INTERVENTIONAL CARDIOLOGY AND SURGERY

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

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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.

Homocysteine lowering treatment with folate, vitamin B12, and vitamin B6 given for six months after percutaneous coronary intervention (PCI) has been shown to reduce the incidence of restenosis at six months¹ and to reduce the need for target vessel revascularisation by 38% at one year.² The reduction in the six month incidence of restenosis was most pronounced in non-stented lesions—10.3% versus 41.9%.¹ Even in the current era, some patients do not undergo stenting for various reasons. There would therefore be considerable patient and economic benefits to be gained if the likelihood of restenosis could be reduced by this apparently safe treatment.

Previous studies of the association between baseline homocysteine concentrations and restenosis have reported conflicting results, with one study finding a positive association³ and the other finding no association.⁴ In reporting their results, neither of these studies distinguished between patients who underwent coronary stenting (54% in one study³ and 31% in the other⁴) and those who did not undergo stenting. The study that did find an association between baseline homocysteine concentrations and restenosis included some patients undergoing PCI on restenotic lesions.³ It therefore remains unclear whether the occurrence of restenosis after PCI without stenting on a de novo lesion is related to homocysteine concentrations at baseline. Thus, the current study was designed to examine the association between baseline homocysteine concentrations and restenosis after a first PCI without stenting.

METHODS

Patients

This single centre, prospective, observational study enrolled patients undergoing elective PCI at Green Lane Hospital in Auckland, New Zealand between 1990 and 1998. Baseline blood samples were collected and stored at -80°C for subsequent analyses to identify new markers and risk factors for restenosis. Patients whose PCI was successful were randomly assigned to receive low molecular weight heparin (dalteparin), simvastatin, or both in a 2×2 factorial design, and subsequently underwent follow up angiography at six months or earlier if restenosis was documented. The study enrolment criteria excluded premenopausal women and patients with insulin dependent diabetes, abnormal baseline liver function tests, or previous coronary artery bypass surgery. The study protocol was approved by the local ethics committee and all patients gave written informed consent before enrolment.

Successful PCI was defined as a reduction of the stenosis in the dilated segment to $< 50\%$ of the vessel diameter, with achievement of TIMI (thrombolysis in myocardial infarction) grade 3 flow⁵ and without major complications (in-hospital death, urgent bypass surgery, or urgent reintervention).

Abbreviations: FACIT, folate after coronary intervention trial; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

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).⁶ 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.⁶

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.⁷ 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 $\geq 50\%$ 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 $\geq 50\%$ 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)⁸ 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) $\mu\text{mol/l}$. 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

	Homocysteine concentration		p Value
	<13.11 $\mu\text{mol/l}$	$\geq 13.11 \mu\text{mol/l}$	
Number of patients	67	67	
Mean (SD) age (years)	57.5 (9.7)	60.8 (10.6)	0.07
Male sex	56 (83.6%)	53 (79.1%)	0.51
Any history of smoking	40 (59.7%)	47 (70.1%)	0.21
Current smoking	2 (3%)	5 (7.5%)	0.44
History of diabetes mellitus*	5 (7.5%)	2 (3%)	0.44
History of hypertension	30 (44.8%)	30 (44.8%)	1.0
History of myocardial infarction	26 (38.8%)	27 (40.3%)	0.86
Number of treated lesions per patient	1 (1–2)	1 (1–2)	0.77
Number of patients undergoing directional atherectomy	5 (7.5%)	6 (9.0%)	0.75
Number of patients undergoing rotational atherectomy	1 (1.5%)	1 (1.5%)	1.0
Laboratory findings			
Creatinine (mmol/l)	0.09 (0.08–0.1)	0.09 (0.09–0.11)	0.04
Fibrinogen (g/l)	3 (2.8–3.5)	2.9 (2.6–3.4)	0.2
Cholesterol (mmol/l)	5.93 (5.25–6.52)	5.96 (5.33–6.46)	0.99
HDL cholesterol (mmol/l)	1.01 (0.85–1.26)	1.08 (0.86–1.32)	0.33
LDL cholesterol (mmol/l)	4.2 (3.5–4.6)	3.8 (3.45–4.36)	0.12
Triglyceride (mmol/l)	1.57 (1.15–2.21)	1.39 (1.11–2.04)	0.3

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

Data are median (interquartile range) or number (%).

HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 Angiographic characteristics of lesions at baseline and follow up

	Homocysteine concentration		p Value
	<13.11 $\mu\text{mol/l}$	$\geq 13.11 \mu\text{mol/l}$	
Number of lesions	96	104	
Reference vessel size (mm)			
Before PCI	2.56 (2.28–2.89)	2.74 (2.31–3.27)	0.03
After PCI	2.63 (2.26–3.05)	2.74 (2.39–3.25)	0.11
At follow up	2.63 (2.33–2.93)	2.78 (2.46–3.24)	0.02
Minimum lumen diameter (mm)			
Before PCI	0.76 (0.48–1.04)	0.87 (0.48–1.20)	0.17
After PCI	1.76 (1.51–2.01)	1.82 (1.57–2.13)	0.5
At follow up	1.35 (0.94–1.75)	1.56 (1.14–1.95)	0.01
Percentage diameter stenosis (%)			
Before PCI	66.9 (60.9–82.1)	68.6 (58.7–82.3)	0.82
After PCI	32.2 (25.2–38.5)	33.2 (25.6–41.0)	0.33
At follow up	45.5 (35.4–62.2)	44.7 (32.5–58.8)	0.31
Late lumen loss (mm)	0.40 (–0.08–0.92)	0.31 (0.02–0.66)	0.24
Number of lesions with restenosis ($\geq 50\%$ diameter stenosis) at follow up	38 (39.6%)	40 (38.5%)	0.87

Data are median (interquartile range).
PCI, percutaneous coronary intervention.

(39.6% *v* 38.5%, $p = 0.87$) and no difference in the degree of late lumen loss (0.40 mm *v* 0.31 mm, $p = 0.24$).

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,⁹ whereas in stented lesions, constrictive remodelling is minimised. Our findings in patients not undergoing stenting are consistent with those of Miner and colleagues⁴ (31% of whose patients received stents) but differ from those of Schnyder and associates³ (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.¹⁰ 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.^{11–12}

Homocysteine may cause vascular damage through various mechanisms, including endothelial damage.¹³ Homocysteine lowering with folate has been shown to reduce coronary endothelial dysfunction,¹⁴ which is a surrogate marker of poor outcomes even for patients with mild angiographic disease.¹⁵ 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.¹⁶ There is also evidence to suggest that folate and other B vitamins may provide benefits through mechanisms other than homocysteine lowering.^{17–18}

The observation that homocysteine lowering may improve outcomes after PCI^{1–2} requires further evaluation. In the recently reported results of FACIT (folate after coronary

Figure 1 Scatter plot showing the association between baseline homocysteine concentrations and the percentage diameter stenosis at six month follow up.

intervention trial),¹⁹ 636 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 *v* 1.74 mm, respectively), with a higher restenosis rate (35% *v* 27%, *p* < 0.001) and a higher target vessel revascularisation rate (15.8% *v* 10.6%, *p* < 0.05).¹⁹ 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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