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How Raised Homocysteine is Correlated with CAD

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Abstract

Atherosclerosis is a process in which blood, fats such as cholesterol and other substances build up on artery walls. Eventually, deposits called plaques may form. The deposits may narrow or block arteries. These plaques can also rupture, causing a blood clot. 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 CAD. If homocystinuria is untreated, about 50 percent of patients have thromboembolic events, and mortality is about 20 percent before the age of 30 years. After the homocysteine theory was presented in 1969, attention has been directed toward the serum homocysteine level as a coronary artery disease risk factor. Large research programs have been focused on the identification of new risk factors to prevent CAD, with special attention to homocysteine (Hcy), due to the known associated increased thrombogenicity, oxidative stress status and endothelial dysfunction. However, controversy still exists on the association between Hcy and CAD. Therefore, aim of the current study was to investigate the association of Hcy with the prevalence and extent of CAD in a group of patients undergoing coronary artery treatment.

Keywords: Atherosclerosis, Homocystinuria, CAD.

Introduction

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. The strongest evidence stems from prospective, nested case–control studies[11-15]; all but onefound 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.

Despite the impressive epidemiologic evidence that mild hyperhomocysteinemia is an independent risk factor for atherosclerotic and atherothrombotic vascular disease, we have become increasingly doubtful as to whether modest elevations of plasma homocysteine may be causally involved in the pathogenesis of atherosclerosis. As will be outlined in this review, there are now substantial indications that a modest elevation of plasma homocysteine is usually benign and is a consequence rather than a cause of atherosclerosis.CAD 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.Both markedly and mildly elevated circulating homocysteine concentrations are associated with increased risk of vascular occlusion. Here we review possible mechanisms that mediate these effects. Inborn errors of homocysteine metabolism result in markedly elevated plasma homocysteine (200–300 μmol/L) and thromboembolic (mainly venous) disease: treatment to lower but not to normalize these concentrations prevents vascular events. Mild homocysteine elevation (>15 μmol/L) occurs in ≈20–30% of patients with atherosclerotic disease. Usually, this is easily normalized with oral folate and ongoing trials are assessing the effect of folate treatment on outcomes. Although there is evidence of endothelial dysfunction with both markedly and mildly elevated homocysteine concentrations, the elevated homocysteine concentration in atherosclerotic patients is also associated with most standard vascular risk factors, and importantly, with early decline in renal function, which is common in atherosclerosis. Decline in renal function alone causes elevated plasma homocysteine (and cysteine). These observations suggest that mild hyperhomocysteinemia could often be an effect rather than a cause of atherosclerotic disease. When plasma folate is below median population concentrations, it appears not to increase cardiovascular risk. Indeed, there is recent evidence suggesting an acute antioxidant effect of folic acid independent of its effect on homocysteine concentrations. This antioxidant mechanism may oppose an oxidant effect of homocysteine and be relevant to treatment of patients with vascular disease, especially those with chronic renal insufficiency. Such patients have moderately elevated plasma homocysteine and greatly increased cardiovascular risk that is largely unexplained.

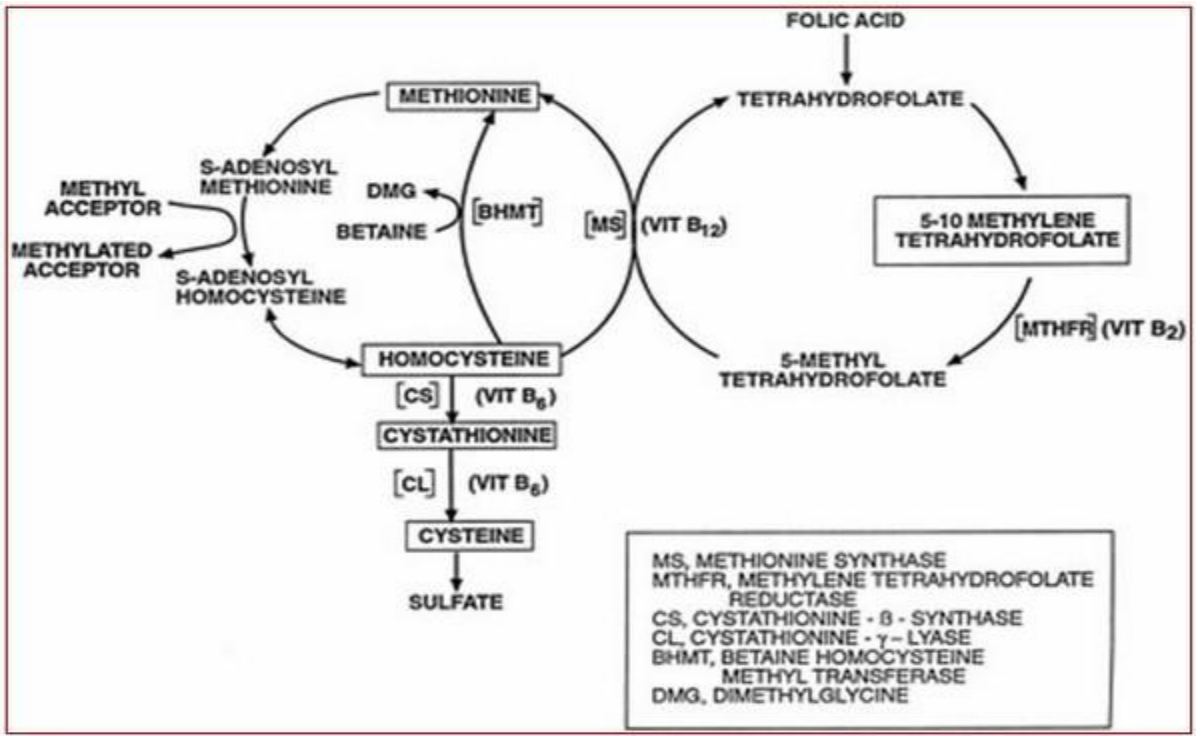
Review

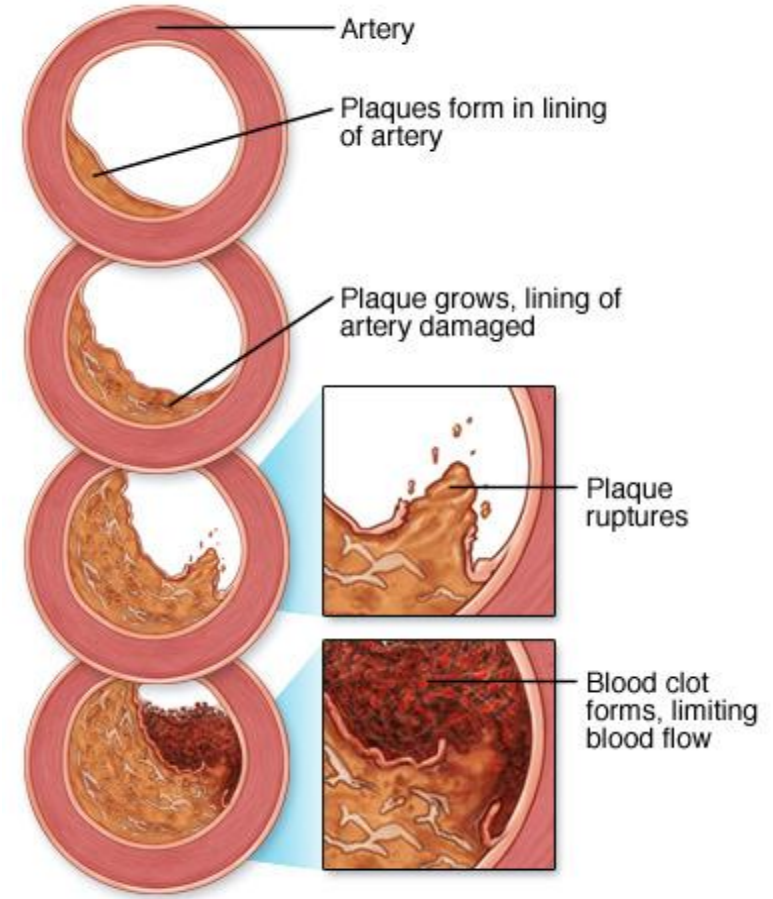
First, it must be emphasized that the vascular disease in homocystinuria due to cystathionine β-

synthase (CBS) deficiency, methylenetetrahydrofolate reductase (MTHFR) deficiency, or inborn errors in cobalamin metabolism bears little resemblance to the atherosclerotic and atherothrombotic vascular disease seen in the adult general population. Atherosclerosis is characterized by a thickening of the arterial wall due to smooth muscle cell proliferation, lipid deposits, and fibrosis[1]. Rupture of the lipid-containing atherosclerotic plaques results in thrombosis (atherothrombosis) and leads to myocardial infarction and stroke [1.] In contrast, homocystinuria seems to be associated with a primary thrombotic disorder that affects veins more often than arteries .Stroke in homocystinuric patients is frequently due to intracranial venous thrombosis, which is a rare cause of stroke in the general population Multifocal old and fresh mural thromboses in different stages of organization are found postmortem [7, 8,11–15.] The changes in the arterial wall are patchy, lack lipid deposits in young patients and have an appearance that may represent the arterial wall repair response to repeated mural thrombosis [8, 11, 15–17.] Therefore, homocystinuria seems to be associated with a factor or factors that primarily cause venous and arterial thrombosis. Whether the same factor (that in homocystinuria does not seem to cause the characteristic changes of primary atherosclerosis) would be atherogenic in much lower concentrations in the general population remains uncertain.In 1969, McCully put forward the homocysteine theory of arteriosclerosis. This was based on the findings of arterial changes in an infant with homocystinuria due to CBS deficiency similar to those in an infant with homocystinuria due to a remethylation defect, one an inborn error involving the transsulfuration pathway (CBS deficiency) and the other an inborn error affecting the remethylation of homocysteine to methionine. The changes in the arterial wall lacked lipid deposits and were classified as arteriosclerosis (not atherosclerosis) [(18)]. Because the 2 different disorders shared markedly elevated homocysteine concentrations as a metabolic consequence of the inborn errors but with widely different concentrations of methionine, homocysteine or a derivative of homocysteine was considered to be the common factor leading to arterial damage [18]. In homocystinuria, there is evidence that the very high homocysteine concentrations are thrombogenic. However, in both CBS deficiency and inborn errors of homocysteine remethylation, the precursor of homocysteine, *S*-adenosylhomocysteine (SAH), will most likely also accumulate. SAH is the demethylated product of numerous *S*-adenosylmethionine (SAM)-dependent transmethylation reactions and a potent feedback inhibitor of the same reactions .It is possible that SAH accumulation leads to hypomethylation of some essential components the tissue-specific sensitivity of which may explain both similarities (thrombosis) and dissimilarities (ectopia lentis, skeletal deformities, and osteoporosis) between the 2 forms of homocystinuria (ie, that due to CBS deficiency or that due remethylation defects). In homocystinuria, therapy that lowers plasma homocysteine concentration also reduces SAH and restores impaired transmethylation reactions. In patients with CBS deficiency, this has been shown to effectively reduce the risk of thrombotic events, although plasma homocysteine concentrations frequently remain well above normal values .This suggests that the threshold of homocysteine concentration for thrombogenesis is clearly higher than the modestly elevated concentrations of homocysteine found in patients with cardiovascular disease.The important core question is: does a modest elevation of plasma homocysteine concentration (eg, from 15 to 20 μmol/L) contribute to the pathogenesis of atherosclerotic vascular disease, or is it merely a marker for increased risk? Several studies established that the association between plasma homocysteine concentration and the risk of cardiovascular disease or severity of atherosclerosis is graded throughout the normal range from low to mildly elevated concentrations .If this graded relation reflects a pathogenic role of homocysteine in the development of cardiovascular disease, one could assume that any cause of longstanding, mild hyperhomocysteinemia would also be associated with increased cardiovascular risk. Well-known, common causes of hyperhomocysteinemia are low serum or red cell folate concentrations [25, 26], vitamin B-12 deficiency ,decline in renal function [(28, 29)], and the *TT* genotype for the common C677T/MTHFR polymorphism in conjunction with low folate status [(30)]. Moreover,

heterozygosity for CBS deficiency is associated with normal or mild elevation of basal homocysteine concentration and frequently with an abnormal response to methionine loading with increased postload hyperhomocysteinemia .The clinical symptoms of untreated vitamin B-12 and folate deficiency are well-known. However, whereas hyperhomocysteinemia in these conditions may be moderate (>30 μmol/L) or even severe (>100 μmol/L) [26], vascular disease is not a known complication of folate or vitamin B-12 deficiency. Folate status (serum or red cell folate or folate intake) is considered to be one of the most important determinants of plasma homocysteine concentration, and folic acid supplementation decreases plasma homocysteine concentration in almost all subjects.

There were a few longitudinal studies in which homocysteine was not measured that assessed cardiovascular outcome related to folate status, with varying results .In addition, there were many studies in which both plasma homocysteine and folate status were assessed. Only one of these studies showed that a low folate status together with elevated homocysteine may constitute a risk factor for cardiovascular disease .Paradoxically, this small retrospective study and another prospective study showed increased incidence or risk of mortality and coronary heart disease in subjects with elevated serum vitamin B-12 concentrations A few other studies indicated that a poor folate status itself may be associated with increased risk but that this risk is only marginally or only partially mediated by homocysteine. Although the bulk of studies confirmed the strong negative relation between folate status and plasma homocysteine concentration on one hand and the relation between increased homocysteine concentrations and cardiovascular disease on the other, the results of these studies do not suggest that the former relation is coupled to the latter. In other words, elevation of plasma homocysteine concentrations due to poor folate status seems to be benign with regard to risk or severity of cardiovascular disease It follows from this that if ongoing intervention studies were to show that folic acid therapy reduces cardiovascular risk, an additional question would be whether the risk reduction was due to lowering of homocysteine or to some other effect of the vitamin. Recently, a prospective study in women showed that an elevated plasma homocysteine concentration predicts myocardial infarction and stroke. Self-reported multivitamin supplement use at baseline was associated with markedly lower concentrations of homocysteine but not with a lower risk of myocardial infarction or stroke during follow-up compared with nonusers.





Materials and Methods

Between February 20014 to Dec. 2015, we studied 150 consecutive adult patients of both sexes who underwent diagnostic cardiac biochemistry for diagnosis. Age group comprised both males and females of >60 years of age. 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. Biochemical Measurements After an overnight fast 10 cc venous blood was drawn just before the coronary angiography. Plasma was immediately separated and stored at –20°C until measurement of total homocysteine. Homocysteine was measured with a chemiluminiscence. All the samples were processed by a single technician on 2 consecutive days to minimize the interobserver error. The upper limit of normal provided by the company was 15 µmol/L.

Observations

Homocysteinuria, an autosomal recessive condition, is usually caused by a deficiency of the enzyme cystathionine β-synthase, which is required for the conversion of homocysteine (tHcy), derived from dietary methionine to cystathionine.[1,2] Homozygotes with homocysteinuria have high levels of circulating tHcy (>100 µmol/l), and may have ocular, skeletal and neurological complications.[1,2] Patients with this condition are at high risk for premature arteriosclerotic vascular disease and venous thrombosis.[1,2] If homocysteinuria remains untreated, about 50% of patients may experience thromboembolic events and mortality could reach 20% before the age of 30 years.[2] Observations in patients with homocysteinuria led to the idea that

tHcy may be involved in the pathogenesis of arteriosclerosis. This concept prompted a large number of epidemiological studies that assessed the relation between moderately elevated tHcy levels and coronary or peripheral arterial disease. Observations in clinical and epidemiological studies suggested that elevated tHcy is a risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism.[3] A meta-analysis showed that tHcy in increments of 5 µmol/l corresponded to a greater risk of coronary artery disease (CAD) in men and women.[4] In contrast, a more recent meta-analysis concluded that tHcy may not be as harmful for the heart as previously thought.[5] The aim of the present study was to evaluate the relation between plasma tHcy levels and CAD. The important core question is: does a modest elevation of plasma homocysteine concentration (eg, from 15 to 20 µmol/L) contribute to the pathogenesis of atherosclerotic vascular disease, or is it merely a marker for increased risk? Several studies established that the association between plasma homocysteine concentration and the risk of cardiovascular disease or severity of atherosclerosis is graded throughout the normal range from low to mildly elevated concentrations .If this graded relation reflects a pathogenic role of homocysteine in the development of cardiovascular disease, one could assume that any cause of longstanding, mild hyperhomocysteinemia would also be associated with increased cardiovascular risk. Well-known, common causes of hyperhomocysteinemia are low serum or red cell folate concentrations vitamin B-12 deficiency decline in renal function and the *TT* genotype for the common C677T/MTHFR polymorphism in conjunction with low folate status .Moreover, heterozygosity for CBS deficiency is associated with normal or mild elevation of basal homocysteine concentration and frequently with an abnormal response to methionine loading with increased postload hyperhomocysteinemia .The clinical symptoms of untreated vitamin B-12 and folate deficiency are well-known. However, whereas hyperhomocysteinemia in these conditions may be moderate (>30 µmol/L) or even severe (>100 µmol/L) (26), vascular disease is not a known complication of folate or vitamin B-12 deficiency. Folate status (serum or red cell folate or folate intake) is considered to be one of the most important determinants of plasma homocysteine concentration, and folic acid supplementation decreases plasma homocysteine concentration in almost all subjects .There were a few longitudinal studies in which homocysteine was not measured that assessed cardiovascular outcome related to folate status, with varying results [39–44]. In addition, there were many studies in which both plasma homocysteine and folate status were assessed. Only one of these studies showed that a low folate status together with elevated homocysteine may constitute a risk factor for cardiovascular disease .Paradoxically, this small retrospective study and another prospective study showed increased incidence or risk of mortality and coronary heart disease in subjects with elevated serum vitamin B-12 concentrations .A few other studies indicated that a poor folate status itself may be associated with increased risk but that this risk is only marginally or only partially mediated by homocysteine. Although the bulk of studies confirmed the strong negative relation between folate status and plasma homocysteine concentration on one hand and the relation between increased homocysteine concentrations and cardiovascular disease on the other, the results of these studies do not suggest that the former relation is coupled to the latter. In other words, elevation of plasma homocysteine concentrations due to poor folate status seems to be benign with regard to risk or severity of cardiovascular disease It follows from this that if ongoing intervention studies were to show that folic acid therapy reduces cardiovascular risk, an additional question would be whether the risk reduction was due to lowering of homocysteine or to some other effect of the vitamin. Recently, a prospective study in women showed that an elevated plasma homocysteine concentration predicts myocardial infarction and stroke. Self-reported multivitamin supplement use at baseline was associated with markedly lower concentrations of homocysteine but not with a lower risk of myocardial infarction or stroke during follow-up compared with nonusers.

Results

The mean total homocysteine level was 11.4 µmol per liter in men and 10.5 µmol per liter in women

Table-1 Showing various risk factors

Risk factor	Case group	Control group	P value
Age (year ± SD)	41.01 ± 3.13	39.1 ± 4.94	0.05
Male gender, n (%)	86(88.7)	93(72.6)	0.01
Family history, n (%)	31(31.9)	34(26.5)	0.75
Hypertension, n (%)	24(24.7)	21(16.4)	0.18
Diabetes mellitus, n (%)	13(13.4)	3(0.02)	0.02
Smoking, n (%)	57(58.7)	57(44.5)	0.36
Hyperlipidemia, n (%)	39(40.2)	25(19.5)	0.01
Laboratory data			
Triglyceride (mg/dl)	194.68 ± 8.5	177.21 ± 12.4	0.25
Cholesterol (mg/dl)	209.8 ± 4.7	189.34 ± 4.0	0.77
LDL (mg/dl)	132.1 ± 4.1	113.33 ± 2.9	0.16
HDL (mg/dl)	37.7 ± 0.83	41.25 ± 0.92	0.02
Homocysteine (µmol/L)	1.7 ± 19.3	0.9 ± 13.9	0.00

(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).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 increased mortality among current smokers and among patients with elevated creatinine levels (>1.4 mg per deciliter), but these relations were not statistically significant..We also studied predictors of coronary artery disease measured at 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 .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. When other potential confounders were included in the final multivariate model the homocysteine–mortality relation was somewhat further attenuated, in particular by the use of aspirin and to a lesser degree by hypertensive therapy. 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), A higher total homocysteine level was also associated with 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 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.). 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.

Table-2 Highlights role of increased Homocysteine levels

Risk factors	Odds ratio (OR)	Confidence interval 95% (CI)	P value
Male gender	3.05	1.28 – 7.27	0.012
Diabetes mellitus	4.91	1.18 – 20.4	0.029
Hyperlipidemia	2.29	1.16 – 4.53	0.017
HDL	2.05	1.09 – 3.84	0.026
Hyperhomocysteinemia	2.42	1.28 – 4.56	0.007

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, close to 80 percent of all deaths in our study were classified as due to cardiovascular disease, on the basis 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.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, and previous studies have shown a direct relation between total homocysteine levels and the number of coronary vessels with stenosis or carotid-artery stenosis. Total homocysteine has been related to mortality due to cardiovascular disease and to total mortality in patients with end-stage renal disease. Adjustment for several other risk factors for cardiovascular disease that have previously been reported to be related to total homocysteine levels— 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.

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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