient Preferences and Clinical Decision

Subjects similar to our patient were included in the present study—about 15% of the patients in each arm had stable angina with documented coronary artery disease. You decide to hold off on the addition of clopidogrel and continue aspirin, increasing his aspirin dose to 162 mg (two baby aspirin) per day.

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D.L. Bhatt et al.; CHARISMA Investigators

Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N. Engl. J. Med. 2006;354:1706-17. Epub 2006 Mar 12.

▶ **Design:** Prospective, multicenter, randomized, double-blind, placebo-controlled study.

▶ **Subjects:** Subjects were eligible for enrollment if they were aged 45 years or older and had multiple atherothrombotic risk factors or documented coronary artery disease, cardiovascular disease, or peripheral vascular disease. Potential subjects were excluded if they were taking antithrombotic medications or NSAIDs on a long-term basis (except cyclooxygenase-2 inhibitors), or had established indications for clopidogrel therapy.

▶ **Intervention:** Subjects were randomly assigned to clopidogrel (75 mg/day) plus low-dose aspirin (ASA) (75-162 mg/day) or placebo plus low-dose ASA. Follow-up evaluations were performed at 1, 3, and 6 months and every 6 months thereafter until the end of the trial.

▶ **Outcomes:** The primary efficacy end point was the first occurrence of MI, stroke (of any cause), or death from cardiovascular causes. End points were adjudicated by the clinical events committee blinded to treatment assignment. The principal secondary efficacy end point was the first occurrence of MI, stroke, death from cardiovascular causes, or hospitalizations from unstable angina, transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral). The primary safety end point was severe bleeding. Analysis was intention to treat.

▶ **Results:** A total of 15,603 patients from 768 sites in 32 countries were randomized to clopidogrel plus ASA (7,802) or ASA plus placebo (7,801) in 2002-2003. The groups were balanced at baseline, with a median age of 64 years; 29.8% were women. At a median of 28 months, the rate of the primary event was 6.8% in the clopidogrel plus ASA group and 7.3% in the ASA group (RR 0.93). The rate of the secondary efficacy end point was significantly lower in the clopidogrel plus ASA group at 16.7%, compared with 17.9% in the ASA group (RR 0.92). Severe bleeding occurred in 1.7% of patients in the clopidogrel plus ASA group and in 1.3% of the ASA group (RR 1.25); this difference was not significant. The rate of moderate bleeding was significantly higher at 2.1% in the clopidogrel plus ASA group, versus 1.3% in the ASA group (RR 1.62). Subgroup analysis revealed that among the 12,153 symptomatic patients (those with documented cardiovascular disease), a marginally significant reduction in the primary end point for the clopidogrel and ASA group was observed (6.9% vs. 7.9% with ASA, RR 0.88). Among asymptomatic patients, there was a significant increase in the rate of death from all causes in the clopidogrel plus ASA group, compared with the ASA group (5.4% vs. 3.8%), and a significant increase in deaths from cardiovascular causes among patients assigned to clopidogrel and ASA (3.9% vs. 2.2%).

Thromboembolism Not Linked to Cabin Pressure

BY JOHN R. BELL
Associate Editor

The low-air-pressure, hypoxic environment experienced in air travel is not likely a cause of the increased risk for venous thromboembolism associated with long-distance flight, a team of British and Dutch researchers has reported.

The investigators, led by Dr. William D. Toff of the University of Leicester (England), performed a single-blind crossover study to compare the effects of a simulated long-haul flight—prolonged sitting in a hypobaric, hypoxic environment—with the effects of prolonged sitting in a normobaric, normoxic control environment.

Study participants in both groups showed significant changes in measures of several blood markers associated with thrombolysis, but these changes were not significantly different between the two exposure environments and were ascribed to circadian rhythm and the act of prolonged sitting, rather than to lowered atmospheric pressure (JAMA 2006; 295:2251-61).

A total of 73 participants were screened for factor V Leiden and prothrombin G202190 mutations (the most common causes of thrombophilia) and stratified into three groups according to their risk of thromboembolism: a younger group (49 people; age 18-40 years; mean 23.5 years) not taking oral contraceptives, a smaller group of oral contraceptive users (12 people; age 18-40 years; mean 23.8 years), and an older group of men and women (12 people; age at least 50 years; mean age 57 years).

The researchers then randomly assigned all participants to one of two exposure groups, which differed only in the order of exposure. One group first sat for 8 hours in a bariatric chamber pressurized to create an environment of hypobaric hypoxia equal to roughly 8,000 feet (the lowest cabin pressure permitted by airline regulations) and 1 week later sat for another 8 hours in the chamber under normobaric normoxia; the second group underwent the same exposure but in the reverse order. Participants were allowed to stand up and move for 5 minutes each hour, could drink nonalcoholic beverages, and were given a light lunch and snacks.

The investigators recorded arterial oxygen saturation via pulse oximetry every hour and took blood samples before and after each 8-hour session to assess coagulation activation, fibrinolysis, platelet activation, and endothelial cell activation for each participant.

As expected, all three risk groups experienced lower arterial oxygen saturation during the low-pressure portion of the study. Notably, though, statistically significant changes were seen in markers of coagulation activation and fibrinolysis during not only the hypobaric exposure but also the normobaric (control) session—leading the investigators to conclude that such changes were associated with long-term sitting and natural circadian patterns, rather than air pressure. For example, the level of tissue plasminogen activator dropped a median of 1.23 ng/mL during normobaric normoxia and a median of 1.00 ng/mL during hypobaric hypoxia.

In addition, these changes were not significantly different between normal pressure and lower pressure for any of the three risk groups.

"In this large, controlled study with measurement of a wide range of markers … we found no procoagulant changes attributable to hypobaric hypoxia," the investigators concluded. "Our findings do not support the hypothesis that hypobaric hypoxia of the degree that might be encountered during long-haul air travel is associated with prothrombotic alterations in the hemostatic system in healthy individuals at low risk of venous thromboembolism."

The researchers did not comment on whether the changed blood marker levels, corresponding with increased risk for venous thromboembolism, are in themselves cause for concern. However, they called these changes "minor."

"It is noteworthy that there was no significant change in endogenous thrombin potential, a global marker of coagulation activation," they added. In some individuals, genetic risk factors might interact with hypoxia to increase the risk of thromboembolism, they conceded.

The study authors noted that reports of venous thromboembolism after long-haul air travel began more than 50 years ago.

In an accompanying editorial, Dr. Peter Bärtsch of the University of Heidelberg (Germany) concurred with the study authors that mild hypoxia and prolonged sitting pose little risk to most people but added that "the small numbers of older participants and individuals taking contraceptives preclude drawing reliable conclusions about these groups" (JAMA 2006;295:2297-9).

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