Clinical relevance of homocysteine levels in patients receiving coronary stenting for unstable angina

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Coronary stent; Restenosis; Unstable angina.

Background. **We prospectively investigated whether plasma homocysteine (HCY) concentrations are related to target lesion revascularization (TLR) rates in patients with unstable angina undergoing stenting.**

Methods. **We enrolled 196 consecutive patients with at least one successful coronary stent implantation for unstable angina.**

Results. **The mean vessel diameter was 3.1 ± 0.5 mm. At follow-up (17.8 ± 7.5 months), patients with higher HCY levels (> 17 μmol/l, 4th quartile) had similar TLR rates to the rest of the sample (11.1 vs 13.2%, p = 0.90). On the other hand, high HCY levels did seem to be associated with higher total (13.3 vs 0.7%, p = 0.001) and cardiac (6.7 vs 0%, p = 0.01) mortality rates. At multivariate analysis, only target vessel diameter independently predicted TLR, while both HCY levels and target vessel size predicted late total mortality.**

Conclusions. **At least in patients with a mean vessel diameter > 3 mm, HCY levels cannot be taken as a prognostic indicator of in-stent restenosis for patients with unstable angina. However, in spite of successful percutaneous revascularization, HCY values do seem to strongly influence late mortality.**

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Introduction

Although stents reduce the incidence of angiographic and clinical restenosis following percutaneous coronary interventions, they do not abolish restenosis altogether[1]. Epidemiological and clinical studies have identified moderately raised concentrations of plasma homocysteine (HCY) as an important and potentially modifiable risk factor for coronary artery disease[2-4]. In particular, raised concentrations of this non-essential amino acid produced by the demethylation of methionine appear to be a strong predictor of late adverse cardiac events in patients admitted with acute coronary events[5]. As seen in homocystinuria, elevated HCY levels increase thrombogenicity[6] and induce vascular damage[7]. Recently, plasma HCY concentrations were correlated with restenosis after percutaneous transluminal coronary angioplasty (PTCA)[8,9]. Unstable angina, as previously reported, is a well-known independent predictor of restenosis after coronary artery stenting[10]. However, little is known about the relevance of HCY levels for the prediction of in-stent restenosis in patients, who owing to their unstable clinical conditions, are at increased risk of restenosis and thrombotic complications. We therefore prospectively investigated whether plasma HCY concentrations are related to the rate of clinical in-stent restenosis (target lesion revascularization-TLR) in this specific subset of patients.

Methods

Study design. Inclusion in the study was restricted to patients presenting in our institution between October 1998 and April 2001 with unstable angina (Braunwald class IIB-IIIB) who received successful stent implantation (< 30% residual stenosis with TIMI 3 flow) of at least one native coronary stenosis ≥ 50%; stent implantation was performed in all dilated lesions. Exclusion criteria were: 1) the presence of factors known to influence HCY levels, such as acute myocardial infarction (ST-segment elevation or non-ST-segment elevation and serum creatine phosphokinase-CPK > 400 IU/l [reference upper limit 200

IU/l] or CPK-MB > 4 U/l) during the 30 days before the procedure, renal impairment (creatinine level > 1.5 mg/dl); 2) presence of malignancies or other illnesses believed to limit life expectancy; 3) concomitant therapy with methotrexate, carbamazepin, phenytoin; 4) PTCA on venous/arterial bypass; 5) presence of occlusive or restenotic lesions. Regarding follow-up, a clinical visit and a stress test was always performed at 12-18 months after PTCA, or on recurrence of angina. Coronary angiography was then performed only if symptoms recurred or if a silent ischemia was documented at stress testing. Written informed consent was obtained from all patients. The local ethics committee approved the study, which was performed in accordance with the Declaration of Helsinki.

The primary endpoint was to assess the existence of a relationship between plasma HCY concentrations and the rate of clinical in-stent restenosis (i.e. TLR) in patients presenting with acute coronary syndromes. Clinical TLR was defined as a ≥ 50% in-stent stenosis diameter in at least one treated lesion at angiographic examination performed on symptomatic recurrence or evidence of ischemia. As secondary endpoints, we examined the possible existence of relationships between plasma HCY concentrations and the incidence of 1) death due to any cause and 2) major clinical events (death, myocardial infarction, re-PTCA or coronary artery bypass). Myocardial infarction (Q wave or non-Q wave) was diagnosed on the basis of the combination of a typical clinical event and ECG evidence of acute myocardial infarction associated with a rise in the CPK concentration to twice the normal upper limit.

Procedure. PTCA and stent implantation were performed according to standard techniques. The choice of balloons, stents, wires, pressures, and use of glycoprotein IIb/IIIa inhibitors were at the discretion of the operator. Stent implantation was performed as an elective procedure in all patients and was considered successful when the residual diameter stenosis in the dilated segment was < 30% with a normal flow pattern. When necessary, more than one stent was used. Periprocedural myocardial infarction was defined by the presence of a total CPK value ≥ 2 the normal upper limit. All patients were treated with aspirin (100-300 mg/day) and ticlopidine (500 mg/day for 30 days). Prescription of beta-blockers, ACE-inhibitors, lipid-lowering therapy, nitrates, or calcium channel blocking agents was at the discretion of the attending physician. Baseline and post-stent angiograms were obtained in two orthogonal views after dilation with nitrates. In all patients, quantitative coronary analysis was performed using an automated edge-detection system (Philips View-Station CDM-3500, Philips, Best, The Netherlands). The tip of the guiding catheter was always used as a scaling device to determine the absolute arterial dimensions. End-frames in the two orthogonal views showing maximal severity of the stenosis were always adopted for measurement of the luminal diameter. The reference vessel diameter, the minimal lumen diameter, the degree of stenosis and the length of the lesions were calculated as the average value of the two views. The angiograms were evaluated by three angiographers (PO, MA and LC) who were blinded to the laboratory results.

Laboratory measurements. Fasting levels of total plasma HCY were measured at hospital admission from a venous blood sample, collected in EDTA and refrigerated at 4°C. Within 4 hours, the samples were centrifuged and stored cryogenically. Plasma HCY was measured by a fluorescence polarization immunoassay (FPIA assay, IMx System, Abbott Diagnostics, Abbott Park, IL, USA) with a range of 4 to 500 μmol/l. For values below the limit of detection, the lower limit value was used for statistical analysis. C-reactive protein was measured using a quantitative nephelometric method (Boehringer, Mannheim, Germany). In our laboratory, the upper normal value of C-reactive protein is < 0.8 mg/dl. Troponin T levels were assessed using the qualitative troponin T test (Boehringer, Mannheim, Germany).

Statistical analysis. Plasma HCY was first considered as a continuous value and then a dichotomous parameter split at the 4th quartile (17 μmol/l) of our study population's HCY levels. Categorical variables are reported as percentages and continuous variables as mean ± SD. For categorical variables, a χ^2 test was used to assess differences between study groups. For the analysis of continuous data, a two-tailed Student's t-test was employed. As regards HCY levels, comparisons were made between patients in the 4th quartile and those in the lower (1st, 2nd and 3rd) quartiles. Comparisons were also made between restenostic and non-restenotic patients. The long-term total survival was assessed using Kaplan-Meier curves, with differences between the two HCY distribution groups being compared using the Mantel-Cox log-rank test. Cox regression survival analysis was used to evaluate the relation between mortality and multiple clinical and angiographic parameters. Multiple logistic regression analysis was used to evaluate the relation between TLR and multiple clinical and angiographic variables. All variables were assessed as possible predictors of the study endpoints at univariate analysis; only those which reached a p value < 0.10 were considered for multivariate analysis. The odds ratios (OR) and 95% confidence intervals (CI) are reported with two-tailed probability values. A p value < 0.05 was considered as statistically significant. Data were prospectively collected and analyzed using SPSS 10.0.5 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. The baseline characteristics of the 196 patients who fulfilled the study requirements

are summarized in table I, which also provides a comparison between patients with HCY levels > 17 μmol/l (75th percentile) and those with lower values. The two groups were comparable as regards most clinical and laboratory characteristics, including cardiovascular risk factors. Patients with HCY levels > 17 μmol/l were older and presented a higher prevalence of multivessel disease; this group also displayed a trend toward a higher left ventricular ejection fraction.

Procedural and angiographic characteristics. The procedural and angiographic characteristics are reported in table II. Most patients (62.3%) underwent single vessel stenting. The two groups of patients divided on the basis of the HCY levels (> 17 vs ≤ 17 μmol/l) showed comparable angiographic and procedural characteristics. Moreover, both groups presented similar rates of glycoprotein IIb/IIIa inhibitor usage and of in-hospital myocardial infarction.

Clinical events at follow-up. All patients received clinical follow-up (mean 17.8 ± 7.5 months). Only patients who reported recurrence of symptoms or displayed evidence of ischemia at stress testing underwent coronary angiography. Overall, 7 (3.6%) patients died and 3 (1.5%) had a myocardial infarction. Re-PTCA or coronary artery bypass grafting was performed in 33 (16.8%) patients. TLR occurred in 25 (12.7%) subjects.

The 3 cardiac deaths and all but one of the 7 deaths from any cause occurred in patients with HCY levels > 17 μmol/l (Table III). A significantly higher mortality rate was recorded among patients with baseline HCY levels > 17 μmol/l (6/45, 13.3% vs 1/151, 0.7%, p = 0.001); the incidence of cardiac death was also higher in this group (3/45, 6.7% vs 0/151, 0%, p = 0.01). Kaplan-Meier curves are shown in figure 1. Patients with baseline HCY levels > 17 μmol/l also showed trends toward more myocardial infarction, coronary artery bypass grafting and a higher cumulative incidence of major clinical events. The incidence of TLR was similar in the two groups. As shown in table IV, patients who achieved TLR at follow-up were younger and had a smaller vessel size; a trend toward lower HCY and fibrinogen concentrations was also observable. Diabetic patients had a higher incidence of TLR, although this did not reach significance. It is noteworthy that patients with HCY levels > 17 μmol/l accompanied by raised C-reactive protein concentrations (≥ 0.8 mg/dl) showed significantly higher mortality rates (5/20, 20% vs 2/176, 1.1%, p < 0.001) but a comparable TLR (1/20, 5% vs 24/176, 13.6%, p = 0.45).

Multivariate predictive models. Variables that showed a trend (p < 0.10) toward risk at univariate analysis were analyzed at multivariate analysis. Logistic regression was performed with TLR as the dependent variable and age, diabetes, previous PTCA, fibrinogen and HCY levels, vessel diameter, and pre-stenting stenosis as independent variables. Only the vessel diameter was found to exert an independent influence on TLR (OR 0.329, 95% CI 0.116 to 0.931, p = 0.03). HCY levels did not show any significant influence on TLR.

Multivariate Cox regression analysis was performed with the total mortality as the dependent variable and age, previous myocardial infarction, diabetes, vessel diameter, lesion length and HCY levels as independent variables. As continuous variables, HCY levels (hazard ratio 1.074, 95% CI 1.017 to 1.134, p = 0.01)

Table I. Patients' clinical characteristics with respect to high/low homocysteine (HCY) levels at baseline.

Variable	HCY ≤ 17 μmol/l	HCY > 17 μmol/l	All patients	p
No. patients	151	45	196	
Age (years)	64.4 ± 10.5	68.3 ± 11.1	65.3 ± 10.7	0.03
Male gender	105 (69.5%)	33 (73.3%)	138 (70.4%)	0.76
Diabetes	23 (15.2%)	9 (20%)	32 (16.3%)	0.59
Hypertension	63 (41.7%)	19 (42.2%)	82 (41.8%)	0.91
Cigarette smokers	46 (30.4%)	15 (33.3%)	61 (31.1%)	0.85
Prior MI	42 (27.8%)	10 (22.2%)	52 (26.5%)	0.69
Prior CABG	7 (4.6%)	2 (4.4%)	9 (4.5%)	0.72
Prior PTCA	12 (7.9%)	2 (4.4%)	14 (7.1%)	0.63
Braunwald class III	67 (44.3%)	22 (48.8%)	89 (45.4%)	0.71
Troponin T positive	17 (21.2%)	5 (21.1%)	22 (21.2%)	0.88
One-vessel disease	76 (50.2%)	13 (28.8%)	89 (45.4%)	
Two-vessel disease	46 (30.5%)	14 (31.1%)	60 (30.6%)	0.008
Three-vessel disease	29 (19.2%)	18 (40%)	47 (23.9%)	
HCY (μmol/l)	12.2 ± 3.1	24.6 ± 8.5	15.2 ± 7.1	0.001
Cholesterol (mg/dl)	199.2 ± 34.4	195.4 ± 33.2	198.3 ± 34.1	0.95
CRP (mg/l)	1.1 ± 1.5	0.9 ± 1.0	1.0 ± 1.3	0.76
Fibrinogen (mg/dl)	351.6 ± 101.4	366.9 ± 119.3	355.3 ± 106.7	0.93
LVEF (%)	63.8 ± 10.8	66.9 ± 8.2	64.7 ± 9.9	0.07

CABG = coronary artery bypass graft; CRP = C-reactive protein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table II. Patients' angiographic and procedural characteristics with respect to high/low homocysteine (HCY) levels at baseline.

Variable	HCY ≤ 17 μmol/l (n=151)	HCY > 17 μmol/l (n=45)	All patients (n=196)	p
No. treated lesions	244	70	314	
Lesions treated/patient	1.5	1.6	1.6	0.94
B2-C lesions	200 (81.9%)	56 (80%)	255 (81.2%)	0.80
Multivessel stenting	55 (36.4%)	19 (42.2%)	74 (37.7%)	0.59
Stenting location				
LAD	71 (47%)	24 (53.3%)	95 (48.4%)	0.56
Cx	48 (31.7%)	13 (28.9%)	61 (31.1%)	0.85
RCA	62 (41.1%)	17 (37.8%)	79 (40.3%)	0.82
Stenting in bifurcation	32 (21.1%)	11 (24.4%)	43 (21.9%)	0.79
Stenting in thrombotic lesions	44 (29.1%)	7 (15.5%)	51 (26.1%)	0.10
GPIIb/IIIa inhibitors	35 (23.1%)	9 (20%)	44 (22.4%)	0.80
Periprocedural MI	7 (4.6%)	2 (4.4%)	9 (4.6%)	0.72
Lesion length (mm)	13.1 ± 1.4	12.4 ± 6.9	12.9 ± 6.2	0.24
Stent length (vessel) (mm)	17.6 ± 8.2	16.8 ± 7.8	17.2 ± 8.1	0.56
Vessel diameter (mm)				
Before stenting	3.1 ± 0.5	3.1 ± 0.6	3.1 ± 0.5	1.00
After stenting	3.2 ± 0.5	3.2 ± 0.4	3.2 ± 0.5	1.00
Minimum lumen diameter (mm)				
Before stenting	0.89 ± 0.78	0.86 ± 0.36	0.88 ± 0.7	0.80
After stenting	2.8 ± 0.6	2.8 ± 1.9	2.8 ± 1.7	1.00
Stenosis diameter (%)				
Before stenting	72.8 ± 11.8	70.4 ± 11.9	72.3 ± 11.9	0.23
After stenting	10.8 ± 11.3	13.7 ± 11.5	11.5 ± 11.4	0.13

Cx = circumflex coronary artery; GP = glycoprotein; LAD = left anterior descending coronary artery; MI = myocardial infarction; RCA = right coronary artery.

Table III. Events at follow-up stratified with respect to high/low homocysteine (HCY) levels at baseline.

	HCY ≤ 17 μmol/l (n=151)	HCY > 17 μmol/l (n=45)	p
Follow-up (months)	17.8 ± 7.6	17.8 ± 7.1	1.00
TLR	20 (13.2%)	5 (11.1%)	0.90
Death (due to any cause)	1 (0.7%)	6 (13.3%)	0.001
Cardiac death	0	3 (6.7%)	0.01
Non-fatal MI	1 (0.7%)	2 (4.4%)	0.26
CABG	1 (0.7%)	2 (4.4%)	0.26
PTCA	26 (17.2%)	4 (8.8%)	0.26
Non-TLR	7 (4.6%)	1 (2.2%)	0.77
Major clinical events*	29 (19.2%)	13 (28.8%)	0.23

CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TLR = target lesion revascularization. * death, non-fatal MI, CABG and PTCA were considered major clinical events.

and vessel diameter (hazard ratio 0.087, 95% CI 0.014 to 0.549, p = 0.009) both appeared to be strong independent predictors of total mortality. None of the other variables appeared to influence mortality.

Discussion

This prospective study shows that in patients with unstable angina, HCY levels do not predict clinical in-stent restenosis. However, in spite of successful percutaneous revascularization, increased HCY concentrations did appear to be related to late mortality.

Prospective studies have implicated HCY as a risk factor for the development of coronary artery disease or late unfavorable secondary events (following acute coronary events or in patients with angiographically documented coronary artery disease)[3-5,11]. Raised HCY levels have also been proposed as a reliable prognostic indicator of post-PTCA restenosis[8]. The mechanisms by which HCY may induce vascular damage and atherogenesis are not clearly understood. Various hypotheses have been postulated, including the development of endothelial dysfunction[12], incremental collagen deposition[13], stimulation of vascular smooth muscle cell proliferation[14], increased oxidative stress[15], ex-

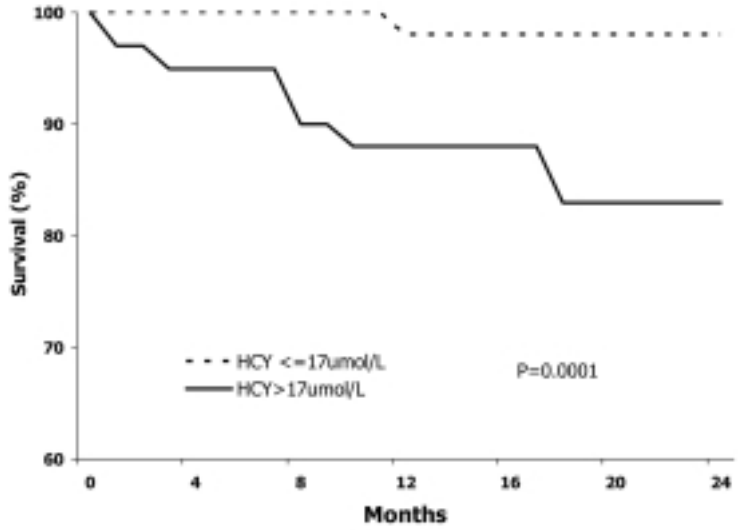

Figure 1. *Kaplan-Meier curves for freedom from death with respect to homocysteine (HCY) levels. Survival was significantly higher among patients with HCY levels ≤ 17 μmol/l.*

Table IV. Clinical characteristics and laboratory findings in patients with or without target lesion revascularization (TLR).

	With TLR (n=25)	Without TLR (n=171)	p
Age (years)	60.1 ± 11.1	65.5 ± 11.7	0.03
Male gender	16 (64%)	119 (69.5%)	0.43
Diabetes	7 (28%)	25 (14.6%)	0.09
Previous PTCA	0	14 (8.1%)	0.09
Previous CABG	1 (4%)	8 (4.6%)	0.85
Previous MI	6 (13.1%)	46 (26.9%)	0.69
CRP (mg/dl)	0.9 ± 0.97	1.03 ± 1.45	0.64
LVEF (%)	68.5 ± 8.4	64.1 ± 80.1	0.10
HCY (μmol/l)	12.7 ± 4.2	15.2 ± 7.2	0.09
Fibrinogen (mg/dl)	317.5 ± 79.3	358.4 ± 107.9	0.07
Cholesterol (mg/dl)	197.5 ± 33.9	198.7 ± 34.3	0.86
Vessel diameter (mm)	2.8 ± 0.4	3.1 ± 0.5	0.007
Lesion length (mm)	12.5 ± 5.6	13.1 ± 5.5	0.67
Minimum lumen diameter (mm)			
Before stenting	0.85 ± 0.3	0.85 ± 0.41	0.97
After stenting	2.67 ± 0.44	2.77 ± 0.56	0.40
Stenosis diameter (%)			
Before stenting	69.3 ± 9.7	73.4 ± 11.5	0.09
After stenting	10.3 ± 12.8	12.2 ± 10.2	0.40
Stent length (mm)	16.3 ± 9.8	17.5 ± 7.2	0.41

CABG = coronary artery bypass graft; CRP = C-reactive protein; HCY = homocysteine; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

cess thrombogenesis through down-regulation of thrombomodulin expression[16], activation of factor V[5], inhibition of protein C activation[17], interaction with tissue plasminogen and/or tissue factor procoagulants[18,19], and increased platelet aggregation[20]. As regards restenosis, this arterial healing response to the injury incurred after PTCA or stenting is mainly due to neointimal proliferation and vascular remodeling. Coronary stenting prevents vascular remodeling but exacerbates vascular smooth muscle cell proliferation. It is thought that high HCY levels could be implicated in the restenotic process because of their ability to act as a mitogen on smooth muscle cells and favor neointimal proliferation[14] or due to their oxidant properties[15] that might affect post-PTCA vascular remodeling.

Homocysteine and restenosis. The primary aim of the present study was to verify whether HCY levels modify in-stent restenosis in patients with unstable angina. In our population of patients treated with stent implantation in all revascularized lesions, only the vessel diameter turned out to be an independent predictor of TLR. Plasma HCY levels showed no relation to the clinical in-stent restenosis rate neither at multivariate

nor at univariate analysis. Furthermore, HCY concentrations were comparable in patients with and without TLR (Table IV). Our data broadly fail to support the concept that plasma HCY concentrations correlate with restenosis rates after PTCA[8,9]. On the other hand, our findings are consistent with those of two recent studies, both regarding patients with stent implantation for stable/unstable coronary artery disease[21,22]. Neither of these studies reported that there was any correlation between HCY levels and in-stent restenosis. In addition, a further study revealed no association between HCY levels and restenosis in 144 patients (with an undefined clinical status) submitted to PTCA, only 31% of whom were additionally provided with stents[23].

Our data derived from the stenting of vessels with a mean size ≥ 3 mm only apparently contrast with those of Schnyder et al.[8], who recently proposed HCY levels as a prognostic indicator of restenosis after PTCA or stenting. This important study showed that HCY levels < 9 μmol/l were associated with a 49% lower rate of coronary restenosis. However, subanalysis revealed that the predictive value of HCY levels was confined to vessels < 3 mm in diameter that were treated with PTCA alone. Our data regarding patients submitted to stenting, mainly for vessels ≥ 3 mm in diameter, strongly reinforce this concept. In another major study on patients treated mainly with PTCA, Schnyder et al.[24] showed that reductions in HCY levels induced by folate treatment roughly halved the incidence of angiographic restenosis, as well as the need for TLR. It should be noted, however, that when the authors considered PTCA and stenting separately, folate treatment was found to lead to a significant reduction of restenosis only in those lesions treated with PTCA. Overall, it appears reasonable to hypothesize that high HCY concentrations may stimulate the restenotic process in small vessels treated by PTCA by exerting a negative effect on coronary artery remodeling. On the other hand, our data and the subanalyses provided by Schnyder et al.[8,24] suggest that stent implantation may almost entirely prevent the pro-restenotic effect of HCY. Specific intravascular ultrasound interventional studies are needed to address this issue directly.

Homocysteine levels and mortality. A secondary aim of our study was to confirm within our specific subset of patients (with unstable angina undergoing stenting) the reported relationship between HCY levels and cardiac mortality[2]. We found that HCY levels independently correlated with the total mortality (and that levels > 17 μmol/l were associated with an increased cardiac mortality at univariate analysis). Interestingly, the influence of HCY levels on mortality occurred in spite of successful percutaneous revascularization (an inclusion criterion for the study). This observation agrees with the concept that percutaneous revascularization does not seem to exert a protective role in patients with high HCY concentrations[2,8,9].

In our study, patients with HCY levels > 17 μmol/l had a higher prevalence of three-vessel coronary artery disease. This raises the critical issue of the possible confounding role of multivessel disease in the analysis of the relationship between HCY and mortality. Previous studies[9,25,26] have shown a direct relation between total HCY levels and the number of stenotic coronary vessels. However, in a large prospective study on patients undergoing cardiac catheterization for suspected coronary artery disease, Nygard et al.[2] found that HCY levels correlated much more strongly with mortality than with the extent of coronary artery disease; in contrast, lipid-related factors correlated strongly with the extent of coronary artery disease and only weakly with mortality. However, other factors such as left ventricular ejection fraction are known to be stronger predictors of mortality after coronary stenting than multivessel disease, which actually correlates more strongly with the recurrence of symptoms due to restenosis or incomplete functional revascularization[27]. In our series of patients, the left ventricular ejection fraction was similar in both the high and low HCY subgroups. Moreover, at multivariate regression analysis, only HCY levels and vessel diameter (and not multivessel disease) appeared to constitute independent risk factors for total mortality. Overall, our data tend to underline the influence of HCY levels on survival. Although this finding deserves caution because of the methodological weakness (multivariate analysis for a small number of events), our results are broadly in line with the concept that elevated total HCY levels appear to be related to the risk of acute cardiac events via thrombosis rather than atherogenic, pro-stenotic mechanisms. Finally, our follow-up data suggest that, in individual patients, the association of raised C-reactive protein values with high HCY levels might confer a further incremental risk of death up to 1 year after successful coronary stenting.

Study limitations. To our knowledge, the present study is the first to specifically focus on patients with an acute coronary syndrome undergoing stent implantation. While this strengthens the reliability of our analysis, it must be remembered that the conclusions of the study cannot automatically be extended to patients with stable angina. Moreover, it must be emphasized that our study included a typical overall population of consecutive patients, and was not designed to confirm the existence of any association between HCY levels and TLR rates in vessels < 3 mm.

It could be argued that our series was not sufficiently large to detect any weak relationships between HCY levels and TLR rate. However, the absence of any evidence of positive trends (even adopting the median HCY value as the cut-off; data not shown) renders the possibility of any such relationship extremely unlikely. Indeed, patients with low HCY levels actually showed slightly higher TLR rates than those with high levels.

Conversely, patients who were submitted to TLR presented slightly lower HCY levels than those in whom this procedure was not performed. It is true, however, that the identification of any correlation between HCY levels and the incidence of TLR could have been hindered by our decision to perform coronary angiography at follow-up only in patients who were symptomatic or who had positive stress test results. While this choice limits the investigative power of the study in absolute terms, it does have the advantage of reflecting clinical practice. Finally, it should be noted that the inclusion of patients with a previous myocardial infarction within the last 6 months was almost certainly responsible[28] for the high mean baseline HCY levels in our series. However, this factor should not have influenced our results, since the distribution of patients with prior myocardial infarction was similar in the two main HCY subgroups.

Conclusions. This prospective study indicates that in the overall population of patients with an acute coronary syndrome and treated with stent implantation, elevated plasma HCY concentrations do not modify the TLR rate. In clinical terms, this finding clearly implies that in a population with a mean vessel size > 3 mm, HCY levels should not be taken as a prognostic indicator of in-stent restenosis. However, it should be noted that our study provides no specific information about vessels < 3 mm for which evidence that HCY levels may predict restenosis does exist in the literature[8,23]. On the other hand, our follow-up data do further stress the concept that HCY levels strongly influence long-term mortality. This knowledge is prompting intervention trials (folic acid supplementation) aimed at reducing the long-term mortality in patients with acute coronary syndromes.

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