Risk stratification in stable coronary artery disease: superiority of N-terminal pro B-type natriuretic peptide over high-sensitivity C-reactive protein, gamma-glutamyl transferase, and traditional risk factors

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Objective **The aim of the study was to compare N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, and gamma-glutamyl transferase (γ-GT) with traditional risk markers for estimating prognosis in patients with stable coronary artery disease (CAD).**

Materials and methods **Evaluation of mortality and a combined clinical endpoint (mortality, need for coronary revascularization, myocardial infarction, hospitalization for cardiac causes, or stroke) during an average 3.2-year follow-up in 394 consecutive patients (73% male patients, age: 67 ± 9 years) with angiographically proven stable CAD.**

Results **Univariate Kaplan–Meier survival rate analysis showed that traditional risk markers, apart from impaired renal function, three-vessel CAD, and a reduced left ventricular function at the time of coronary angiography, were not of prognostic relevance for prediction of outcome. NT-proBNP, high-sensitivity C-reactive protein, and gamma-glutamyl transferase were significant predictors of mortality; however, only NT-proBNP was a significant predictor of the combined endpoint. In age-adjusted and sex-adjusted multivariate Cox regression analysis, NT-proBNP was the strongest independent predictor of the combined endpoint (odds ratio 2.92, 95% confidence interval: 1.72–4.94, first vs. third tertile). All three laboratory parameters remained independent risk markers for mortality in multivariate analysis. NT-proBNP, however, revealed the highest odds ratio (5.23, 95% confidence interval: 1.17–23.23, first vs. third tertile). Concentrations greater than 356 ng/l predicted mortality with a sensitivity of 70%, a specificity of 71%, a positive likelihood ratio of 2.4, and a negative likelihood ratio of 0.42.**

Conclusion **In comparison with other tested novel biomarkers and traditional risk markers, NT-proBNP was the most predictive prognostic marker in multivariate analysis in patients with stable CAD.** *Coron Artery Dis* **23:91–97** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: gamma-glutamyl transferase, high-sensitivity C-reactive protein, N-terminal pro B-type natriuretic peptide, prognosis, risk factor, stable coronary artery disease

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Introduction

Traditional risk factors, such as cholesterol, hypertension, and smoking, are powerful tools for risk stratification in primary prevention and contribute for over 90% of the population-attributable risk for the development of first acute myocardial infarction in the general population [1]. However, they may have less prognostic value in the secondary prevention setting, and in part this may result from the more aggressive management of these risk factors in patients with established coronary artery disease (CAD) and the relative importance of CAD severity as a risk factor for future coronary events [2]. Plaque rupture and intracoronary thrombus formation are the triggers of acute coronary syndromes and several biomarkers are elevated during and may capture these dynamic pathophysiological processes [3]. However, the importance of recommended biomarkers for risk stratification remains to be further evaluated in patients with stable CAD in the context of multimarker testing, traditional risk factors, and traditional risk markers.

B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) are mainly released because of increased myocardial wall stretch [3]. In clinical practice, NT-proBNP is mainly used for diagnosis of heart failure and for risk stratification in heart failure patients. NT-proBNP is a potentially useful marker for risk stratification in stable CAD, because myocardial ischemia may increase natriuretic peptides by causing diastolic or systolic ventricular dysfunction, and myocardial ischemia itself is also a stimulus for BNP expression within the myocardium and subsequent BNP and NT-proBNP release from the heart [4,5].

In addition, atherosclerosis shows features of an inflammatory process [6]. Among inflammatory markers,

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high-sensitivity C-reactive protein (hs-CRP), an acute phase protein synthesized in the liver, has consistently been proven to be the most useful risk predictor of cardiovascular events in various clinical settings [7–9].

Gamma-glutamyl transferase (γ-GT; EC 2.3.2.2.), in contrast, is an enzyme that has recently also gained interest as a cardiovascular risk marker [10–12]. Cell membrane-associated γ-GT is directly involved in the extracellular catabolism of glutathione, the main thiol antioxidant in humans, by hydrolysis of the γ-glutamyl bond between glutamate and cysteine [13]. The extracellular catabolism of glutathione may exert prooxidant effects, and the resulting thiol can initiate the oxidation of LDL. Additionally, γ-GT is bound to LDL particles [14], and the localization of γ-GT within the human coronary plaque colocalized with LDL and foam cells provides a potential pathophysiological basis for being a coronary risk marker [15].

So far no comparative study on these three recently proposed risk markers has been published in patients with stable CAD, and the present prospective study was planned to further examine the importance of these markers in the context of multimarker testing, traditional risk factors, and traditional risk markers.

Methods

We enrolled 525 consecutive patients with stable CAD between March 2004 and January 2005 in whom CAD was verified by coronary angiography (CAG). Patients with a history of acute coronary syndromes, with heart valve disease, or after heart transplantation were excluded from this study. Standard cardiovascular risk factors and risk markers were assessed by standardized questionnaire and blood chemistry. From the total 525 consecutive patients, 394 (75%) could be followed-up. The remaining 131 patients could either not be reached by telephone or declined to provide further information. Patients with and without follow-up only differed slightly but significantly ($P = 0.001$) in age (67 ± 9 vs. 63 ± 11 years). All other parameters showed no significant differences. Table 1 summarizes the clinical characteristics of the final study population.

Routine methods from Roche Diagnostics (Mannheim, Germany) were used to determine serum concentrations of standard biochemical parameters, such as glucose, γ-GT and other liver enzymes, creatinine, urea, uric acid, triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol. NT-proBNP, hs-CRP, and γ-GT were measured as part of the routine laboratory testing before CAG. NT-proBNP was measured in heparinized plasma by a commercially available immunoassay on an E170 Analyzer (Elcsys proBNP; Roche Diagnostics), hs-CRP concentration was determined by an immunoturbidimetric test (Tina-quant CRPLX; Roche Diagnostics), and γ-GT was measured with a liquid test from Roche Diagnostics. The glomerular filtration rate in milliliters per minute per 1.73 m^2 was calculated using the 'modification of diet in renal disease' equation as described previously [16].

Table 1 Baseline clinical characteristics of the final study population

	Median or percentage	25% percentile	75% percentile
Age (years)	68	61	74
Male	73%		
AP symptoms	78%		
Hypertension	77%		
Known diabetes	18%		
Smoker	19%		
Positive family history	18%		
Decreased LVEF	30%		
Three-vessel disease	24%		
BMI	26	24	29
NT-proBNP (ng/l)	184	86	540
γ-GT (U/l)	30	22	50
hs-CRP (mg/l)	2.5	1.2	6.1
AST (U/l)	27	22	34
ALT (U/l)	25	19	37
Fasting glucose (mg/dl)	100	91	117
Cholesterol (mg/dl)	191	164	219
LDL (mg/dl)	120	100	148
HDL (mg/dl)	51	43	61
TG (mg/dl)	129	98	183
Creatinine (mg/dl)	0.99	0.87	1.12
eGFR <60 ml/min/ 1.73 m^2	19%		

Data are given as median and interquartile range or as percentages.
ALT, alanine aminotransferase; AP, angina pectoris; AST, aspartate aminotransferase; decreased LVEF, decreased left ventricular ejection fraction (<60% in levocardiography or <50% in echocardiography); eGFR, estimated glomerular filtration rate calculated by modification of diet in renal disease equation; γ-GT, gamma-glutamyl transferase; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; TG, triglycerides.

CAG was performed using the standard Judkins technique, CAD severity was assessed by standard angiographic criteria, and left ventricular function was quantified by ventriculography or echocardiography as previously described [16]. A decreased left ventricular ejection fraction was defined as less than 60% in levocardiography or less than 50% in echocardiography.

Mortality and a combined endpoint (defined as mortality, need for coronary revascularization, myocardial infarction, rehospitalization for cardiac causes, or stroke) were evaluated with the help of death registry data, chart review, or telephone interviews. The average follow-up period was 1177 days (ranging from 1001 to 1328 days). The mortality rate was 10.2% and the combined endpoint rate was 31%. This study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1996, and people of the final study population who were contacted by telephone gave informed consent for inclusion.

Statistical analysis

All statistical analyses were performed using SPSS 18.0 (International Business Machines Corporation, Armonk,

New York, USA) and MedCalc 11.3 (Med Calc Software bvba, Mariakerke, Belgium) statistical software packages. Continuous data are given as mean and SD or median and interquartile range, dichotomous variables as percentages. The *t*-test, Mann–Whitney *U*-test, and the χ^2-test were used for group comparisons. The prognostic value of each variable was assessed univariately by means of Kaplan–Meier survival rate analysis, and differences in survival were assessed using the log-rank test. Biomarkers were grouped as tertiles in Kaplan–Meier survival analysis. Additionally, a multivariate Cox regression analysis was performed. We included only variables with a *P* value less than 0.1 in univariate analysis into sex-adjusted and age-adjusted multivariate Cox regression model. For assessing the prognostic performance, we further performed receiver operating characteristics (ROC) curve analysis for each biomarker. For the statistical comparison of ROC curves, the method of De Long was used. All statistical testings were carried out two-sided, and *P* values less than 0.05 were considered statistically significant.

Results

Univariate prognostic value of biomarkers, clinical variables, and traditional risk factors

Univariate Kaplan–Meier analysis (see Table 2) showed that three-vessel CAD and a reduced left ventricular function predicted both mortality and the combined clinical endpoint. The traditional risk markers apart from impaired renal function at the time of CAG were of no prognostic relevance for the prediction of outcome. Previous coronary bypass surgery or coronary intervention only predicted mortality. The newer biomarkers NT-proBNP, hs-CRP, and γ-GT were all significant predictors of mortality; however, only NT-proBNP was a significant predictor of the combined endpoint (see Fig. 1 and Table 2).

Table 2 Predictors of outcome: univariate Kaplan–Meier analysis log-rank test results

Variable	*P*-value mortality	*P*-value combined endpoint
NT-proBNP	**<0.001**	**<0.001**
γ-GT	**0.004**	0.679
hs-CRP	**0.004**	0.341
AST	0.089	0.227
ALT	0.119	0.282
Cholesterol	0.620	0.075
LDL	0.408	0.127
Triglycerides	0.219	0.854
Creatinine	**0.029**	0.336
LDL/HDL ratio	0.849	0.165
Angina pectoris symptoms	0.082	0.439
Hypertension	0.901	0.717
Status post CABG/PCI	**0.002**	0.347
Three-vessel disease	**0.003**	**0.001**
eGFR <60 ml/min/1.73 m^2	**0.009**	0.183
Family history (positive)	0.353	0.588
Diabetes mellitus	0.069	0.736
Smoker	0.542	0.111
Decreased LVEF	**<0.001**	**0.043**

P-values <0.05 are given in bold.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; decreased LVEF, decreased left ventricular ejection fraction (<60% in levocardiography or <50% in echocardiography); eGFR, glomerular filtration rate calculated by modification of diet in renal disease equation; γ-GT, gamma-glutamyl transferase; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention; TG, triglycerides.

Prognostic significance of traditional risk factors, clinical variables, and biomarkers in multivariate analysis

In the age-adjusted and sex-adjusted multivariate analysis, previous coronary artery bypass grafting or coronary intervention and all newer biomarkers (NT-proBNP, hs-CRP, γ-GT) remained independent risk markers for mortality with NT-proBNP revealing the highest odds ratio (5.23) of all variables in the model remaining (see Fig. 2). In age-adjusted and sex-adjusted multivariate Cox regression analysis for the prediction of the combined endpoint, only CAD severity and NT-proBNP significantly predicted the outcome, and NT-proBNP was the strongest independent predictor (odds ratio 2.92) among all variables remaining in this model (see Fig. 3).

ROC analysis for NT-proBNP compared with other biomarkers for prediction of mortality and morbidity

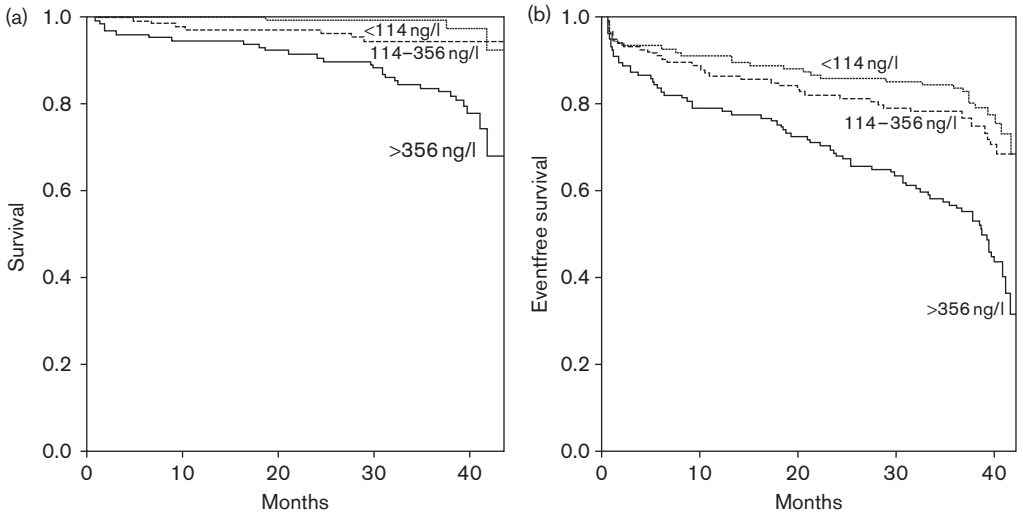
In the ROC curve analysis for the prediction of mortality, NT-proBNP revealed a good predictive accuracy [area under receiver operating characteristics curve (AUC) of 0.81], which was significantly better than that of γ-GT ($P = 0.017$), but not of hs-CRP ($P = 0.072$; see Table 3). hs-CRP and γ-GT were significant and independent, although they are weaker predictors of mortality in patients with stable CAD. At a NT-proBNP cut-off point of 356 ng/l, the sensitivity was 70% and the specificity was 71% for the prediction of mortality (see Table 3).

Despite being a significant predictor of the combined clinical endpoint, the NT-proBNP AUC for predicting the combined clinical endpoint was markedly lower (0.54: 95% confidence interval: 0.47–0.61) indicating poor predictive performance on routine use. The AUCs of hs-CRP (0.50) and γ-GT (0.48) for predicting the combined endpoint indicate that both markers are worthless tests in this indication.

Discussion

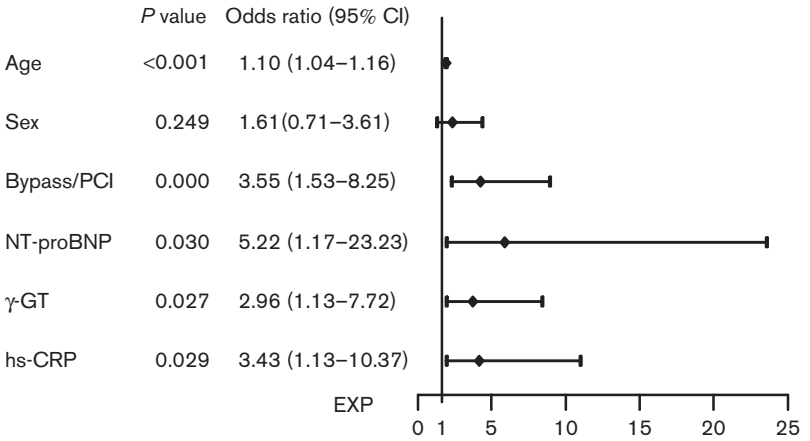
In a previously published study [16], comparing NT-proBNP, hs-CRP, and γ-GT as predictors of CAD severity assessed by CAG, only NT-proBNP was a statistically significant independent predictor of CAD in patients with clinically suspected CAD who were referred for CAG. Its predictive value as the most informative biochemical marker tested, however, was small compared with traditional risk factors. The present study extends these findings and demonstrates that NT-proBNP was the superior marker for risk stratification during an average 3.2-year follow-up in patients with angiographically documented proven stable CAD. NT-proBNP was

Fig. 1



N-terminal pro B-type natriuretic peptide Kaplan–Meier curves for prediction of mortality (a) and the combined endpoint (b).

Fig. 2

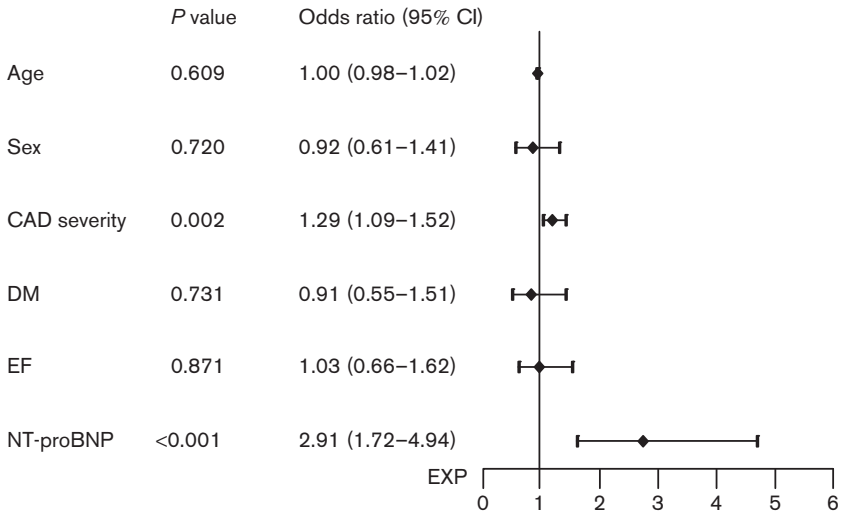


Cox regression model for the prediction of mortality. Odds ratios are given per year for age and for the comparison of first vs. third tertile for biomarkers. CI, confidence interval; Bypass/PCI, previous aortocoronary bypass grafting or percutaneous coronary intervention; γ-GT, gamma-glutamyl transferase; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide.

also superior compared with traditional risk factors and markers for estimating prognosis in this patient group.

This follow-up study in patients with angiographically verified stable CAD is unique as it is the first comparative study of NT-proBNP, hs-CRP, and γ-GT in the context of conventional risk factors and angiographic, hemodynamic, and clinical characteristics for the prediction of morbidity and mortality in long-term follow-up. In contrast to the majority of published studies on risk prediction in stable CAD, the biomarkers were measured routinely in fresh samples without storage of blood samples. In other studies, samples have been stored for many years before biomarker measurement without demonstrating analyte stability under these storage conditions [17]. In contrast, sample stability is not an issue in our study, and the reported discriminator values can be used in clinical routine without verification of freshly drawn blood samples. Our study has several key findings: (a) of all tested biomarkers, clinical variables, and traditional risk factors, NT-proBNP baseline concentrations were the strongest independent predictors of morbidity and

Fig. 3



Cox regression model for the prediction of the combined endpoint. Odds ratios are given per year for age and for the comparison of first vs. third tertile for biomarkers. CI, confidence interval; CAD, coronary artery disease; DM, diabetes mellitus; EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 3 Performances of NT-proBNP, hs-CRP, and γ-GT for the prediction of mortality

	NT-proBNP	hs-CRP	γ-GT
Cut-off value (>2nd tertile)	356 ng/l	4.5 mg/l	40 U/l
Sensitivity	70% (CI 54–84)	55% (CI 38–71)	56% (CI 38–72)
Specificity	71% (CI 66–75)	69% (CI 64–74)	69% (CI 64–74)
PPV	21% (CI 14–29)	16% (CI 10–24)	16% (CI 10–23)
NPV	96% (CI 92–98)	94% (CI 90–96)	94% (CI 90–97)
+LR	2.4 (CI 1.9–3.0)	1.8 (CI 1.3–2.4)	1.8 (CI 1.3–2.4)
−LR	0.42 (CI 0.30–0.70)	0.65 (CI 0.40–1.0)	0.64 (CI 0.40–1.0)
AUC	0.81 (CI 0.77–0.85)	0.71 (CI 0.66–0.76)	0.68 (CI 0.63–0.73)

95% confidence intervals are given in parentheses.
AUC, area under receiver operating characteristics curve; CI, confidence interval; γ-GT, gamma-glutamyl transferase; hs-CRP, high-sensitivity C-reactive protein; −LR, negative likelihood ratio; +LR, positive likelihood ratio; NPV, negative predictive value; NT-proBNP, N-terminal pro B-type natriuretic peptide; PPV, positive predictive value.

mortality in multivariate analysis; (b) hs-CRP and γ-GT remained independent but much weaker predictors only of mortality in multivariate analysis; (c) traditional risk factors had no predictive value in this secondary prevention scenario; (d) in univariate analysis, renal function, CAD severity, and left ventricular function predicted outcome; and (e) previous coronary artery bypass grafting and percutaneous coronary interventions did not improve, but rather were risk markers for mortality in our patients with stable CAD in multivariate analysis.

Increasing information has become available with regard to the utility of BNP and NT-proBNP as prognostic markers in CAD [17–24]. Consistently in our population with angiographically verified stable CAD, we found that NT-proBNP baseline concentrations greater than 356 ng/l predicted mortality with an odds ratio of 5.2 compared with patients with concentrations lesser than 114 ng/l. ROC analysis revealed an AUC of 0.81 indicating acceptable predictive performance for routine use. The odds ratio for mortality is in the range of a previous report in stable CAD (6.80) using a comparable NT-proBNP discriminator value (> 400 ng/l) [18], and the AUC (0.76) is similar to the one reported by Ndrepepa *et al.* [22] in a more heterogeneous population of stable and unstable CAD. NT-proBNP was the only biomarker that significantly predicted survival and the combined clinical endpoint, although the predictive power for the combined endpoint was markedly lower than that for mortality. The results of ROC analysis suggest that NT-proBNP is probably only useful for predicting mortality and not for predicting the combined endpoint in clinical routine. As this is the first study comparing the prognostic value of NT-proBNP, hs-CRP, and of γ-GT in stable CAD, we cannot directly compare our results with

previous studies. NT-proBNP was the best predictor of mortality and morbidity in multivariate analysis, but we also found that hs-CRP and γ-GT are significant and independent, although weaker risk markers in univariate and multivariate survival analysis for predicting all cause mortality (odds ratios: γ-GT 2.96 and hs-CRP 3.43, respectively). Given the fact that these three biomarkers – as outlined in the Introduction – depict different aspects of the pathophysiology of atherosclerosis, our finding has a pathophysiological basis. NT-proBNP and hs-CRP, however, have been compared previously as risk markers in stable CAD and our results are in agreement with previous reports on different patient populations [19,20,21,23,24]. Huang *et al.* [20] reported that NT-proBNP and hs-CRP were additive risk markers for predicting cardiovascular events in 205 patients with suspected CAD referred for CAG. In the Heart and Soul Study [22] in which, in contrast to our study, the diagnosis of CAD was not based on CAG in all patients, NT-proBNP and hs-CRP remained independent significant predictors of events in multivariate analysis. Our study results are also consistent with the comparison of NT-proBNP and hs-CRP in the subpopulation of patients with stable CAD of the AtheroGene Study [24]. NT-proBNP was superior to hs-CRP for risk prediction in this population. Of the tested biomarkers in the Heart Outcomes Prevention Evaluation Study [23] that enrolled patients with known cardiovascular diseases or diabetes, NT-proBNP provided the best prognostic information in this secondary prevention population, and the predictive value of hs-CRP was markedly lower. In agreement with the latter study Omland *et al.* [19] reported that BNP was superior to hs-CRP and to conventional risk factors for estimating prognosis in patients with stable CAD. We confirm these results and assume – as also previously reported [2] – that the lower predictive performances of conventional risk factors compared with NT-proBNP observed in our study may be because of effective secondary prevention strategies, which were initiated during hospitalization for CAG at our Department of Cardiology. Our study confirms the independent, although comparatively lower prognostic value for mortality of γ-GT in CAD patients [11,12]. Similar to findings by Emdin *et al.* [11], γ-GT and hs-CRP were independent risk markers of mortality after adjustment for confounders in our population.

In conclusion, we found that NT-proBNP is a clinical relevant risk marker in stable well-characterized CAD patients being superior to hs-CRP and γ-GT as well as being independent of cardiovascular risk factors, coronary atherosclerosis severity, and cardiac function, which is a novel finding. NT-proBNP concentrations less than 356 ng/l identify patients with a low mortality with a high negative predictive value. NT-proBNP greater than 356 ng/l should alert for very careful clinical work-up with consequent treatment of traditional risk factors, heart failure, and CAD. However, the immediate therapeutic consequences of this promising risk marker in the individual patient with stable CAD remain to be demonstrated by future intervention trials based on NT-proBNP baseline concentrations.

Acknowledgements

Conflicts of interest

During recent years Johannes Mair received lecture honoraria (Roche Diagnostics, Siemens Medical Solutions) and consulting fees (Abbott Diagnostics, Philipps Health Care Incubator). All other authors have no conflicts of interest to declare regarding the content of the manuscript.

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