Results Will Influence Practice

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higher mortality among patients randomized to the atenolol-based regimen as well as worse outcomes on several secondary measures.

When all the data were tallied, all-cause mortality occurred at a rate of 13.9 per 1,000 patient-years in the amlodipine group and 15.5 per 1,000 patient-years in the atenolol group, an 11% relative reduction in favor of amlodipine that was statistically significant, Björn Dahlöf, M.D., reported at the annual congress of the European Society of Cardiology.

Cardiovascular mortality was cut from a rate of 6.5 per 1,000 patient-years in the atenolol group to 4.9 per 1,000 patient-years in the amlodipine group, a 24% relative reduction that was also statistically significant.

The ASCOT results appeared to sharply break from those of ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial), which in a 2002 report showed that a calcium channel blocker or an ACE inhibitor was no better than the diuretic chlorthalidone for preventing events in patients with hypertension in 2002. But experts pointed to major differences between the two studies.

First, the patients enrolled into ASCOT had a much lower baseline risk for cardiovascular events than did those who were enrolled into ALLHAT, said Peter S. Sever, M.B., an ASCOT coinvestigator and professor of clinical pharmacology and therapeutics at Imperial College in London.

Second, ALLHAT was designed to compare individual drugs, while ASCOT was designed to compare two forms of combination therapy, said Dr. Jamerson.

ASCOT enrolled 19,342 patients with hypertension in the United Kingdom and five other northern European countries during 1998-2000. Patients were eligible if they were 49-79 years old and had at least three of these cardiovascular risk factors: male gender, age of at least 55 years, smoking, total- to HDL-cholesterol ratio of at least 6, family history of premature coronary heart disease, left ventricular hypertrophy, type 2 diabetes, peripheral artery disease, or prior stroke or transient ischemic attack.

The combination also significantly dropped the rate of strokes and peripheral artery disease, as well as the incidence of new-onset diabetes and renal impairment.

Patients were treated with either amlodipine, adding perindopril when needed to reach the blood pressure target, or with atenolol (Tenormin), adding bendroflumethiazide and potassium when needed to reach the goal pressure. Throughout the trial, an average of 50% of patients in the amlodipine arm were on both amlodipine and perindopril, and an average of 55% in the atenolol arm were on atenolol and the thiazide.

The study's primary end point was the rate of nonfatal myocardial infarctions and coronary heart disease deaths, but this difference just missed being statistically significant. The rate was 8.2 per 1,000 patient-years in the amlodipine group and 9.1 per 1,000 patient-years in the atenolol group, a 10% relative reduction.

Part of the reason why the primary end point set in 1998 failed to reach significance was that many physicians now take a more aggressive approach to vascular intervention, which probably prevented many of these events, said Dr. Sever.

A more appropriate reflection of current practice is to tally myocardial infarctions, coronary heart disease deaths, and coronary revascularizations, he said. By this measure, the amlodipine regimen cut events by a relative 14%, a statistically significant difference.

The impact of the amlodipine and perindopril regimen was also notable for the range of events that it prevented. In addition to deaths and myocardial infarctions, it also significantly dropped the rate of strokes and peripheral artery disease, as well as the incidence of new-onset diabetes and renal impairment.

Throughout the study, the amlodipine arm had a systolic pressure that averaged 2.7 mm Hg lower than the amlodipine arm and a diastolic pressure that averaged 1.9 mm Hg lower. A complex statistical analysis by the study team established that the difference in blood pressure reduction between the two arms of the study accounted for about half of the difference in coronary events and about 40% of the difference in stroke events, suggesting that some of the difference was because of effects of amlodipine and perindopril that go beyond blood pressure lowering. Evidence from other studies has suggested that calcium channel blockers are especially effective at reducing stroke risk, and that ACE inhibitors are effective at lowering coronary disease risk, said Dr. Sever.

The study leaders, as well as Dr. Jamerson and Dr. Yusuf, all said that they were confident that the advantages seen for amlodipine and perindopril in the study represent class effects for calcium channel blockers and ACE inhibitors.

The ASCOT study was sponsored by Pfizer, which makes Norvasc, and the researchers who ran the study served as consultants to and received honoraria, travel expenses, and research support from Pfizer. But the researchers emphasized that the study was designed, run, and analyzed independently of any input from the sponsor. ■

Reducing Homocysteine Doesn't Cut Cardiovascular Risk

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — Lowering plasma homocysteine with B vitamin therapy does not prevent subsequent MIs and strokes in patients who have had an MI—to the contrary, it may even be harmful, according to the results of the first large randomized treatment trial to examine the issue.

"The homocysteine hypothesis is dead. Homocysteine is not a causal risk factor. It is an innocent bystander," Kaare Harald Bonaa, M.D., told this newspaper at the annual congress of the European Society of Cardiology.

Homocysteine's relationship to cardiovascular disease has been a topic of intense investigation in the past decade. The homocysteine story would now appear to illustrate the hazards of extrapolating from epidemiologic association to clinical practice in the absence of favorable treatment outcome studies.

On the strength of considerable epidemiologic evidence linking high plasma homocysteine to increased MI and stroke rates, many American and European physicians have in recent years suggested B vitamin therapy to reduce homocysteine levels in their patients at high cardiovascular risk. The rationale was that since such therapy was inexpensive, was thought safe, and could have turned out to have a big payoff in reduced clinical events, it might have been a reasonable strategy to use while awaiting results of randomized treatment outcome studies.

But now the Norwegian Vitamin Trial (NORVIT) has shown that such therapy doesn't prevent cardiovascular events; indeed, it may even increase the risk. And there was also a disturbing trend, albeit not statistically significant, for an increase in cancer, said Dr. Bonaa, professor of cardiology at the University of Tromsø (Norway).

Dr. Bonaa was the principal investigator in NORVIT, a randomized, double-blind, multicenter trial in which 3,749 Norwegian patients were followed for 3.5 years after assignment to 0.8 mg/day of folic acid; 40 mg/day of vitamin B_6; both; or placebo during their hospitalization for an acute MI. Participants also received all of the standard drugs given post MI.

Patients in the two folic acid arms of NORVIT experienced a rapid and sustained mean 28% decrease in homocysteine. The rationale for including the vitamin B_6 arms in the trial came from epidemiologic studies showing that people with low dietary intake of this nutrient also have increased risks of stroke and MI.

The primary end point in NORVIT was a composite of fatal and nonfatal MI and stroke. It occurred in 18% of the placebo group and in a similar percentage of those who got folic acid or vitamin B_6 alone. However, the incidence in patients randomized to both folic acid and vitamin B_6 was 20% higher, a highly significant difference. (See box.)

In a multivariate analysis, combination therapy was associated with statistically significant 20% increased relative risks of three study end points—MI, MI and stroke, and death—compared with the other three study groups, along with a more than 30% increase in cancer, which was not statistically significant.

No patient subgroup benefited from B vitamin therapy. Those with a high baseline homocysteine—that is, in excess of 13 mcg/L—fared worst, with a 27% increase in cardiovascular events regardless of whether or not they received B vitamins.

Studies are being planned to learn whether folic acid accelerates cancer cell growth.

Discussant Ian M. Graham, M.D., was unwilling to declare the homocysteine hypothesis dead and buried.

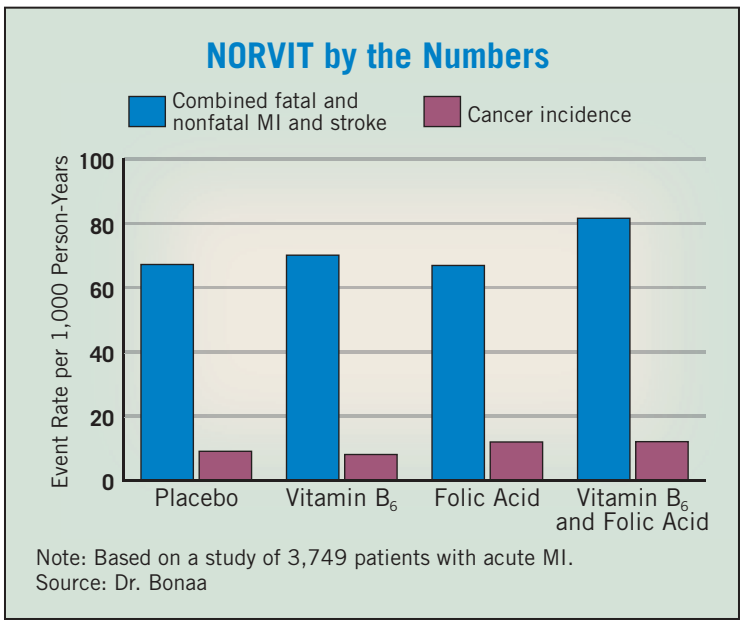
Because of NORVIT's complex two-by-two factorial design, the study was underpowered to firmly conclude that B vitamin therapy was without benefit or indeed harmful.

But there is certainly no evidence from this or any other source that the relationship between homocysteine and vascular disease is causal, said Dr. Graham, professor of epidemiology and public health at the Royal College of Surgeons, and a cardiologist at Trinity College, Dublin.

He agreed that the NORVIT cancer findings warrant further study.

While epidemiologic data suggest a diet rich in folate protects against cancer, there is also evidence from in vitro studies to support the argument that folate promotes cancer cell growth.

NORVIT was sponsored by the Norwegian Research Council, the Norwegian Council on Cardiovascular Research, and other nonprofit institutions, with no industry support. ■



Note: Based on a study of 3,749 patients with acute MI.
Source: Dr. Bonaa