Women Get Different Benefit

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women, compared with men. In this study of women, strokes were more common than MIs, and aspirin's benefit was largely in stroke prevention. In contrast, results from prior studies in healthy men, including the very similarly designed Physicians' Health Study, showed that MIs were the primary threat and that the benefit from aspirin prophylaxis was greatest for MI prevention.

"The finding that women behave differently than men with respect to aspirin was not what we expected, but we shouldn't be that surprised. Many of us look for genetic effects, and gender is the ultimate genetic effect," said Paul M. Ridker, M.D., director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston and coprincipal investigator for the study along with Dr. Buring, professor of epidemiology at Harvard School of Public Health, Boston.

The study enrolled 39,876 healthy, female health professionals during the early 1990s who reported their baseline health data by returning a questionnaire. In general, these women had few CVD risk factors. As rated by the Framingham Risk Score, 84% of the enrollees had a less than 5% risk of coronary heart disease in the ensuing 10 years, 12% had a 5%-9.9% risk, and 4% had a risk that was 10% or greater for developing coronary heart disease during the 10 years after they entered the study. The women were randomized to the aspirin regimen or placebo, which they continued during an average follow-up of 10.1 years. During follow-up, 999 participants had a first, major cardiovascular event: nonfatal MI, nonfatal stroke, or death from cardiovascular causes.

The rate of major cardiovascular events, the study's primary end point, was about 2.4% in the women who took aspirin and about 2.6% in those who didn't, a relative risk reduction of 9% that failed to achieve statistical significance. But the rate of ischemic stroke for the entire group was cut by aspirin use by a relative rate of 24%, a statistically significant difference, Dr. Ridker reported. The study's results were published in the online edition of the New England Journal of Medicine (http://content.nejm.org/cgi/reprint/NEJMoa050613v1.pdf) concurrently with Dr. Ridker's presentation.

The downside to aspirin treatment was a very small increase in the rate of hemorrhagic strokes with aspirin use, a total of 10 additional cases in the aspirin group that was a statistically nonsignificant difference. Aspirin also led to small, but statistically significant, increases in the rates of all GI bleeding episodes, GI bleeds that needed transfusions, peptic ulcers, hematuria, and easy bruising.

The analysis also assessed the impact of aspirin in a variety of study subgroups. Most clinical factors, such as BMI, blood pressure, diabetes, and baseline Framingham risk score, failed to identify subgroups that had a better or worse benefit from aspirin.

But age made a difference. Among the 4,097 women in the study aged 65 or older, aspirin led to significant drops in ischemic strokes, MIs, and all major cardiovascular events. In this subgroup, aspirin use, compared with placebo, led to 44 fewer major CVD events and 16 more GI bleeds that required transfusions. In the two younger subgroups, women 45-54 years old and those 55-64 years old did not show statistically significant benefits from aspirin.

While the findings established that low-dose aspirin can prevent cardiovascular disease, and especially strokes, in a significant fraction of women, physicians will now face the challenge of identifying women in their practices who, on balance, are good candidates for starting an aspirin regimen.

Prophylactic aspirin is an option for women aged 65 or older if their blood pressure is controlled. "Many women older than 65 have uncontrolled hypertension and may have an increased risk of hemorrhagic stroke," commented Lori Mosca, M.D., director of preventive cardiology at New York-Presbyterian Hospital.

In addition, many older women take medications for arthritis or other conditions that boost their risk for GI bleeding, another factor that should be taken into account, she said. Other women who are potential candidates for aspirin are those with an intermediate risk of CVD events based on a Framingham risk score of 10% or greater. Although the study's findings failed to show a benefit among such women that was statistically significant, there was a trend toward benefit that probably failed to reach significance because there were few women in the study with such a high risk score, she told this newspaper.

Current recommendations from both the American Heart Association and the U.S. Preventive Services Task Force say that physicians should use a person's Framingham risk score when deciding whether or not to prescribe aspirin for primary prevention of CVD events. The recommendations use a threshold 10-year risk of 6% and 10%, respectively. But these recommendations were drawn from prior study results, which were obtained mostly from men. "We'll need to carefully think about" continuing to use the Framingham risk score for deciding whether or not to recommend aspirin to women, Dr. Ridker told this newspaper. ■

Vitamin E Fails to Prevent CVD Events

The same Women's Health Study that proved a benefit from prophylactic aspirin among certain women showed essentially no benefit whatsoever from a prophylactic regimen of vitamin E.

"Taken together, the totality of published studies indicates no statistically significant or clinically important effects of vitamin E on cardiovascular disease," Dr. Buring said. "The data do not support the use of vitamin E supplements for prevention of cardiovascular disease."

Using a two-by-two factorial design, the same study that randomized 39,876 women to treatment with aspirin or placebo also randomized them to every-other-day treatment with either 600 IU vitamin E or placebo. Again, the women were followed for an average of 10.1 years, and the primary end point was the incidence of major CVD events.

The analysis failed to show any suggestion of benefit or harm for virtually every clinical parameter examined. The sole exception was a statistically significant 24% relative drop in the rate of cardiovascular death among the women who took vitamin E. But this finding was very unexpected, given that the study failed to show any indication that vitamin E use was linked with a drop in the incidence of strokes or MIs. This fact left Dr. Buring and her coinvestigators at a loss to explain the difference in cardiovascular death.

Instead of focusing on vitamin E for preventing cardiovascular disease, women should eat a healthy diet, maintain a healthy lifestyle, and control known risk factors, Dr. Buring recommended.

TNT Trial Shows Lower Is Better in Treating High Cholesterol

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — "Lower IS better" was the mantra at the annual meeting of the American College of Cardiology following the presentation of the Treating to New Targets trial of intensive lipid lowering in patients with stable coronary heart disease.

"We have entered a new era in the treatment of established coronary disease," declared Treating to New Targets (TNT) Steering Committee Chairman John C. LaRosa, M.D. "Treating patients with established coronary heart disease to an LDL of 77 mg/dL with 80 mg/day of atorvastatin from their starting LDL of 100 mg/dL [on 10 mg/day of atorvastatin] provided a highly significant reduction in their risk of major coronary events."

Driving LDL levels far below the National Cholesterol Education Program's recommended target of 100 mg/dL also resulted in other benefits, including a 25% reduction in the relative risk of stroke (2.3% vs. 3.1%) and a 26% decrease in hospitalization for heart failure (2.4% vs. 3.3%), added Dr. LaRosa, president of the State University of New York Health Science Center at Brooklyn.

TNT was a Pfizer-sponsored double-blind, multinational study that randomized 10,001 patients with stable coronary heart disease (CHD) to 10 or 80 mg/day of atorvastatin (Lipitor). After a median 4.9 years of follow-up, the primary study end point—major cardiovascular events as defined by a composite of death due to CHD, nonfatal MI unrelated to a revascularization procedure, fatal or nonfatal stroke, or resuscitation after cardiac arrest—occurred in 8.7% of the high-dose atorvastatin group and 10.9% of those on 10 mg/day.

TNT participants received state-of-the-art background secondary prevention therapy. This was reflected in the fact that mortality in both treatment arms was lower than in any prior major secondary prevention trial. It's a measure of the advances made in secondary prevention in recent years that in this population of 10,000 patients with documented CHD followed for 5 years on atorvastatin, cardiovascular disease was not the number-one cause of death, Dr. LaRosa observed.

The safety profile of 80 mg/day of atorvastatin was noteworthy. The incidence of persistently elevated liver enzyme tests more than three times the upper limit of normal was 1.2%. Treatment-related myalgia was reported by 4.8% of patients. There were no cases of rhabdomyolysis meeting ACC/American Heart Association criteria in either treatment arm. This was particularly reassuring because in the Aggrastat to Zocor (A to Z) trial, roughly 1 in 250 patients on high-dose simvastatin developed serious muscle complications, David D. Waters, M.D., a TNT steering committee member, told this newspaper.

Discussant Carl J. Vaughan, M.D., of the University of Cork (Ireland), said TNT is best appreciated in the context of the earlier Heart Protection Study (HPS) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials. Subgroup analysis in the nearly 21,000-patient HPS showed that patients with relatively low baseline LDL-cholesterol levels had the same clinical benefit from intensive statin therapy as those with higher levels. Last year PROVE-IT showed the superiority of high- over moderate-intensity statin therapy in acute coronary syndrome patients, again regardless of baseline LDL-cholesterol level.

"This is a very impressive trial," Sidney C. Smith Jr., M.D., told this newspaper. "We're going to have to get this information into our revised guidelines," added Dr. Smith, director of the center for cardiovascular science and medicine at the University of North Carolina at Chapel Hill, and a member of the committee responsible for joint ACC/AHA secondary prevention guidelines.

The only question remaining in many observers' minds was when the National Cholesterol Education Program will get around to revising its target LDL recommendations for patients with known CHD.

Many physicians don't feel the need to wait for the NCEP. "There are always more data coming along, but I would say this, taken together with HPS and PROVE-IT, is enough," said Dr. Waters, professor of medicine at the University of California, San Francisco.

The TNT results were published concurrently with the presentation (http://content.nejm.org/cgi/reprint/NEJMoa050461v1.pdf). ■