Homocysteine lowering treatment improved outcomes after percutaneous coronary intervention


QUESTION: In patients having percutaneous coronary intervention (PCI), does homocysteine lowering treatment with folic acid, vitamin B₁₂, and vitamin B₆ reduce adverse coronary outcomes?

Design
Randomised (unclear allocation concealment*), blinded (clinicians, patients, and outcome assessors),* placebo controlled trial with 12 months of 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 (≥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 treatment with folic acid, 1 mg/day; vitamin B₁₂, 400 µg/day; and vitamin B₆, 10 mg/day (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 revascularisation for proven ischaemia, 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 revascularisation and repeated target lesion revascularisation (table). Adjustment for age, sex, and risk factors known to influence the need for repeated revascularisation 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 treatment with folic acid, vitamin B₁₂, and vitamin B₆ reduced the need for repeated revascularisation and adverse coronary outcomes.* See glossary.

Homocysteine lowering treatment v placebo after percutaneous coronary intervention†

<table>
<thead>
<tr>
<th>Outcomes at 1 year</th>
<th>Homocysteine lowering</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome</td>
<td>15.4%</td>
<td>22.8%</td>
<td>69% (50 to 97)</td>
<td>15 (9 to 167)</td>
</tr>
<tr>
<td>Repeated revascularisation</td>
<td>14.0%</td>
<td>19.9%</td>
<td>29% (1.8 to 46)</td>
<td>18 (11 to 281)</td>
</tr>
<tr>
<td>Repeated target lesion revascularisation</td>
<td>9.9%</td>
<td>16.0%</td>
<td>37% (4.6 to 57)</td>
<td>17 (11 to 136)</td>
</tr>
</tbody>
</table>

†Composite outcome included death, cardiac death, nonfatal myocardial infarction, or need for repeated revascularisation. 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 concentrations of homocysteine and risk of atherothrombotic vascular disease. Furthermore, blood concentrations of homocysteine can be lowered in most patients using folate containing multivitamin treatment. However, uncertainty still exists about the relation between homocysteine and vascular disease, especially whether it is causal (and modifiable) or confounded (high homocysteine concentrations may simply be a marker of another causal risk factor), or whether high homocysteine concentrations in the blood may simply be a consequence of the atherosclerotic disease process or its complications.

The study by Schneider et al 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 revascularisation with folate based homocysteine lowering treatment. 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 treatment seem to provide a strong rationale for routine use of folic acid and vitamins B₁₂ and B₆ in patients receiving PCI. However, confirmatory data further evaluating the “homocysteine hypothesis” of atherothrombosis would be welcome."