Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B12, and Vitamin B6 on Clinical Outcome After Percutaneous Coronary Intervention: The Swiss Heart Study: A Randomized Controlled Trial Original Contribution

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FROM ABSTRACT

Context
Plasma homocysteine level has been recognized as an important cardiovascular risk factor that predicts adverse cardiac events in patients with established coronary atherosclerosis and influences restenosis rate after percutaneous coronary intervention.

Objective
To evaluate the effect of homocysteine-lowering therapy on clinical outcome after percutaneous coronary intervention.

Design, Setting, and Participants
Randomized, double-blind placebo-controlled trial involving 553 patients referred to the University Hospital in Bern, Switzerland, enrolled after successful angioplasty of at least 1 significant coronary stenosis (50%).

Intervention
Participants were randomly assigned to receive a combination of folic acid (1 mg/d), vitamin B12 (cyanocobalamin, 400 μg/d), and vitamin B6 (pyridoxine hydrochloride, 10 mg/d) (n = 272) or placebo (n = 281) for 6 months.

Main Outcome Measure
Composite end point of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization, evaluated at 6 months and 1 year.

Results
After a mean (SD) follow-up of 11 months, the composite end point was significantly lower at 1 year in patients treated with homocysteine-lowering therapy (15.4% vs 22.8%).

Conclusion
Homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 significantly decreases the incidence of major adverse events after percutaneous coronary intervention.

THESE AUTHORS ALSO NOTE:

"Despite technical improvements, restenosis and overall adverse events after percutaneous coronary interventions remain important limitations of this procedure."

"Epidemiological evidence suggests that total plasma homocysteine level is an independent cardiovascular risk factor, correlates with the severity of coronary artery disease, predicts mortality in patients with established coronary atherosclerosis, and may have a potential role with regard to outcome after coronary interventions."

"Plasma homocysteine levels predict outcome after coronary angioplasty, and homocysteine-lowering therapy significantly decreases restenosis rate after coronary angioplasty."

RESULTS

553 patients were randomly assigned either to receive folate+B12+B6 (n = 272) or placebo (n = 281).

"Mean homocysteine levels (SD) at 6 months were significantly lower with folate+B12+B6 therapy compared with placebo."

STUDY END POINTS

After a follow-up of 11 months, 14.0% of patients treated with folate+B12+B6 underwent repeat revascularization vs. 19.9% of control patients.

"Among patients who received folate+B12+B6, 9.9% had repeat target lesion revascularization vs. 16.0% in the placebo group, a relative reduction of 38%."

Compared with controls, patients treated with folate+B12+B6 with the highest levels of cholesterol (>228 mg/dL) had the greatest risk reduction for revascularization.

In the folate+B12+B6 therapy group there was a lower incidence of nonfatal myocardial infarction, cardiac deaths, and overall deaths. The incidence of major adverse events was significantly lower in patients receiving folate+B12+B6 therapy at 6 months.

COMMENT

"This study provides evidence that homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 improves outcome after percutaneous coronary intervention by reducing the need for repeat revascularization and decreasing the overall incidence of major adverse events 1 year after successful coronary angioplasty."

"These results are consistent with those of recent randomized trials with homocysteine-lowering therapy showing decreased risk of atherosclerotic coronary events among healthy patients, halting in the progression of carotid plaque, improved arterial endothelial function, and significant benefit on restenosis rate after coronary angioplasty."

"This study further suggests that the benefit obtained with homocysteine-lowering therapy at 6 months is maintained at 1 year despite cessation of folate+B12+B6 therapy at 6 months."

"The current study confirms that a 6-month course of this inexpensive treatment has minimal adverse effects and helps to control excessive restenosis mechanisms."

"Elevated homocysteine levels stimulate vascular smooth muscle cell growth and collagen synthesis, which promote intimal-medial thickening."

"Elevated homocysteine levels decrease the release of nitric oxide and promote the generation and accumulation of hydrogen peroxide, thus rendering nitric oxide more susceptible to oxidative inactivation."

"Elevated plasma homocysteine levels promote lipid peroxidation, which alters growth factor production and influences smooth muscle cell proliferation."

This study supports the conclusion that the combination of folic acid, vitamin B12, and vitamin B6, by lowering of homocysteine levels, "is an effective therapy for improving outcome in patients undergoing coronary angioplasty."

KEY POINTS FROM DAN MURPHY

(1) Plasma homocysteine levels are an important cardiovascular risk factor.

(2) Plasma homocysteine levels are lowered by taking folic acid, vitamin B12, and vitamin B6, and this significantly protects one from cardiovascular disease.

(3) The amounts taken in this study were:
Folic acid = 1mg/d; Vitamin B12, cyanocobalamin = 400 µg/d
Vitamin B6, pyridoxine hydrochloride = 10 mg/d.