

# Homocysteine-lowering therapy improved outcomes after percutaneous coronary intervention

Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. *JAMA*. 2002;288:973-9.

## QUESTION

In patients having percutaneous coronary intervention (PCI), does homocysteine-lowering therapy with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> reduce adverse coronary outcomes?

## DESIGN

Randomized (unclear allocation concealment\*), blinded (clinicians, patients, and outcome assessors),\* placebo-controlled trial with 12-month follow-up.

## SETTING

A university hospital in Bern, Switzerland.

## PATIENTS

553 patients (mean age 63 y, 80% men) who received angioplasty to treat at least 1 significant coronary stenosis ( $\geq 50\%$ ). Exclusion criteria were unstable angina, myocardial infarction (MI) within the past 2 weeks, renal insufficiency, or receipt of vitamin supplements. Follow-up was 83%; all patients were included in the analysis.

## INTERVENTION

Patients were allocated to homocysteine-lowering therapy with folic acid, 1 mg/d; vita-

min B<sub>12</sub>, 400  $\mu\text{g}/\text{d}$ ; and vitamin B<sub>6</sub>, 10 mg/d ( $n = 272$ ) or to placebo ( $n = 281$ ) for 6 months.

## MAIN OUTCOME MEASURES

Adverse events defined as all-cause mortality, cardiac death, nonfatal MI, need for repeated revascularization for proven ischemia, or a composite of adverse events.

## MAIN RESULTS

Analysis was by intention to treat. The composite endpoint of any major coronary adverse outcome was lower in the homocysteine-lowering group than the placebo group, as was the need for repeated revascularization and repeated target lesion revascularization (Table). Adjustment for age, sex,

and risk factors known to influence the need for repeated revascularization did not affect the results. The groups did not differ for nonfatal MI, cardiac death, or all-cause mortality.

## CONCLUSION

In patients having PCI, homocysteine-lowering therapy with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> reduced the need for repeated revascularization and adverse coronary outcomes.

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\*See Glossary.

## Homocysteine-lowering therapy vs placebo after percutaneous coronary intervention†

Outcomes at 1 y	Homocysteine-lowering	Placebo	RRR (95% CI)	NNT (CI)
Composite outcome	15.4%	22.8%	69% (50 to 97)	15 (9 to 167)
Repeated revascularization	14.0%	19.9%	29% (1.8 to 46)	18 (11 to 281)
Repeated target lesion revascularization	9.9%	16.0%	37% (4.6 to 57)	17 (11 to 136)

†Composite outcome included death, cardiac death, nonfatal myocardial infarction, or need for repeated revascularization. Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article using Cox proportional-hazards ratio.

## COMMENTARY

Systematic reviews have consistently shown a strong relation between elevated blood levels of homocysteine and risk for atherothrombotic vascular disease (1, 2). Furthermore, blood levels of homocysteine can be lowered in most patients using folate-containing multivitamin therapy (3). However, uncertainty still exists about the relation between homocysteine and vascular disease, especially whether it is causal (and modifiable) or confounded (high homocysteine levels may simply be a marker of another causal vascular risk factor), or whether high homocysteine levels in the blood may simply be a consequence of the atherosclerotic disease process or its complications (4).

The study by Schnyder and colleagues provides further support for a causal association between homocysteine and vascular disease by showing, for the first time, a reduction in major clinical vascular events, including death, MI, and target-vessel revascularization with folate-based homocysteine-lowering therapy. Although the risk reductions for death or MI were not statistically significant, the consistency of the treatment effect compared with the overall risk reduction suggests that the reduction in these outcomes is real.

A potential limitation of this study is that 13% of patients were lost to follow-up; imbalances in clinical outcomes between the 2 treatment groups after loss to follow-up could alter the study results. However, this is unlikely because the baseline characteristics and disease severity of patients lost to follow-up did not differ from the rest of the study

population and a similar proportion was lost from both treatment groups.

What are the implications for clinical practice? Although causality of association between homocysteine and atherothrombosis remains unproven, the substantial benefits of simple, inexpensive, nontoxic, multivitamin therapy seem to provide a strong rationale for routine use of folic acid and vitamins B<sub>6</sub> and B<sub>12</sub> in patients receiving PCI. However, confirmatory data further evaluating the "homocysteine hypothesis" of atherothrombosis would be welcome (4).

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## References

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