PLASMA HOMOCYSTEINE LEVELS AND MORTALITY IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

Background Elevated plasma homocysteine levels are a risk factor for coronary heart disease, but the prognostic value of homocysteine levels in patients with established coronary artery disease has not been defined.

Methods We prospectively investigated the relation between plasma total homocysteine levels and mortality among 587 patients with angiographically confirmed coronary artery disease. At the time of angiography in 1991 or 1992, risk factors for coronary disease, including homocysteine levels, were evaluated. The majority of the patients subsequently underwent coronary-artery bypass grafting (318 patients) or percutaneous transluminal coronary angioplasty (120 patients); the remaining 149 were treated medically.

Results After a median follow-up of 4.6 years, 64 patients (10.9 percent) had died. We found a strong, graded relation between plasma homocysteine levels and overall mortality. After four years, 3.8 percent of patients with homocysteine levels below 9 μmol per liter had died, as compared with 24.7 percent of those with homocysteine levels of 15 μmol per liter or higher. Homocysteine levels were only weakly related to the extent of coronary artery disease but were strongly related to the history with respect to myocardial infarction, the left ventricular ejection fraction, and the serum creatinine level. The relation of homocysteine levels to mortality remained strong after adjustment for these and other potential confounders. In an analysis in which the patients with homocysteine levels below 9 μmol per liter were used as the reference group, the mortality ratios were 1.9 for patients with homocysteine levels of 9.0 to 14.9 μmol per liter, 2.8 for those with levels of 15.0 to 19.9 μmol per liter, and 4.5 for those with levels of 20.0 μmol per liter or higher (P for trend = 0.02). When death due to cardiovascular disease (which occurred in 50 patients) was used as the end point in the analysis, the relation between homocysteine levels and mortality was slightly strengthened.

Conclusions Plasma total homocysteine levels are a strong predictor of mortality in patients with angiographically confirmed coronary artery disease.
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HOMOCYSTINURIA refers to a group of rare inborn errors of metabolism resulting in high levels of circulating homocysteine (>100 μmol per liter) and urinary homocysteine. A characteristic feature in patients with this condition is premature vascular disease. If homocystinuria is untreated, about 50 percent of patients have thromboembolic events, and mortality is about 20 percent before the age of 30 years.[1] Observations in patients with homocystinuria[2-4] led to the idea that homocysteine may be involved in the pathogenesis of arteriosclerosis[5] and prompted a large number of epidemiologic studies of the relation between moderately elevated homocysteine levels and vascular disease.

More than 75 clinical and epidemiologic studies have shown a relation between total homocysteine levels and coronary artery disease, peripheral artery disease, stroke, or venous thrombosis.[6-10] The strongest evidence stems from prospective, nested case–control studies[11-15]; all but one[11] found a relation between total homocysteine levels and the frequency of vascular disease.

The prevailing view of the pathogenesis of coronary heart disease involves a slow progression of coronary atherosclerosis, followed by unstable angina, myocardial infarction, or sudden death. The acute event is frequently due to rupture or erosion of an atherosclerotic plaque with associated thrombus formation.[16] There is increasing evidence that homocysteine may affect the coagulation system and the resistance of the endothelium to thrombosis[17] and that it may interfere with the vasodilator and antithrombotic functions of nitric oxide.[18] Notably, the vascular complications reported in patients with homocystinuria are related to thrombosis rather than to atherosclerosis,[1,19] and a relation between total homocysteine levels and the incidence of thrombotic events has recently been reported in patients with systemic lupus erythematosus.[20] Previous investigations of total homocysteine levels have not focused on acute events or mortality among patients with established coronary artery disease.

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In 1991 and 1992, we measured plasma total homocysteine in consecutive patients who underwent coronary angiography for suspected ischemic heart disease. Cross-sectional analysis showed that the total homocysteine level was weakly related to the extent of coronary artery disease but strongly related to the history with respect to myocardial infarction. We therefore assessed the relation between total homocysteine levels and mortality in the cohort five years after coronary angiography.

METHODS

Study Population

Between February 1991 and June 1992, we studied 802 consecutive adult patients of both sexes who underwent diagnostic coronary angiography at the Cardiology Department of Haukeland University Hospital in Bergen, Norway. For patients who were admitted for recatheterization during that period, only the first study was considered. In the present study, we excluded 139 patients who were examined for reasons other than suspected ischemic heart disease and 25 patients who had previously been treated with percutaneous transluminal coronary angioplasty (PTCA) or who had a prior myocardial infarction but a normal coronary angiogram. These exclusions did not affect the overall results. Among the remaining 638 patients, coronary artery disease was diagnosed in 587; the other 51 were classified as free of coronary artery disease and were therefore excluded from the study cohort.

Informed consent was obtained from all the patients. All completed a one-page questionnaire that provided information about any history of angina pectoris, hypertension, diabetes mellitus, and previous myocardial infarction. We also recorded any family history of premature coronary heart disease (documented coronary heart disease in at least one first-degree relative before the age of 55 years for men or 60 years for women), noncardiovascular diseases, use of medications, adherence to a lipid-lowering diet, and smoking habits.

The subjects were classified as current smokers, former smokers, or nonsmokers. Current smokers, including those who had stopped less than one month before angiography, were divided into three groups according to how many cigarettes they smoked per day: 1 to 9, 10 to 19, or ≥20. The information from the questionnaire was checked against the patients' medical records; in all cases with discrepancies or missing information, the patients were telephoned by the primary investigator for clarification.

Classification of Previous Episodes of Vascular Disease

Cerebrovascular disease was defined as a history of transient ischemic attacks (in 10 patients), unspecified stroke (7), thrombotic stroke (6) or hemorrhagic stroke (1) verified by computed tomography, carotid-artery stenosis verified by Doppler echocardiography (4) or surgically treated (3), or the finding of a strong bruit over a carotid artery (6). A diagnosis of peripheral atherosclerotic disease was given to patients with typical symptoms and clinical signs (63) and to those who had undergone surgery for this disorder (16). The diagnosis of previous myocardial infarction (in 337 patients) was based on the medical history and records or on the finding of typical sequelae of infarction on ventricular angiography.

Angiographic Evidence of Coronary Artery Disease

Angiograms were assessed by cardiologists who were unaware of the patients' risk-factor profiles, and coronary stenoses were confirmed in orthogonal views. Coronary artery disease was defined as a stenosis of at least 50 percent of the vessel diameter in any of the main coronary arteries (the left main coronary artery or the left anterior descending coronary artery with its major diagonal branches, the right coronary artery, or the circumflex coronary artery with its major marginal branch). Depending on dominance, the descending or posterior descending coronary artery was included as part of the right coronary artery or the circumflex coronary artery. The extent of coronary artery disease was scored as 0 (minimal or no disease), 1 (single-vessel disease), 2 (two-vessel disease), or 3 (three-vessel disease), according to the number of main vessels with stenosis. Stenosis of a left main-stem artery without stenosis of the right coronary artery was classified as two-vessel disease. The left ventricular ejection fraction was assessed by ventriculography.

Follow-up and Causes of Death

From the National Population Register, we obtained the dates of death for all patients who died between the time of angiography in 1991 or 1992 and April 30, 1996. Causes of death were obtained from death certificates kept at Statistics Norway. Fifty of the 64 deaths (78 percent) were classified as due to cardiovascular causes. These included acute myocardial infarction (26 deaths); coronary atherosclerosis (15 deaths; 10 of these deaths were also coded as sudden death from cardiac causes or as due to fatal arrhythmia, 2 as due to congestive heart failure, 1 to asphyxia, and 1 to rejection of a heart transplant; 1 was not further subclassified); cerebrovascular events (6); ruptured abdominal aneurysm (1); and aortic stenosis (1). One patient whose death was listed in the register only as sudden death was also included among the 50 cases classified as due to cardiovascular disease. The 14 deaths due to noncardiovascular causes were due to cancer (10), diabetes mellitus (1), an accident (1), renal failure (1), and ulcerative colitis (1).

Biochemical Measurements

After the patients had fasted overnight, samples of venous blood were drawn into tubes containing EDTA. Plasma was separated from blood cells by immediate centrifugation. Plasma total homocysteine, which includes the sum of protein-bound and free homocysteine, was measured by high-performance liquid chromatography with fluorescence detection.[21,22]

Serum total cholesterol and triglycerides were measured by a Technicon Chem 1 assay (Technicon Instruments, Tarrytown, N.Y.), and high-density lipoprotein cholesterol was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with heparin–manganese chloride. Low-density lipoprotein cholesterol was calculated by the formula of Friedewald et al.[23] for patients with serum triglyceride concentrations below 354 mg per deciliter (4.0 mmol per liter). Serum apolipoprotein A-I and apolipoprotein B were assayed by laser nephelometry with standards and antiserum from Behring Diagnostics (Behringwerke, Marburg, Germany). Serum Lp(a) lipoprotein was assayed with a radioimmunoassay (Pharmacia, Uppsala, Sweden). These seven indexes are referred to as lipid-related factors.

The serum folate concentration was assayed with use of the Quantaphase folate radioassay (Bio-Rad, Hercules, Calif.). Serum vitamin B_{12} was measured with a microparticle enzyme intrinsic-factor assay run on an IMx system (Abbott, Abbott Park, Ill.).

The coefficients of variation within and between days for the assays were 5 percent or less, except for the Lp(a) lipoprotein assay (3 to 6 percent) and the apolipoprotein B assay (6 to 10 percent).

Statistical Analysis

Because the distributions of values for total homocysteine, Lp(a) lipoprotein, triglycerides, vitamin B_{12}, folate, and creatinine were markedly skewed, these variables were logarithmically transformed, and geometric means are presented. In subgroups of patients, mean levels were compared by analysis of variance and adjusted means by analysis of covariance. Survival was studied with Kaplan–Meier methods and Cox regression. Adjusted survival curves were estimated in a model stratified according to the total homocysteine level with use of S-PLUS software.[24] The log-rank test and score tests were used throughout, and tests for linear trend were used to assess graded associations. Median follow-up

time was calculated by the reverse Kaplan–Meier method.[25] In all regression analyses, the covariates were represented by indicator variables to allow for nonlinear dose–response relations. The dose–response relation between the total homocysteine level and mortality was also estimated with generalized additive logistic regression,[26] as implemented in S-PLUS. This method generates a graphic representation of the relation between the total homocysteine level and mortality on a logit scale, after adjustment for other covariates.

The analyses were performed with BMDP[27] or S-PLUS[24] software. Two-sided P values below 0.05 were considered to indicate statistical significance.

RESULTS

Characteristics of the Patients

The median age of the 478 men and 109 women with coronary artery disease was 62 years; 15 percent were younger than 50 years, and an equal proportion were 70 years of age or older. A total of 128 patients had unstable angina, 337 had had a previous myocardial infarction, and 64 had previously undergone coronary-artery bypass grafting. Diabetes mellitus had been diagnosed in 44 patients, 159 were being treated for hypertension, 156 were smokers, and 284 were former smokers. Aspirin was used by 45 percent of the patients, a beta-blocker by 73 percent, a calcium-channel blocker by 44 percent, an angiotensin-converting–enzyme inhibitor by 9 percent, and a lipid-lowering drug by 6 percent.

Angiography revealed that 94 patients had single-vessel disease, 172 had two-vessel disease, and 321 had three-vessel disease. Seventy-four patients had a left ventricular ejection fraction below 50 percent. After the angiographic study in 1991 or 1992, 120 patients were referred for PTCA and 318 for coronary-artery bypass grafting; 72 patients had no indication for revascularization therapy, whereas 77 patients were not accepted for revascularization therapy because of diffuse peripheral coronary artery disease (65 patients), a high risk entailed by the procedure (8), or serious noncardiac disease (4).

Predictors of Plasma Total Homocysteine Levels

The mean total homocysteine level was 11.4 μmol per liter in men and 10.5 μmol per liter in women ($P=0.02$), and it increased by 1.3 μmol per liter, on average, with each additional 20 years of age ($P<0.001$). The mean level was 1.0 μmol per liter higher in patients with a previous myocardial infarction than in those without such a history ($P<0.001$), 1.2 μmol per liter higher in patients with a left ventricular ejection fraction below 50 percent than in those with higher values ($P=0.01$), 0.7 μmol per liter higher in patients receiving hypertensive therapy than in those not receiving such therapy ($P=0.03$), and 0.4 μmol per liter higher in patients with unstable angina than in those with stable symptoms ($P=0.28$). After adjustment for age and sex, the strongest predictors of the total homocysteine level were the serum folate level ($r=-0.36$, $P<0.001$), the serum creatinine level ($r=0.30$, $P<0.001$), the serum uric acid level ($r=0.17$, $P<0.001$), the serum vitamin B_{12} level ($r=-0.15$, $P<0.001$), and the left ventricular ejection fraction ($r=0.13$, $P<0.001$).

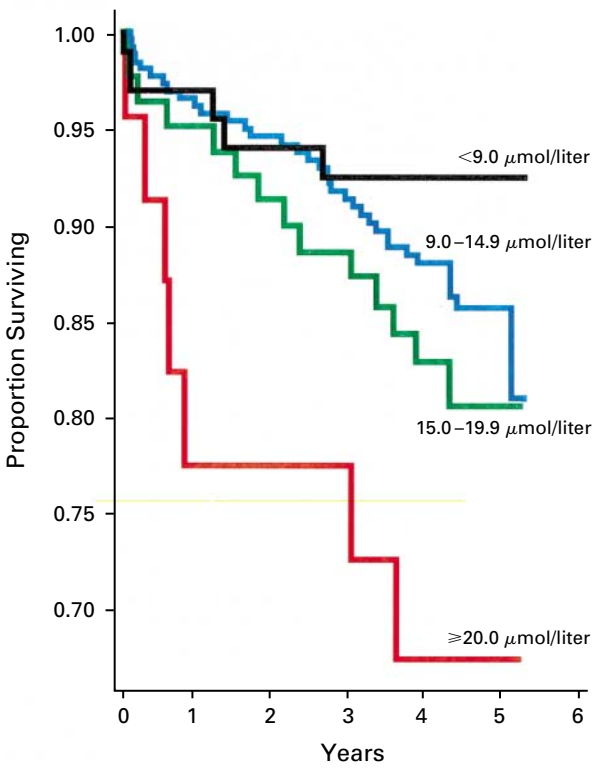

Figure 1. Estimated Survival among Patients with Coronary Artery Disease, According to Plasma Total Homocysteine Levels.
The figure shows estimated survival for 55-year-old male former smokers with three-vessel disease, a left ventricular ejection fraction of 55 percent, a creatinine level of 1.5 mg per deciliter (130 μmol per liter), and a total cholesterol level of 241 mg per deciliter (6.24 mmol per liter) at four different total homocysteine levels. Survival curves have been estimated in a stratified Cox regression analysis.

Plasma Total Homocysteine Levels and Overall Mortality

After a median follow-up of 4.6 years (range, 3.9 to 5.3), 53 men (11.1 percent) and 11 women (10.1 percent) had died. There was a strong, graded dose–response relation between the total homocysteine level and overall mortality. At four years, Kaplan–Meier estimates of mortality were 3.8 percent for patients with total homocysteine levels below 9 μmol per liter, 8.6 percent for those with levels of 9 to 14.9 μmol per liter, and 24.7 percent for those with levels of 15 μmol per liter or higher (P for trend <0.001). The clear, graded dose–response relation was also evident in the Cox-adjusted survival plot (Fig. 1).

Table 1 shows the results of the Cox regression

TABLE 1. MORTALITY RATIOS DURING A MEDIAN FOLLOW-UP OF 4.6 YEARS AMONG 587 PATIENTS WITH ANGIOGRAPHICALLY CONFIRMED CORONARY ARTERY DISEASE IN 1991 OR 1992, ACCORDING TO PROGNOSTIC VARIABLES.*

PROGNOSTIC VARIABLE	NO. OF SUBJECTS	NO. OF DEATHS (%)	WITH ADJUSTMENT FOR SEX AND AGE		WITH ADJUSTMENT FOR SEX, AGE, AND PROGNOSTIC VARIABLES IN THIS TABLE		WITH ADJUSTMENT FOR MULTIPLE RISK FACTORS†	
			MORTALITY RATIO (95% CI)	P FOR TREND	MORTALITY RATIO (95% CI)	P FOR TREND	MORTALITY RATIO (95% CI)	P FOR TREND
Total homocysteine (μmol/liter)	587			<0.001		0.004		0.02
<9.0‡	130	5 (3.8)	1.00		1.00		1.00	
9.0–14.9	372	37 (9.9)	2.35 (0.92–6.03)		1.84 (0.71–4.80)		1.92 (0.73–5.09)	
15.0–19.9	59	15 (25.4)	5.75 (2.05–16.1)		2.83 (0.92–8.72)		2.78 (0.86–8.98)	
≥20.0	26	7 (26.9)	7.04 (2.23–22.4)		5.52 (1.58–19.2)		4.51 (1.22–16.6)	
Left ventricular ejection fraction (%)	586			<0.001		<0.001		<0.001
≥70‡	205	10 (4.9)	1.00		1.00		1.00	
55–69	243	21 (8.6)	1.74 (0.82–3.71)		1.70 (0.78–3.72)		1.51 (0.69–3.33)	
40–54	108	24 (22.2)	5.01 (2.38–10.6)		4.77 (2.18–10.5)		4.68 (2.09–10.4)	
<40	30	9 (30.0)	6.86 (2.77–17.0)		5.49 (2.13–14.2)		4.69 (1.70–12.9)	
Creatinine (μmol/liter)§	578			<0.001		0.008		0.006
<80‡	79	7 (8.9)	1.00		1.00		1.00	
80–119	426	34 (8.0)	0.82 (0.36–1.88)		0.75 (0.32–1.76)		0.64 (0.27–1.54)	
120–149	46	12 (26.1)	2.70 (1.04–7.06)		1.71 (0.61–4.77)		1.81 (0.63–5.14)	
≥150	27	10 (37.0)	3.87 (1.43–10.5)		2.51 (0.83–7.60)		2.55 (0.82–7.92)	
Total cholesterol (mmol/liter)¶	574			0.50		0.57		0.57
<5.50‡	84	9 (10.7)	1.00		1.00		1.00	
5.50–6.99	228	23 (10.1)	0.94 (0.43–2.05)		0.72 (0.32–1.65)		0.84 (0.34–2.06)	
7.00–8.99	222	25 (11.3)	1.10 (0.51–2.38)		0.84 (0.37–1.90)		0.89 (0.37–2.15)	
≥9.00	40	6 (15.0)	1.44 (0.49–4.24)		1.51 (0.50–4.57)		1.59 (0.50–5.07)	
Extent of coronary artery disease	587			0.09		0.13		0.18
Single-vessel‡	94	5 (5.3)	1.00		1.00		1.00	
Two-vessel	172	17 (9.9)	1.67 (0.61–4.54)		1.76 (0.62–5.01)		1.69 (0.59–4.84)	
Three-vessel	321	42 (13.1)	2.11 (0.83–5.39)		2.10 (0.79–5.57)		1.99 (0.74–5.34)	

*For definitions of coronary artery disease, see the Methods section. Total homocysteine was measured in plasma, and total cholesterol and creatinine in serum. CI denotes confidence interval.

†The mortality ratios have been adjusted for sex, age, all the prognostic variables in this table, treatment for hypertension (yes or no), history of diabetes mellitus (yes or no), smoking status (in four groups), platelet count (<300,000 or ≥300,000 per cubic millimeter), and use of aspirin (yes or no).

‡The patients in this category served as the reference group.

§To convert values for creatinine to milligrams per deciliter, divide by 88.4.

¶To convert values for cholesterol to milligrams per deciliter, divide by 0.02586.

analyses. After adjustment for sex and age, the strongest predictors of mortality were the left ventricular ejection fraction, the total homocysteine level, and the creatinine level. The inclusion of all these factors in the same model weakened the predictive power of each, but they all remained strong and significant. The total homocysteine level and the creatinine level each weakened the effect of the other on the prediction of mortality, whereas they had less effect on the relation between the left ventricular ejection fraction and mortality. The left ventricular ejection fraction attenuated the relation of homocysteine levels to mortality more than it did the relation of creatinine levels to mortality.

When other potential confounders were included in the final multivariate model (Table 1), the homocysteine–mortality relation was somewhat further attenuated, in particular by the use of aspirin and to a lesser degree by hypertensive therapy. Additional adjustment for prognostic variables such as presence or absence of treatment with PTCA or coronary-artery bypass grafting, use of medication, presence or absence of unstable angina, history with respect to myocardial infarction, and the uric acid level had minimal effect, and these variables were not included in the final model.

The association between homocysteine levels and mortality was also studied in various subgroups. In these analyses, we compared mortality among patients with total homocysteine levels of at least 15 μmol per liter to that among patients with lower levels. Higher total homocysteine levels were associated with a significant increase in mortality among both sexes, in nonsmokers, in both older people (≥65 years) and younger ones (<65 years), in subjects with and those without a previous myocardial infarction, in those with a reduced ejection fraction (<50 percent) and those with a normal ejection fraction, in those with normal creatinine levels (<1.4 mg per deciliter [<120 μmol per liter]), and in those referred for subsequent treatment with coronary-artery bypass grafting and those treated conservatively. A higher total homocysteine level was also associated with increased mortality among current

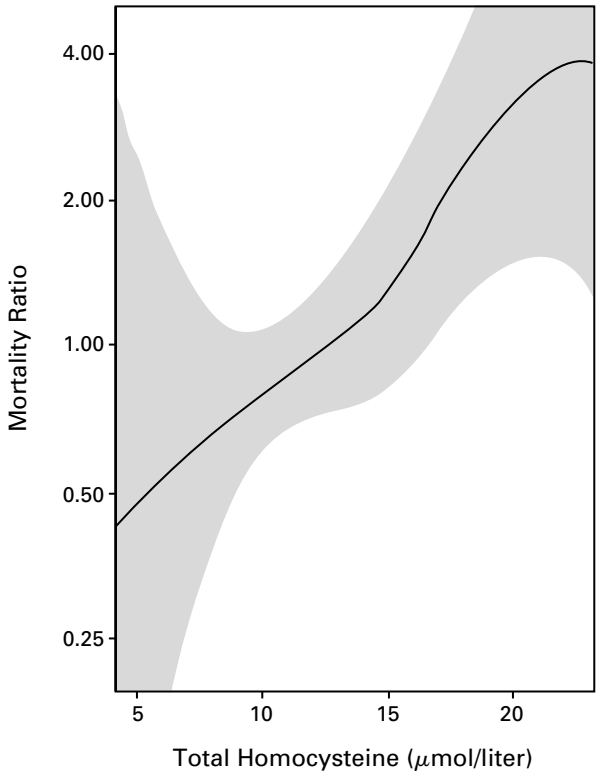

Figure 2. Dose–Response Relation between Plasma Total Homocysteine Levels and Mortality.

The values have been adjusted for age, sex, left ventricular ejection fraction, creatinine level, total cholesterol level, and the extent of coronary artery disease with the use of generalized additive logistic regression. The relative mortality was approximated by the odds ratio. The solid line indicates the estimated dose–response curve, and the shaded area the 95 percent confidence interval.

smokers and among patients with elevated creatinine levels (≥1.4 mg per deciliter), but these relations were not statistically significant.

When we used generalized additive logistic regression to estimate the adjusted dose–response relation between total homocysteine levels and mortality (Fig. 2), we found that the relation was nearly linear from a total homocysteine level below 5 μmol per liter to one above 20 μmol per liter, but with a steeper slope above 15 μmol per liter. On the basis of this dose–response relation, we estimated that the mortality ratio for an increase of 5 μmol per liter in the total homocysteine level was 1.6 between 10 and 15 μmol per liter and 2.5 between 15 and 20 μmol per liter.

The lipid-related factors showed either no relation or a much weaker relation to mortality than the total homocysteine level. Among these measurements, apolipoprotein A-I showed the strongest relation to mortality, but with borderline significance. We found only a weak, nonsignificant inverse relation between the serum folate level and the risk of death; this association disappeared after we adjusted for the plasma total homocysteine level. The serum concentration of vitamin B_{12} was not related to mortality, and adjustment for the serum folate or vitamin B_{12} level had no influence on the relation between total homocysteine and mortality.

Plasma Total Homocysteine Levels and Mortality from Cardiovascular Causes

When the end point analyzed was the deaths classified as due to cardiovascular causes (50 deaths, or 78 percent of the total), the relation between homocysteine and mortality was slightly strengthened. With a total homocysteine level below 9 μmol per liter as the reference category and with adjustment for age and sex, the mortality ratio was 3.3 for patients with total homocysteine levels of 9.0 to 14.9 μmol per liter, 6.3 for those with levels of 15.0 to 19.9 μmol per liter, and 9.9 for those with levels of 20.0 μmol per liter or higher (P for trend <0.001). With further adjustment for the left ventricular ejection fraction, creatinine level, total cholesterol level, and the number of coronary arteries with stenosis (as in the second model in Table 1), the corresponding mortality ratios were 2.3, 2.5, and 7.8 (P for trend = 0.01).

Predictors of Coronary Artery Disease and Previous Myocardial Infarction

We also studied predictors of coronary artery disease measured at base line in 1991 or 1992. In these analyses, we included the 51 patients without clinically significant coronary-artery stenosis. The extent of coronary artery disease (graded as no coronary artery disease or single-vessel, two-vessel, or three-vessel disease) was only weakly related to the total homocysteine level but was strongly associated with the lipid-related factors. Lp(a) lipoprotein was the strongest predictor in both sexes (Table 2). In contrast, having had a previous myocardial infarction was not associated with the lipid-related blood values but was strongly associated with total homocysteine (P< 0.001). Serum folate and vitamin B_{12} were related neither to the extent of coronary artery disease nor to the history with respect to myocardial infarction.

DISCUSSION

We found a strong, graded association between the plasma total homocysteine level and overall mortality in patients with angiographically confirmed coronary artery disease. The relation between the total homocysteine level and mortality was already apparent within a few months of the base-line coronary angiogram. In line with previous prospective studies of patients with coronary heart disease,[28] close to 80 percent of all deaths in our study were classified as due to cardiovascular disease, on the ba-

TABLE 2. BIOCHEMICAL MEASUREMENTS ACCORDING TO THE EXTENT OF CORONARY ARTERY DISEASE AMONG 142 WOMEN AND 496 MEN WHO UNDERWENT CARDIAC CATHETERIZATION FOR SUSPECTED ISCHEMIC HEART DISEASE IN 1991 OR 1992.*

VARIABLE	NO. OF MAIN CORONARY ARTERIES WITH CLINICALLY SIGNIFICANT STENOSIS				P VALUE FOR LINEAR TREND
	0	1	2	3	
No. of patients	51	94	172	321	
Total homocysteine (μmol/liter)					0.05
Mean	10.4	10.9	10.9	11.4	
95% CI	9.53–11.4	10.2–11.6	10.4–11.4	11.0–11.8	
Total cholesterol (mmol/liter)					<0.001
Mean	6.32	6.69	6.76	7.01	
95% CI	5.92–6.72	6.40–6.97	6.55–6.95	6.86–7.16	
High-density lipoprotein cholesterol (mmol/liter)					0.04
Mean	1.20	1.03	1.04	1.04	
95% CI	1.10–1.29	0.96–1.10	0.99–1.09	1.00–1.07	
Lp(a) lipoprotein (U/liter)					<0.001
Mean	115	206	303	305	
95% CI	80.0–164	160–266	251–364	266–350	

*The levels have been adjusted for differences in sex and age between the groups. Log-transformed levels of homocysteine and Lp(a) lipoprotein were used in the analysis. Total homocysteine was measured in plasma, and cholesterol and Lp(a) lipoprotein in serum. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. CI denotes confidence interval.

sis of the information on the death certificate. The number of events was too small to permit detailed, cause-specific analyses, but the relation between total homocysteine and mortality was strengthened when death due to cardiovascular causes was used as the end point.

The dose–response relation was observed within the range of total homocysteine values from about 5 μmol per liter to more than 20 μmol per liter. Although the relation with mortality was strongest for total homocysteine levels above 15 μmol per liter, the association was also substantial for lower levels. Notably, we calculated an adjusted mortality ratio of 1.6 for patients with total homocysteine levels of 15 μmol per liter as compared with those with values of 10 μmol per liter. A meta-analysis of data from previous observational studies of patients with coronary artery disease demonstrated a similar increase in risk for each increase of 5 μmol per liter in the total homocysteine level.[7] A graded relation between total homocysteine levels and cardiovascular events has been demonstrated in some, but not all, previous studies.[11-15,29]

In comparison with the strong relation between total homocysteine levels and either mortality or previous myocardial infarction, total homocysteine levels were associated only weakly with the number of coronary arteries with stenosis. In contrast, the lipid-related factors were strongly related to the extent of coronary artery disease, but only weakly to mortality or previous infarction. These observations suggest that elevated total homocysteine values are strongly related to the risk of acute events leading to death. However, risk factors for cardiovascular disease are not exclusively atherogenic or thrombogenic,[30,31] and previous studies have shown a direct relation between total homocysteine levels and the number of coronary vessels with stenosis[32-35] or carotid-artery stenosis.[36,37]

A critical question is whether the relation of homocysteine and mortality is due to confounding by an association of total homocysteine levels with other strong predictors of mortality, such as the serum creatinine level, left ventricular ejection fraction, or history with respect to myocardial infarction. Adjustment for these factors weakened the predictive power of total homocysteine levels somewhat. However, impaired renal function increases total homocysteine levels,[38] and high total homocysteine levels are a risk factor for myocardial infarction,[12,13,29] which, in turn, is the primary determinant of the left ventricular ejection fraction in patients with coronary disease. Thus, if high total homocysteine levels and these strong prognostic factors share a common causal pathway, adjustment for any of these factors may cause the true relation between the total homocysteine level and mortality to be underestimated. In fact, total homocysteine has been related to mortality due to cardiovascular disease and to total mortality in patients with end-stage renal disease.[38]

To evaluate further the possibility of confounding, patients were divided into subgroups according to the presence or absence of the other strong predictors of a higher mortality rate — elevated serum creatinine levels, previous myocardial infarction, and a reduced left ventricular ejection fraction. The rela-

tion of total homocysteine to mortality was strong in all these subgroups, further suggesting that the homocysteine–mortality relation is not explained completely by these factors.

Adjustment for several other risk factors for cardiovascular disease that have previously been reported to be related to total homocysteine levels[33,39,40] — including smoking status, total cholesterol levels, other lipid-related factors, and the presence or absence of hypertension or diabetes mellitus — only weakly attenuated the strong relation of homocysteine and mortality.

In conclusion, we found that the plasma total homocysteine level was the strongest modifiable predictor of overall mortality and mortality due to cardiovascular causes among patients with angiographically confirmed coronary artery disease. This prospective study does not prove a causal relation between total homocysteine and mortality, but our results should serve as an additional strong incentive to the initiation of intervention trials with homocysteine-lowering therapy.

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