Lack of association between baseline plasma homocysteine concentrations and restenosis rates after a first elective percutaneous coronary intervention without stenting


**Objective:** To evaluate the association between baseline homocysteine concentrations and restenosis rates in patients electively undergoing their first percutaneous coronary intervention (PCI) without stenting.

**Design:** Prospective, single centre, observational study.

**Setting and patients:** Patients electively undergoing their first PCI without stenting at a tertiary referral centre between 1990 and 1998.

**Methods:** Blood samples were collected from all patients at baseline and assayed to determine the patients’ homocysteine concentrations. Patients whose PCI was successful underwent repeat angiography at a median of 6.4 (interquartile range 6–6.8) months. Their baseline and follow up angiograms were compared by quantitative coronary angiography to assess the incidence of restenosis. For the analysis, the patients were divided into two groups based on whether their baseline homocysteine concentrations were above or below the median value. These two groups were compared to determine whether there was any association between their baseline homocysteine concentrations and the incidence of restenosis at six months.

**Results:** 134 patients had a successful first PCI without stenting (involving 200 lesions). At six month angiography, restenosis was observed in 33 patients (49.3%) with baseline homocysteine concentrations above the median value and in 31 patients (46.3%) with concentrations below the median value (p = 0.74). There was no difference in the percentage of lesions developing restenosis (38 (39.6%) v 40 (38.5%), respectively, p = 0.87) or late lumen loss (0.40 mm v 0.31 mm, respectively, p = 0.24). On multivariable analysis, there was no association between homocysteine concentrations and late lumen loss (r = −0.11, p = 0.11) or the percentage diameter stenosis at follow up (r = −0.07, p = 0.32).

**Conclusion:** Baseline homocysteine concentrations were not associated with six month restenosis rates in patients electively undergoing their first PCI without stenting.
Neither dalteparin nor simvastatin was shown to have any effect on restenosis rates at six months.

**Quantitative coronary angiography**

After sublingual administration of glyceryl trinitrate, coronary angiography was performed in orthogonal projections that optimally displayed the lesions undergoing PCI. The procedure was duplicated at follow up angiography, including use of the same angulations and table height. Computer assisted quantitative evaluation of the paired angiograms was undertaken by an experienced technician (BJW) using the Cardiovascular Measurement System (CMS-Medis Imaging System, Leiden, the Netherlands). Orthogonal projections with the treated lesion in the centre of the frame at end diastole, free of foreshortening or superimposed structures, were chosen for analysis. The minimum lumen diameter and the reference diameter were measured with the known diameter of the guiding catheter tip used for calibration so that the percentage of the stenosis could be calculated. The accuracy of the measurements of both the minimum lumen diameter and the reference diameter was within 0.01 mm. The precision of both was 0.17 mm.

**Homocysteine assay**

Fasting blood samples were collected in the morning, placed into citrate tubes, and centrifuged within one hour to obtain plasma, which was then stored at −80°C. Plasma concentrations of homocysteine were measured with the Abbott AxSYM homocysteine assay L2002 (Abbott Park, Illinois, USA), a newer generation fluorescence polarisation immunoassay modified from the Abbott IMx analyser. Further details of this assay are available from the manufacturer (Abbott AxSYM system for homocysteine assay. Ref 5F51.20 and AxSYMHC.fm, 7/9/01 (1100), revision 1, produced by Axis-shield, Oslo, Norway for Abbott Laboratories, Illinois, USA).

**Statistical analysis**

Homocysteine concentrations and their association with angiographic outcome variables were analysed both as continuous variables and as dichotomous variables with the median value serving as the cut off point. Restenosis was defined as stenosis of ≥ 50% of the minimum lumen diameter at follow up angiography. Late lumen loss was defined as the minimum lumen diameter immediately after PCI minus the minimum lumen diameter at follow up angiography.

Spearman’s test was used to calculate the association between baseline homocysteine concentrations and the percentage stenosis at follow up, as well as the association between baseline homocysteine concentrations and late lumen loss. Multivariable analysis was performed with logistic regression for binary restenosis of ≥ 50% diameter reduction and a generalised linear model for late lumen loss. Factors previously reported as being associated with increased rates of restenosis (namely, a history of diabetes, a smaller reference vessel diameter, and a smaller minimum lumen diameter of the lesion before and after PCI) were entered into the model, together with age, sex, smoking history, creatinine concentration, and assigned treatment.

All results are presented as medians and interquartile ranges. Groups were compared by t tests or the Mann-Whitney U test where appropriate. Probability values of p < 0.05 were considered significant.

**RESULTS**

Of 199 patients who had a successful first PCI without stenting, 134 patients had stored plasma samples that had not been previously thawed for other purposes. Of these 134 patients, 83 had PCI on one lesion, 40 had PCI on two lesions, and 11 had PCI on more than two lesions, giving a total of 200 successfully treated lesions.

The median plasma homocysteine concentration at baseline was 13.11 (interquartile range 10.61–16.13) μmol/l. There was no difference in baseline characteristics between patients with lower homocysteine concentrations and those with higher concentrations (table 1).

At follow up angiography, at a median of 6.4 (interquartile range 6–6.8) months, restenosis was documented in 33 patients (49.3%) with lower baseline homocysteine concentrations versus 31 patients (46.3%) with higher concentrations (p = 0.73). A total of 78 lesions exhibited restenosis. Table 2 lists the baseline and follow up angiographic findings in the two groups. There was no difference between the groups in the percentage of lesions developing restenosis.

### Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Homocysteine concentration</th>
<th>&lt;13.11 μmol/l</th>
<th>≥13.11 μmol/l</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>57.5 (9.7)</td>
<td>60.8 (10.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Male sex</td>
<td>56 (83.6%)</td>
<td>53 (79.1%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Any history of smoking</td>
<td>40 (59.7%)</td>
<td>47 (70.1%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2 (3%)</td>
<td>5 (7.5%)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of diabetes mellitus*</td>
<td>5 (7.5%)</td>
<td>2 (3%)</td>
<td>0.44</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>30 (44.8%)</td>
<td>30 (44.8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>26 (38.8%)</td>
<td>27 (40.3%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Number of treated lesions per patient</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Number of patients undergoing directional atherectomy</td>
<td>5 (7.5%)</td>
<td>6 (9.0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of patients undergoing rotational atherectomy</td>
<td>1 (1%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>0.09 (0.08–0.1)</td>
<td>0.09 (0.09–0.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3 (2–8.3)</td>
<td>2.9 (2.6–3.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.93 (5.25–6.52)</td>
<td>5.96 (5.33–6.46)</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.01 (0.85–1.26)</td>
<td>1.08 (0.86–1.32)</td>
<td>0.33</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>1.0 (0.75–1.15)</td>
<td>1.12 (0.83–1.26)</td>
<td>0.12</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.57 (1.5–2.21)</td>
<td>1.39 (1.11–2.04)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Insulin dependent diabetes mellitus was an exclusion criterion in this trial.

Data are median (interquartile range) or number (%).
Association between homocysteine concentrations and restenosis

Homocysteine concentrations (assessed as a continuous variable) were not found to be associated with late lumen loss ($r = -0.11, p = 0.11$) or the percentage diameter stenosis at follow up ($r = -0.07, p = 0.32$). Figure 1 plots the percentage diameter stenosis of lesions at follow up according to the baseline homocysteine concentration. There was no identifiable homocysteine threshold above which restenosis was more common. On multivariable analysis, the only predictor of restenosis was a smaller pre-PCI minimum lumen diameter, whereas late lumen loss was predicted by a larger post-PCI minimum lumen diameter and a smaller pre-PCI reference diameter. The baseline homocysteine concentration was not a predictor of restenosis in either model.

DISCUSSION

This study did not find an association between the baseline homocysteine concentration and restenosis at six months after a first successful PCI without stenting. Analysis of restenosis took into account both the percentage diameter stenosis at follow up and late loss of the minimum lumen diameter. There was no association between baseline homocysteine concentrations and either measure of the restenosis process, irrespective of whether the homocysteine concentration was analysed as a dichotomous variable or as a continuous variable.

In non-stented lesions, both constrictive remodelling and neointimal thickening are mechanisms of restenosis, whereas in stented lesions, constrictive remodelling is minimised. Our findings in patients not undergoing stenting are consistent with those of Miner and colleagues (31% of whose patients received stents) but differ from those of Schnyder and associates (54% of whose patients received stents). In the Schnyder study, over a third of the patients had a history of PCI but the percentage of restenotic lesions was not reported, nor was the rate of stenting in this subgroup. Furthermore, 27.3% of patients in the Schnyder study had diabetes, whereas our study excluded patients with prior PCI or insulin dependent diabetes, and only 5% of our patients had non-insulin dependent diabetes. The different rates of previous PCI and diabetes may explain the difference in findings between the two studies.

In a recent meta-analysis of 30 studies (performed between 1966 and 1999) of patients without pre-existing cardiovascular disease, totalling 5073 coronary events and 1113 stroke events as end points, a 25% lower homocysteine concentration was associated with an 11% lower risk of coronary artery disease and a 19% lower risk of stroke. Among patients with known coronary disease, an increase in homocysteine concentrations has previously been found to be associated with a graded increase in mortality over 3–5 years. Homocysteine may cause vascular damage through various mechanisms, including endothelial damage. Homocysteine lowering with folate has been shown to reduce coronary endothelial dysfunction, which is a surrogate marker of poor outcomes even for patients with mild angiographic disease. Despite these rational bases for the benefit of homocysteine lowering, there are few published data that support or refute the hypothesis that homocysteine lowering reduces cardiovascular risk. The results of large scale, randomised, placebo controlled trials are awaited. There is also evidence to suggest that folate and other B vitamins may provide benefits through mechanisms other than homocysteine lowering.

The observation that homocysteine lowering may improve outcomes after PCI requires further evaluation. In the recently reported results of FACIT (folate after coronary intervention)
intervention trial), intervention trial, 636 patients who had undergone successful PCI were randomly assigned to receive either supplemental folate and vitamin B or a placebo for six months. At six months, those who had received folate and vitamin B were found to have lesions with a significantly smaller average minimum lumen diameter (the primary end point) than those in the placebo group (1.5 mm vs 1.74 mm, respectively), with a higher restenosis rate (35% vs 27%, p < 0.001) and a higher target vessel revascularisation rate (15.8% vs 10.6%, p < 0.05). Further research is needed to elucidate the association between homocysteine concentrations, pharmacological intervention with folate and vitamin B, and restenosis.

Conclusions
No association was found between the baseline homocysteine concentration and restenosis at six months in patients undergoing their first PCI without stenting.

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