

B Vitamin Therapy Not Beneficial

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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 following assignment to 0.8 mg/day of folic acid; 40 mg/day of vitamin B₆; 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 homocys-

teine. The rationale for including the vitamin B₆ 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.

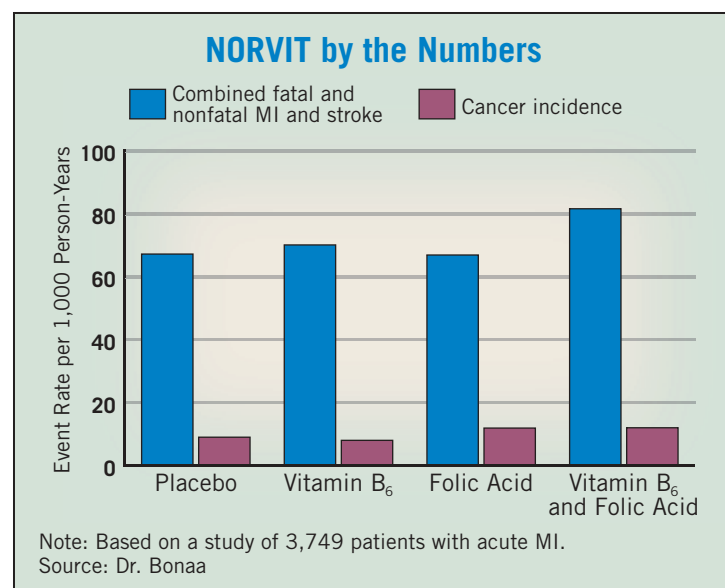
The primary end point in NORVIT was a composite of fatal and nonfatal MI and stroke.

It occurred in 18% of the placebo group and in a similar percentage of those who got folic acid or vitamin B₆ alone. However, the incidence in patients randomized to both folic acid and vitamin B₆ 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 car-



diovascular 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. ■

Good Prognosis for 'Mild' Coronary Artery Disease Discredited

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — The prognosis of nonobstructive coronary artery disease may be far less benign than generally assumed, according to two studies presented at the annual congress of the European Society of Cardiology.

Patients with less than 50% luminal stenosis upon diagnostic coronary angiography aren't considered candidates for percutaneous intervention; they are typically told they have "mild" CAD with a very good prognosis. For this reason, critical pathways for risk assessment and treatment of such patients have never been developed, according to Raffaele Bugiardini, M.D., of the University of Bologna, Italy.

The assumption that nonobstructive CAD carries a good prognosis is not based on hard data, and had not been examined in a large study until recently. And now that it has, the assumption turns out to be incorrect, the cardiologist said.

Dr. Bugiardini presented a secondary analysis of three published, randomized clinical trials from the Thrombolysis in Myocardial Infarction (TIMI) program involving 10,915 patients with acute coronary syndromes (ACS) for whom angiographic data

were available. The studies were the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI 22), Orbofiban in Patients With Unstable Coronary Syndromes (OPUS-TIMI 16), and TIMI II-B studies. The prevalence of nonobstructive CAD in this ACS population was 8.3%. Slightly more than half of the 910 affected patients had mild CAD as defined by a stenosis of less than 50%, whereas the remainder had angiographically normal, smooth coronary arteries.

The primary outcome measure in Dr. Bugiardini's analysis was the combined 1-year rate of death, MI, stroke, coronary revascularization, and/or unstable angina requiring rehospital-

ization. It occurred in 11.2% of patients with nonobstructive CAD. The incidence was 8.8% in ACS patients with angiographically normal arteries and 13.5% in those with less than 50% stenosis.

Those rates will strike most physicians as surprisingly high. Even more disturbing was the unexpectedly high rate of the most serious outcomes—death or nonfatal MI—in this supposedly low-risk population. The overall incidence was 2% at 1 year, with a 2.8% rate of death or nonfatal MI among patients with mild CAD and 1.3% in those with angiographically normal coronary arteries, Dr. Bugiardini said.

Now that the prevailing as-

sumption—that mild CAD carries a good prognosis—has been discredited, it becomes important for physicians to risk-stratify patients with nonobstructive CAD so that their management can be tailored appropriately, he said. The validated and widely used TIMI risk score for patients with unstable angina/non-ST-segment elevation MI can play a useful role here, he added.

When he applied the TIMI risk score to the 665 eligible patients, the associated 1-year risk of death or MI climbed from 0% (in those with a TIMI score of 0) to 4.1% (in those with a score of 4 or more). (See box.)

"The 0.6% death or MI rate seen with a TIMI score of 1 is the expected rate in the general population of asymptomatic subjects. But when you go to a score of 3 points, you see a completely unacceptable 2.8% rate of death or MI. That's unbelievable. So patients with a score of 3 or 4 are really at great risk," said Dr. Bugiardini.

Separately, Sylvie Swales, M.D., presented data from the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease project (MONICA) Belgian substudy. This prospective survey of the 130,000 residents of the Belgian province of Luxembourg identified all those who underwent coronary angiography for

the first time in any Belgian hospital during 1985-1996.

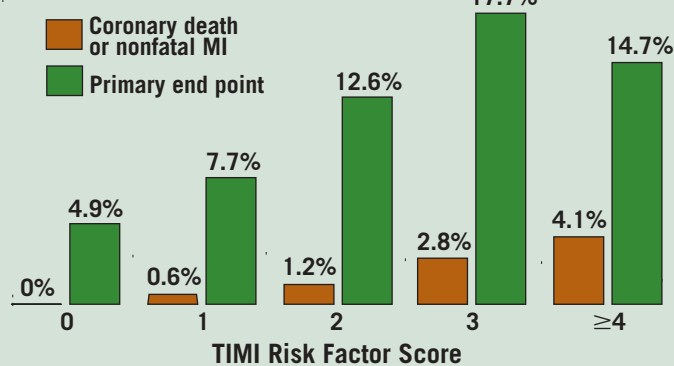
The subsequent 5-year incidence of coronary death among 274 subjects with mild CAD as defined by a less than 50% stenosis was 7.8%, similar to the 8.1% rate among 377 others with angiographically significant single-vessel disease not treated with angioplasty or bypass surgery. The 5-year rate of coronary death or nonfatal MI was 10.3% in the group with mild CAD and 14.8% in those with significant single-vessel CAD as defined by a 50% or greater stenosis.

The prognosis was far better for the 763 individuals whose angiogram showed smooth vessels. Their 5-year rate of coronary death was just 0.7%, while their rate of coronary death or nonfatal MI was 1.2%, noted Dr. Swales of the Catholic University of Leuven (Belgium).

Dr. Bugiardini said that although it's possible some cases that are labeled as "nonobstructive" CAD represent misclassification of the angiogram, it has been his clinical observation that poor patient compliance with secondary prevention measures is a much bigger factor.

"When told they have nonobstructive coronary artery disease, patients relax more than the doctors," said Dr. Swales. "So often, after 6 months or maybe even 2 months, they give up on taking their drugs. It's going to be necessary to have a public education campaign." ■

TIMI Score Can Stratify Risk in Nonobstructive CAD



Note: Based on data from 665 patients with acute coronary syndromes. Primary end point was combined 1-year rate of death, MI, stroke, unstable angina requiring rehospitalization, and/or coronary revascularization.
Source: Dr. Bugiardini