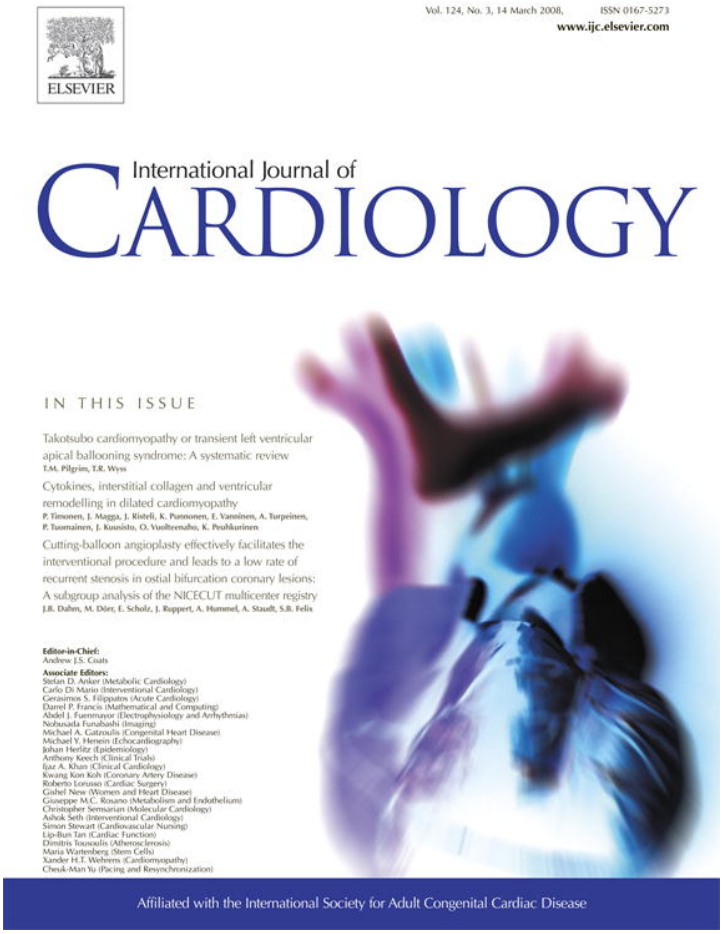

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The impact of circulating total homocysteine levels on long-term cardiovascular mortality in patients with acute coronary syndromes

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Abstract

Background: To evaluate the possible independent impact of circulating total homocysteine (tHcy) levels on long-term cardiovascular mortality, in patients with either ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation acute coronary syndromes (NSTE-ACS).
Methods: A total of 458 STEMI and 476 NSTE-ACS patients who presented consecutively, within the first 12 and 24 h of index pain respectively were studied. Each cohort was divided according to tertiles of circulating tHcy levels upon presentation. Early (30 days) and late (31 days through 5 years) cardiovascular mortality was the predefined study endpoint.
Results: There was no difference in the risk of 30-day cardiovascular death among the tertiles of tHcy in patients with STEMI (7.2%, 8.5% and 12.4% for the first, second and third tertiles respectively; $p_{trend}=0.3$) or NSTE-ACS (3.1%, 3.8% and 5.7% for the first, second and third tertiles respectively; $p_{trend}=0.5$). Patients in the upper tHcy tertile were at significantly higher unadjusted risk of late (from 31 days trough 5 years) cardiovascular death than those in the other two tertiles in STEMI (23.4%, 27.9% and 41.8% for the first, second and third tertiles respectively; $p_{trend}<0.001$), and NSTE-ACS (24.7%, 28.1% and 45.6% for the first, second and third tertiles respectively; $p_{trend}<0.001$) cohorts. However, after adjustment for baseline differences, there was no significant difference in the risk of late cardiovascular death among tHcy tertiles in either cohort. When circulating tHcy levels were treated as a continuous variable, they were significantly associated with late cardiovascular death ($p<0.001$ for both cohorts) by univariate Cox regression analysis, but not by multivariate Cox regression analysis ($p=0.8$, and $p=1$ for STEMI and NSTE-ACS cohorts, respectively).
Conclusions: Based on the present data circulating tHcy levels determined upon admission do not serve as an independent predictor of long-term cardiovascular mortality in patients with either STEMI or NSTE-ACS.

Keywords: Homocysteine; Acute coronary syndromes; Prognosis; Risk stratification

1. Introduction

Previous studies have evaluated the impact of circulating total homocysteine (tHcy) on clinical outcome in patients with stable or unstable coronary artery disease [1–7]. This amino acid is the derivative of methionine demethylation. Significantly elevated circulating tHcy levels (>100 μmol/l) observed in patients with homocystinuria, a genetically inherited enzyme defect of Hcy metabolism, have been shown to be associated with aggressive and premature vascular disease [8–10]. Thus, it has been presumed that moderately elevated circulating tHcy levels might also have some prognostic implication in several manifestations within the wide spectrum of coronary artery disease.

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Yet the place and significance of circulating tHcy levels in the setting of acute coronary syndromes have not been definitively clarified. On the contrary, it seems that the limited existing data are rather controversial [3–7]. Since the possible pathophysiologic mechanisms remain obscure, the critical question is whether the observed relation might be accounted to the reported association of tHcy levels with known cardiovascular disease risk factors that possibly act as confounders [11–13].

The present study was designed to attempt a further elucidation of the aforementioned controversy. We prospectively evaluated the possible association of admission circulating tHcy levels with late clinical outcome during a five-year follow-up period after an acute coronary syndrome.

2. Methods

2.1. Study population

Consecutive eligible patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndromes (NSTE-ACS) who were admitted to our institute from September 1998 through December 2000 were recruited. Patients with STEMI were required to have: 1) continuous chest pain upon presentation, refractory to nitrates, and lasting ≥30 min; 2) ST-segment elevation of ≥2 mm in ≥2 contiguous precordial leads, or ≥1 mm in ≥2 contiguous limb leads; 3) presentation in the first 12 h from index pain. Patients with NSTE-ACS were required to have angina like chest pain at rest in the last 24 h of ≥5 min in duration, with associated ST depression of ≥1 mm in ≥2 contiguous leads upon presentation. Patient with 1) angina of secondary etiology; 2) active infection, or chronic inflammatory diseases; 3) significant hepatic or renal dysfunction; 4) malignancy; or 5) major surgery, coronary revascularization or myocardial infarction in the last month, were not included. Due to the fact that primary percutaneous coronary angioplasty was not the standard of care at the time that it was started, patients who receive this type of reperfusion were not included.

2.2. Blood sample collection and biochemical assays

Venous blood samples were obtained upon presentation and prior to any administration of drugs. The acquired serum samples were coded and stored at −80 °C until the performance of tHcy, hs-CRP and cTnI measurements. Circulating tHcy and cTnI levels were measured by an enzyme based immunoassay (Abbot Diagnostics, Illinois). Circulating hs-CRP levels were measured by a nephelometric method (BNII Dade Behring Inc., Germany) with a lower limit of detection at 0.2 mg/L.

2.3. Follow-up and study end point

In-hospital and post-discharge follow-up data were prospectively collected on pre-designed case report forms. Before discharge, all patients were advised for smoking cessation, body weight reduction, regular exercise and lipids monitoring. After discharge, patients were followed-up at 30 days and subsequently every 6 months for a total period of 5 years, on an outpatient basis or by telephone interview. Cardiovascular death was the pre-specified primary endpoint. In particular, the incidence of early (30 days) and late (from 31 days trough 5 years) cardiovascular death was evaluated. Cardiovascular death was considered, as sudden unexplained death, death due to fatal myocardial infarction, death after re-hospitalization because of heart failure or possible acute myocardial ischemia and death related to stroke or peripheral artery disease. The diagnosis of cardiovascular death was verified by review of death certificates, discharge medical reports, hospitals records, or contact with the attending physicians.

Table 1
Baseline characteristics among the tHcy tertiles of the STEMI cohort

Variable	First (n=152) (3–11.2 μmol/L)	Second (n=153) (>11.2–19.4 μmol/L)	Third (n=153) (>19.4–69 μmol/L)	p Value
Age (years)	59.5±10.9	59.2±10.7	63.3±12.3	0.001
Men	75.7%	77.8%	78.4%	0.8
Hypertension	45.4%	48.4%	54.9%	0.2
Current smoker	64.5%	71.2%	62.1%	0.2
Diabetes	27.6%	24.8%	28.8%	0.7
Hypercholesterolemia	62.5%	65.4%	62.1%	0.8
Familial coronary artery disease	39.5%	40.5%	36.6%	0.8
History of angina > 1 month	8.6%	11.8%	26.8%	<0.001
History of myocardial infarction [a]	8.6%	10.5%	20.3%	0.005
History of coronary angioplasty [a]	9.9%	11.8%	18.3%	0.08
History of coronary artery bypass grafting [a]	7.9%	6.5%	15.7%	0.01
History of heart failure	2.6%	5.9%	10.5%	0.02
History of CVD or PAD	5.3%	3.3%	16.3%	<0.001
Anterior STEMI [b]	48.7%	54.2%	54.2%	0.5
Killip class II–IV	9.2%	13.7%	19.6%	0.03
From index pain to treatment (h)	4.3±1.6	4.1±1.5	4.5±2.1	0.2
Treatment with thrombolysis	63.8%	64.7%	48.4%	0.005
cTnI median (range) (ng/ml)	24 (0–132.5)	24 (0–184)	28 (2.3–235)	0.03
hs-CRP median (range) (mg/L)	4.1 (1–68.3)	4.5 (1–68.7)	5.1 (1–72.3)	0.002

Values are mean±SD or percent or as given.
cTnI=Cardiac troponin I, CVD or PAD=cerebrovascular or peripheral artery disease, hs-CRP=high sensitivity C-reactive protein, STEMI=ST-segment elevation myocardial infarction.
[a] Occurrence ≥1 months before study.
[b] Or new (or presumably new) left bundle branch block.

2.4. Statistical analysis

Normally distributed continuous variables were expressed as mean±SD. Non-normally distributed variables were expressed as median with range and natural logarithm transformation was used for regression analysis. Normal distribution was evaluated with Kolmogorov–Smirnov test. Comparisons of continuous variables were made using ANOVA test, or Kruskal–Wallis test, as appropriate. Bonferroni in ANOVA, *t*-test or Mann–Whitney *U* test were used, as appropriate, for pairwise comparisons of continuous variables. Dichotomous variables were presented as percentages. Associations between dichotomous variables were tested by χ^2 or Fisher's exact test as appropriate. Each cohort was divided into 3 groups according to the tertiles of circulating tHcy levels upon presentation. Unadjusted or adjusted differences in the risk of early (30 days) and late (from 31 days trough 5 years) cardiovascular death were evaluated by univariate or multivariate Cox regression analysis in each cohort.

Table 2
Baseline characteristics among the tHcy tertiles of the NSTEACS cohort

Variable	First (n=159) (3.4–13.8 μmol/L)	Second (n=159) (>13.8–21.8 μmol/L)	Third (n=158) (>21.8–83.3 μmol/L)	p Value
Age (years)	68.4±7.8	69.7±8.1	72.5±7.3	<0.001
Men	69.8%	63.5%	63.9%	0.4
Hypertension	60.4%	62.3%	70.3%	0.1
Current smoker	52.8%	45.3%	38.0%	0.03
Diabetes	32.1%	35.2%	35.4%	0.8
Hypercholesterolemia	66%	65.4%	73.4%	0.2
Familial coronary artery disease	40.9%	37.7%	39.9%	0.8
History of angina >1 month	24.5%	30.2%	52.5%	<0.001
History of myocardial infarction [a]	23.9%	23.9%	39.9%	0.001
History of coronary angioplasty [a]	11.3%	14.5%	21.5%	0.04
History of coronary artery bypass grafting [a]	9.4%	11.9%	24.1%	0.001
History of heart failure	8.8%	9.4%	22.8%	<0.001
History of CVD or PAD	3.1%	7.5%	22.8%	<0.001
Killip class II–IV	10.1%	13.2%	31.6%	<0.001
From index pain to treatment (h)	8.5±4.5	8.5±5.1	9.1±5.6	0.3
cTnI median (range) (ng/ml)	9.2 (0–102)	9.2 (0–145)	13.9 (0–163)	0.009
hs-CRP median (range) (mg/L)	5 (1–72.3)	5.3 (1–72.5)	6.1 (1–72.5)	0.02

Values are mean±SD or percent or as given.
cTnI=Cardiac troponin I, CVD or PAD=cerebrovascular or peripheral artery disease, hs-CRP=high sensitivity C-reactive protein, NSTEACS=non-ST-segment elevation acute coronary syndromes.
[a] Occurrence ≥1 months before study.

Table 3
Hazard of early cardiovascular death between the tHcy tertiles in either cohort

	HR (95% CI)	p Value
STEMI		
Third vs. First	1.4 (0.8–2.3)	0.2
Third vs. Second	1.3 (0.8–1.9)	0.3
Second vs. First	1.1 (0.7–1.7)	0.7
NSTE-ACS		
Third vs. First	1.4 (0.7–2.9)	0.3
Third vs. Second	1.3 (0.7–2.4)	0.4
Second vs. First	1.1 (0.6–2.1)	0.8

CI=Confidence interval, HR=hazard ratio, NSTEACS=non-ST-segment elevation acute coronary syndromes, STEMI=ST-segment elevation myocardial infarction.

Freedom of late cardiovascular death among tHcy tertiles was initially analyzed with the Kaplan–Meier method and log-rank was used for comparisons among the curves. Subsequently, freedom of late cardiovascular death was tested with Cox adjusted curves to evaluate any significant difference among tHcy tertiles after adjustment for the other predictors of late cardiovascular death. A multivariate Cox regression model was constructed for each cohort in order to evaluate the value of tHcy, treated as continuous variable, for the prediction of late cardiovascular death. Patients who died because of non-cardiovascular causes were censored at the time of death. To avoid overadjustment by using too many variables in the multivariate models, all variables were subjected to univariate analysis in a first step. Variables with a $p<0.1$ by univariate analysis were included in the multivariate models. All tests were two-tailed and a $p<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS statistical software (release 13.0, SPSS Inc., Chicago, Illinois).

Table 4
Unadjusted and adjusted hazard of late cardiovascular death between the tHcy tertiles in either cohort

	Unadjusted		Adjusted [a]	
	HR (95% CI)	p Value	HR (95% CI)	p Value
STEMI				
Third vs. First	1.6 (1.1–2.1)	0.001	1.1 (0.7–1.3)	0.7
Third vs. Second	1.4 (1.1–1.8)	0.02	1 (0.7–1.4)	1
Second vs. First	1.1 (0.8–1.5)	0.4	1.1 (0.8–1.7)	0.6
NSTE-ACS				
Third vs. First	1.6 (1.2–2.2)	<0.001	1 (0.6–1.6)	0.8
Third vs. Second	1.5 (1.1–1.9)	0.002	1.1 (0.8–1.9)	0.7
Second vs. First	1.1 (0.8–1.4)	0.5	0.7 (0.5–2.1)	0.8

CI=Confidence interval, HR=hazard ratio, NSTEACS=non-ST-segment elevation acute coronary syndromes, STEMI=ST-segment elevation myocardial infarction.
[a] Adjusted for the significant differences between tHcy tertiles.

3. Results

3.1. Baseline characteristics

During the recruiting period, 458 patients with STEMI and 476 with NSTE-ACS were included in the study. Baseline characteristics within the tertiles of tHcy, for each cohort, are presented in Tables 1 and 2. Patients in the upper tHcy tertile were significantly older and had more unfavorable risk profile than those in the other two tertiles; this observation was true for both cohorts. In particular, the frequency of prior angina, myocardial infarction, heart failure, peripheral artery disease, and coronary revascularization were significantly higher within the upper tertile compared to the other tHcy tertiles. Moreover, patients in the upper tHcy tertile were more frequently at Killip class II–IV and had significantly higher circulating cTnI and hs-CRP values upon presentation than those in the other two tHcy tertiles (Tables 1 and 2).

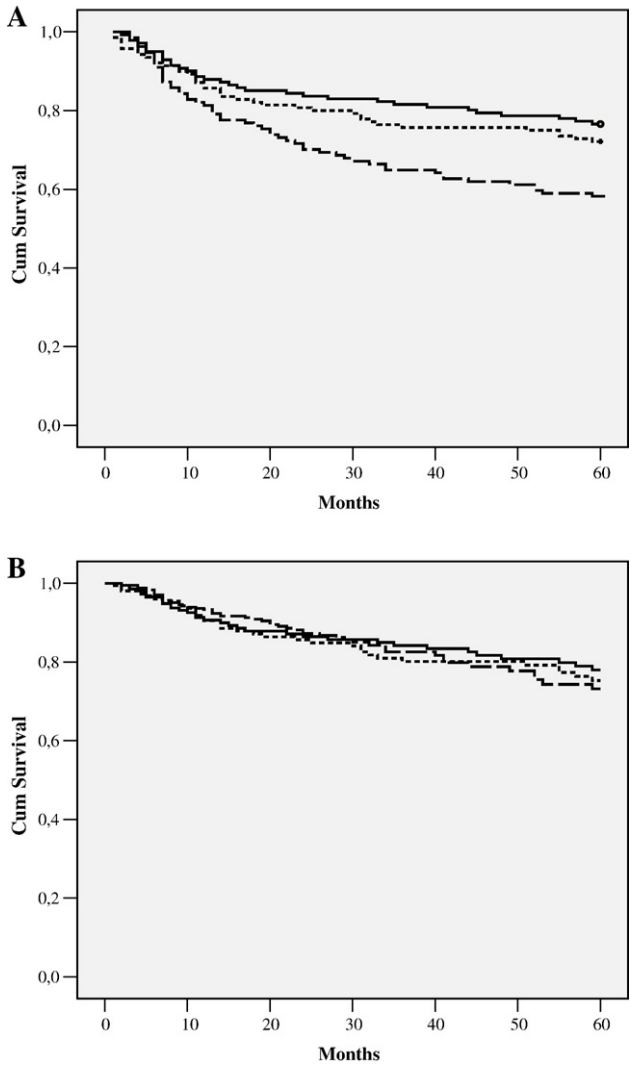

Fig. 1. Kaplan–Meier (A) and Cox adjusted (B) curves among the first (−), second (···) and third (− −) tHcy tertiles in STEMI cohort. tHcy=Total homocysteine, STEMI=ST-segment elevation myocardial infarction.

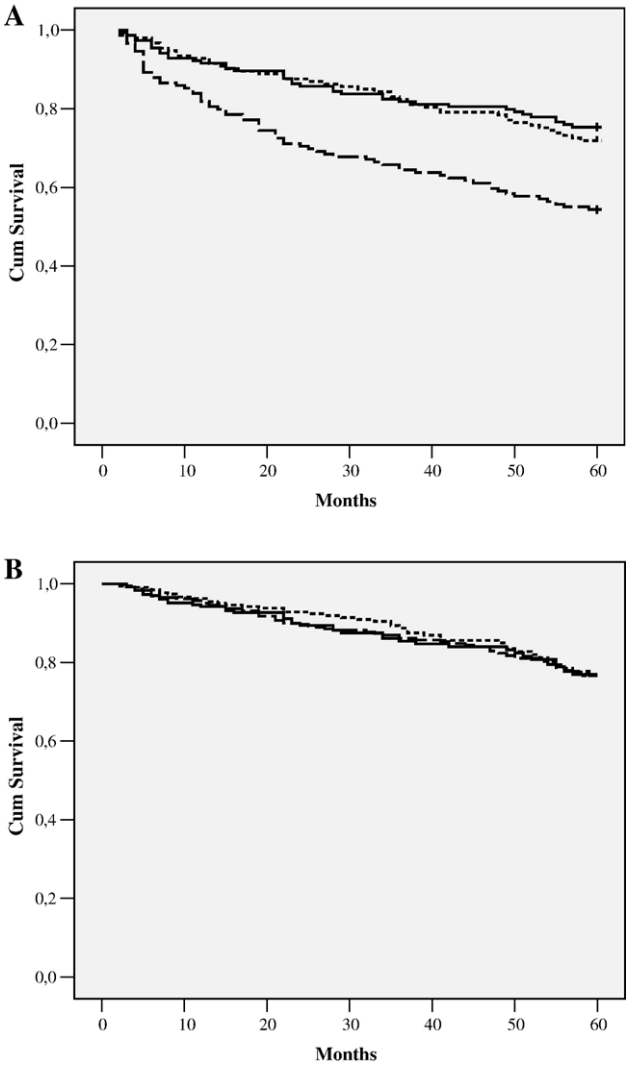

Fig. 2. Kaplan–Meier (A) and Cox adjusted (B) curves among the first (−), second (···) and third (− −) tHcy tertiles in NSTE-ACS cohort. tHcy=Total homocysteine, NSTE-ACS=non-ST-segment elevation acute coronary syndromes.

3.2. Study end point

Five-year mortality data were obtained for all patients and cardiovascular mortality rate during the whole follow-up period was 37.3% (171/458) and 35.5% (169/476) in patients with STEMI and NSTE-ACS respectively. Early (30-day) cardiovascular mortality was 9.4% (43/458; 7.2%, 8.5% and 12.4% for the first, second and third tertiles respectively; $p_{trend}=0.3$) in patients with STEMI, and 4.2% (20/476; 3.1%, 3.8% and 5.7% for the first, second and third tertiles respectively; $p_{trend}=0.5$) in those with NSTE-ACS. Moreover late (from 31 days trough 5 years) cardiovascular mortality was 30.8% (128/415; 23.4%, 27.9% and 41.8% for the first, second and third tertiles respectively; $p_{trend}<0.001$)

Table 5
Univariate and multivariate predictors of late cardiovascular death in STEMI cohort

	Univariate Cox proportional hazard regression		Multivariate Cox proportional hazard regression	
	HR (95%CI)	*p* Value	HR (95%CI)	*p* Value
Age (per 10 years)	1.8 (1.5–2.2)	<0.001	1.4 (1.1–1.7)	0.03
Men	0.6 (0.4–0.9)	0.02	1 (0.6–1.6)	0.9
Hypertension	1.3 (0.9–1.8)	0.1	1.2 (0.8–1.9)	0.5
Current smoker	0.6 (0.4–0.8)	0.001	1 (0.6–1.6)	1
Diabetes	3.8 (2.7–5.4)	<0.001	1.9 (1.3–2.9)	0.001
History of angina > 1 month	1.9 (1.3–2.9)	0.001	1 (0.6–1.9)	0.7
History of myocardial infarction [a]	5.9 (4–8.7)	<0.001	2.2 (1.4–3.4)	0.001
History of coronary angioplasty [a]	1.5 (1.1–2.6)	0.02	1.1 (0.7–1.9)	0.8
History of coronary artery bypass grafting [a]	2 (1.3–3.3)	0.004	0.8 (0.4–1.4)	0.4
History of heart failure	8.1 (4.8–13.7)	<0.001	1.8 (1.4–3.2)	0.004
History of CVD or PAD	2.4 (1.5–3.9)	0.02	1.4 (1.2–2.9)	0.03
Anterior STEMI [b]	2.6 (1.8–3.9)	<0.001	1.4 (1.2–2.2)	0.03
Killip class II–IV	5.5 (3.8–8.1)	<0.001	2.6 (1.7–3.9)	<0.001
From index pain to treatment (h)	4.2 (2.9–6.3)	<0.001	1.4 (1.1–2.9)	0.04
Treatment with thrombolysis	0.4 (0.3–0.6)	<0.001	0.7 (0.5–0.9)	0.03
cTnI (ng/ml) [c]	3 (2.3–3.8)	<0.001	1.9 (1.5–2.4)	<0.001
hs-CRP (mg/L) [c]	2.4 (2.1–2.9)	<0.001	1.7 (1.5–2.1)	<0.001
tHcy (μmol/L) [c]	1.9 (1.4–2.5)	<0.001	1.1 (0.8–1.4)	0.8

CI=Confidence interval, cTnI=cardiac troponin I, CVD or PAD=cerebrovascular or peripheral artery disease, HR=hazard ratio, hs-CRP=high sensitivity C-reactive protein, STEMI=ST-segment elevation myocardial infarction, tHcy=total homocysteine.
[a] Occurrence ≥1 month before study.
[b] Or new (or presumably new) left bundle branch block.
[c] Values were logarithmically transformed.

in patients with STEMI, and 32.7% (149/456; 24.7%, 28.1% and 45.6% for the first, second and third tertiles respectively; $p_{trend}<0.001$) in those with NSTE-ACS.

Hazard ratios of early and late cardiovascular mortality among tHcy tertiles are presented in Tables 3 and 4 respectively. Kaplan–Meier and Cox adjusted estimates for late cardiovascular mortality among tHcy tertiles, for each cohort, are presented in Figs. 1 and 2. There was no difference in the risk of 30-day cardiovascular death among the tertiles of tHcy (Table 3). Patients in the upper tHcy tertile were at significantly higher unadjusted risk of late cardiovascular death than those in the other two tertiles (Table 4, Figs. 1A and 2A). However, after adjustment for baseline differences, there was no significant difference in the risk of late cardiovascular death among tHcy tertiles (Table 4, Figs. 1B and 2B). When tHcy was treated as a continuous variable, it was significantly associated with late cardiovascular death by univariate, but not by multivariate Cox regression analysis (Tables 5 and 6 in patients with STEMI and NSTE-ACS respectively).

4. Discussion

The primary outcome of the present study is that circulating tHcy levels upon admission seem to lack independent value in the prediction of long-term cardiovascular mortality within a five-year follow up period after an acute coronary syndrome. Despite the significant relation demonstrated for both STEMI and NSTE-ACS patients, by means of univariate analysis, statistically non-significant results were produced when tHcy levels were included along with all other univariate predictors in the multivariate model.

Limited data regarding the relation between tHcy levels and clinical outcome in the setting of acute coronary syndromes exist. Moreover despite the almost unanimously admitted lack of use in short-term prognosis, previous investigations addressing the possible long-term predictive value of tHcy have produced controversial results [3–7]. In point of fact our findings seem apparently conflicting with most previous studies which suggest that tHcy levels strongly and independently predict late cardiac events in acute coronary syndromes. However it is also true that whether a potential prognostic factor might be considered as being independent depends vastly on the possible confounding factors included in the multivariate model.

A number of studies have reported associations of elevated tHcy levels with age, sex, current smoking, previous

Table 6
Univariate and multivariate predictors of late cardiovascular death in the NSTE-ACS cohort

	Univariate Cox proportional hazard regression		Multivariate Cox proportional hazard regression	
	HR (95%CI)	*p* Value	HR (95%CI)	*p* Value
Age (per 10 years)	2.6 (2.1–3.4)	<0.001	1.6 (1.2–2.1)	<0.001
Men	0.7 (0.5–0.9)	0.03	0.8 (0.6–1.1)	0.2
Hypertension	1.5 (1.1–2.2)	0.02	0.9 (0.6–1.4)	0.8
Current smoker	0.6 (0.4–0.8)	0.01	1 (0.7–1.4)	0.9
Diabetes	3.7 (2.7–5.2)	<0.001	1.9 (1.4–2.7)	<0.001
History of myocardial infarction [a]	4.7 (3.4–6.5)	<0.001	1.8 (1.3–2.6)	0.001
History of coronary angioplasty [a]	2.2 (1.5–3.3)	<0.001	1 (0.6–1.4)	0.9
History of coronary artery bypass grafting [a]	1.3 (1.1–2.4)	0.03	0.7 (0.5–1.2)	0.2
History of heart failure	5.9 (4.1–8.5)	<0.001	2.1 (1.4–3.1)	0.004
History of CVD or PAD	3.4 (2.3–5)	<0.001	1.6 (1.1–2.4)	0.02
Killip class II–IV	7.1 (5.1–9.9)	<0.001	1.6 (1.1–2.6)	0.03
cTnI (ng/ml) [b]	3.1 (2.6–5.3)	<0.001	1.7 (1.2–2.4)	0.01
hs-CRP (mg/L) [b]	3.1 (2.6–3.6)	<0.001	1.9 (1.5–2.6)	<0.001
tHcy (μmol/L) [b]	1.8 (1.3–2.3)	<0.001	1 (0.7–1.3)	1

CI=Confidence interval, cTnI=cardiac troponin I, CVD or PAD=cerebrovascular or peripheral artery disease, HR=hazard ratio, hs-CRP=high sensitivity C-reactive protein, NSTEACS=non-ST-segment elevation acute coronary syndromes, tHcy=total homocysteine.
[a] Occurrence ≥1 month before study.
[b] Values were logarithmically transformed.

myocardial infarction, peripheral artery disease, cerebrovascular disease, peak cTnT and other predictors [3–7,10]. Indeed, earlier investigations, addressing the same issue as the present study, have attempted adjustments for a range of associated factors as they should before concluding to the independent predictive value of tHcy. Nevertheless, a number of important, speculated or established in our days, clinical and biochemical indices were often absent from those analyses.

Omland et al. were the first to investigate the possible relation of tHcy with mortality following acute coronary syndromes, in a rather selected cohort of 579 patients out of a total of 1561 admissions during the study period [3]. In their otherwise comprehensive analysis important clinical factors such as peripheral artery or cerebrovascular disease were not included. As far as biomarkers are concerned, only peak creatine kinase MB, peak cTnT, LDL-cholesterol and serum creatinine were considered. Only the latter was included in the multivariate model, which demonstrated a significant weakening of the initial association. Published in the same year, the work of Stubbs et al. reached similar conclusions but still the aforementioned clinical as well as important biochemical markers such as CRP, were not examined [4]. Another report by Matetzky et al., with a study population limited to 157 patients with acute myocardial infarction also yielded an association of elevated tHcy levels with a higher risk of cardiac death independent of other risk factors, which still did not include cardiac troponin and inflammatory biomarkers [5].

In fact, Facila et al. were, the first to present a cohort with NSTE-ACS where tHcy retained its independent value predicting all-cause mortality at one-year follow up, despite the inclusion of CRP in the multivariate regression analysis [6]. However, in another study coming from the same center also concerning NSTE-ACS patients the previous finding seems to be challenged [7]. The latter study investigating cardiac death within the first 6 months following the acute event demonstrated too that circulating tHcy levels were a potent predictor in univariate analysis. Yet, when all univariate predictors, including CRP, were entered in the multivariate analysis tHcy did not reach statistical significance, while CRP retained an independent value.

In the present study the prognostic value of tHcy was evaluated in relation to a number of clinical predictors and biochemical markers such as cTnI and hs-CRP. The presented data are of a relatively large population, compared to previous works, including STEMI as well as high risk NSTE-ACS patients that were followed-up for the most extensive period reported so far in similar investigations. Addressing the previous controversial data under the light of the current findings, it seems that an attempt to attribute causality in the relation between tHcy and cardiovascular mortality following acute coronary syndromes might not have enough evidence to be supported. Since there has not been a clearly demonstrated pathophysiologic mechanism explaining the possible involvement of tHcy in the multifactorial process of acute coronary syndromes its role and value cannot be undoubtedly determined. According to the present results though, circulating tHcy levels seem to have a more indirect relation with mortality than previously believed, serving rather as an index of disease severity than a modifiable risk factor exploitable for secondary prevention in patients suffering acute coronary syndromes.

One possible limitation of the present study is related to the fact that tHcy levels typically rise after an acute vascular event in response to tissue damage or repair and remain elevated for months following the acute event [2]. Thus, the independent predictive value of tHcy may have been missed because of its measurement during the acute phase, rather than during the stable phase.

In conclusion, according to the current data circulating tHcy levels determined upon admission do not serve as independent predictor of long-term cardiac mortality in patients with either STEMI or NSTE-ACS. A crucial remaining issue is whether the association of circulating tHcy levels with other strong predictors of mortality, some of them observed and conveyed in previous studies, might produce a confusing relation with mortality. If this finding is confirmed by larger prospective studies circulating tHcy levels might be an unsuitable target for risk profile modification in patients with acute coronary syndromes.

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