N-Terminal Pro–Brain Natriuretic Peptide and Other Risk Markers for the Separate Prediction of Mortality and Subsequent Myocardial Infarction in Patients With Unstable Coronary Artery Disease

A Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV Substudy

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Background—Biochemical markers are useful for prediction of cardiac events in patients with non–ST-segment-elevation acute coronary syndrome (ACS). The associations between *N*-terminal pro–brain natriuretic peptide (NT-proBNP) and other biochemical and clinical risk indicators, as well as their prognostic value concerning the individual end points of death and myocardial infarction (MI), were elucidated in a large cohort of ACS patients.

Methods and Results—NT-proBNP, troponin T, and C-reactive protein (CRP) were analyzed in blood samples obtained at a median of 9.5 hours from symptom onset in 6809 of 7800 ACS patients in the Global Utilization of Strategies To Open occluded arteries-IV (GUSTO-IV) trial. Levels of NT-proBNP were correlated independently with age, female gender, low body weight, diabetes, renal dysfunction, history of MI, heart failure, heart rate, ongoing myocardial damage, and time since onset of ischemia. Increasing quartiles of NT-proBNP were related to short- and long-term mortality that reached 1.8%, 3.9%, 7.7%, and 19.2%, ($P<0.001$), respectively, at 1 year. Levels of troponin T, CRP, heart rate, and creatinine clearance, in addition to ST-segment depression, were also correlated independently with 1-year mortality, but NT-proBNP was the marker with the strongest relation. In contrast, only troponin T, creatinine clearance, and ST-segment depression were independently related to future MI. The combination of NT-proBNP and creatinine clearance provided the best prediction, with a 1-year mortality of 25.7% with both markers in the top quartile vs 0.3% with both markers in the bottom quartile.

Conclusions—The use of NT-proBNP appears to add critical prognostic insight to the assessment of patients with ACS. (***Circulation*. 2003;108:275-281.**)

Key Words: angina ■ myocardial infarction ■ coronary disease ■ natriuretic peptides ■ mortality

Patients with acute coronary syndromes (ACS) without ST-segment elevation constitute a high-risk population with a mortality 1 year after the index event of 7% to 8%.[1] The risk for subsequent cardiac events can be estimated by the clinical history, ECG, and biochemical indicators of myocardial infarction (MI)[2] and dysfunction,[3] renal dysfunction,[4] and inflammatory activity.[2,5]

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Brain natriuretic peptide (BNP) is a neurohormone synthesized and released from the cardiac ventricles in response to increased wall tension.[6] The serum levels of BNP are increased in patients with heart failure, and these levels increase in proportion to the degree of left ventricular dysfunction.[7] BNP levels also increase after MI and in unstable angina pectoris.[8] BNP is produced as a prohormone, pro-BNP, which is enzymatically cleaved into BNP and the amino-terminal portion of the prohormone, NT-proBNP.[9] Recently, it has been shown that BNP,[10] as well as NT-proBNP,[11] levels obtained in the first few days after ACS provide independent, predictive information on mortality.[3,12,13]

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TABLE 1. Baseline Characteristics for Patient Strata According to Quartiles of NT-proBNP

	Quartiles of NT-proBNP, ng/L				
Characteristics	≤237	238–668	669–1869	>1869	*P*
Personal factors					
Age, y*	58.7±10.5	63.5±10.4	66.7±10.2	71.8±9.4	<0.001
Weight, kg*	79.8±13.4	78.3±13.5	77.1±12.9	73.6±13.8	<0.001
Female gender, % (n)	34.1 (581)	33.3 (565)	38.0 (645)	47.4 (806)	<0.001
Time from symptoms, h†	7.5 (4.2–13.4)	9.2 (4.8–16.2)	10.3 (5.5–17.5)	11.2 (5.9–17.5)	<0.001
Risk factors					
Current smoking, % (n)	28.5 (486)	24.8 (421)	21.2 (361)	15.7 (268)	<0.001
Hypertension, % (n)	44.5 (756)	50.8 (859)	53.9 (916)	57.9 (984)	<0.001
Hypercholesterolemia, % (n)‡	31.9 (514)	32.7 (525)	31.4 (508)	27.8 (448)	0.013
Diabetes mellitus, % (n)	13.7 (233)	19.0 (322)	22.6 (384)	28.4 (481)	<0.001
Creatinine, μmol/L†	82 (71–96)	83 (71–97)	87 (72–100)	94 (79–116)	<0.001
Previous cardiovascular disease					
Angina pectoris, % (n)	42.0 (714)	45.2 (759)	48.4 (817)	52.8 (891)	<0.001
MI, % (n)	17.9 (304)	28.0 (473)	33.5 (567)	42.9 (723)	<0.001
Revascularization, % (n)	11.3 (193)	16.2 (274)	17.5 (298)	15.9 (270)	<0.001
Heart failure, % (n)	2.8 (47)	5.0 (85)	6.6 (112)	15.4 (259)	<0.001
Stroke, % (n)	1.0 (17)	1.8 (31)	2.3 (40)	3.8 (65)	<0.001
Treatment at randomization					
ACE inhibitor, % (n)	25.3 (431)	27.9 (474)	32.9 (562)	39.1 (666)	<0.001
β-Blocker, % (n)	50.6 (863)	59.2 (1004)	61.4 (1047)	61.4 (1045)	<0.001
Aspirin, % (n)	79.9 (1361)	83.7 (1697)	86.0 (1467)	85.3 (1452)	<0.001
Risk markers at baseline					
Heart rate, bpm	70.1±14.5	69.0±14.2	70.1±15.2	75.4±17.1	<0.001
ST-segment depression >0.5 mm, % (n)	84.8 (1445)	78.1 (1326)	77.6 (1324)	83.2 (1416)	0.21
Troponin T, μg/L†	0.01 (0.01–0.09)	0.07 (0.01–0.3)	0.2 (0.03–0.6)	0.4 (0.1–0.9)	<0.001
CRP, mg/L†	2.7 (1.3–5.2)	3.4 (1.6–7.2)	4.4 (2.2–10.2)	7.6 (3.0–20.0)	<0.001

*Mean±SD.
†Median (25th–75th percentile).
‡History of hypercholesterolemia requiring medical therapy.

The present study evaluated the characteristics of patients with elevation of NT-proBNP and the prognostic information it provided in relation to ECG, biochemical markers, and other clinical risk indicators in a very large cohort of patients with non–ST-segment-elevation ACS.

Methods

Patient Selection and Randomized Treatment

The Global Utilization of Strategies To Open occluded arteries-IV (GUSTO-IV) trial included 7800 patients with non–ST-segment-elevation ACS from 458 centers in 24 countries during 1999 and 2000. The detailed design and main results of the trial have been published.[14] Eligible patients were ≥21 years of age with 1 or more episodes of angina lasting ≥5 minutes, within 24 hours of admission, and either a positive cardiac troponin test or ≥0.5 mm of ST-segment depression. The study was conducted in a double-blinded fashion, with patients randomly assigned to abciximab infusion for 24 hours or 48 hours or corresponding placebo infusion. All patients received aspirin for long-term treatment, as well as either unfractionated heparin infusion or subcutaneous dalteparin. Coronary angiography was not to be performed during or within 12 hours after the completion of study agent infusion. Myocardial infarction was defined as either a new Q-wave or creatinine kinase-MB value ≥3 times the normal upper limit, as previously presented in detail.[14] During 30 days of follow-up, mortality and the rate of all adjudicated MIs were recorded. At 12 months, only all-cause mortality information was collected.

Laboratory Analyses

Venous blood samples were obtained by direct venous puncture at randomization. After centrifugation, serum was frozen at −20°C in aliquots and sent for central laboratory analyses of creatinine kinase-MB levels. One aliquot of the samples at baseline was stored at −70°C and sent in batches of 500 to the Department of Clinical Chemistry, University of Uppsala, Uppsala, Sweden, for analyses of troponin T, C-reactive protein (CRP), and NT-proBNP. One batch was unfortunately lost during transportation. The levels of troponin T were determined by a third-generation assay on an Elecsys (Roche Diagnostics), with a detection limit 0.01 μg/L. CRP concentrations were measured with a chemiluminescent enzyme-labeled immunometric assay (Immulite CRP, Diagnostic Products Corp), with a detection limit of 0.1 mg/L. Serum NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostics). The analytical range extends from 20 to 35 000 ng/L. At the central laboratory, the total coefficient of variation was 3.3% (n=21) at a level of 209 ng/L and 3.0% (n=21) at a level of 7431 ng/L. In a healthy population (n=407) matched to the FRISC II population[15] for age (range, 40 to 75 years) and gender (32% female), the 97.5 percentile was 290 ng/L. Serum creatinine was analyzed at local laboratories for 7703 patients. The creatinine clearance rate was

TABLE 2. Associations Between Levels of NT-proBNP*, Clinical Variables, and Biochemical Markers at Baseline

		Multiple Linear Regression	
Baseline Factors	Correlation, *R*	B	95% Confidence Interval
Personal factors			
Age, y	0.46	0.040	0.037 to 0.042
Weight, kg	−0.18	−0.012	−0.014 to −0.01
Gender		0.26	0.20 to 0.32
Time from symptoms, h	0.13	0.007	0.003 to 0.01
Risk factors			
Current smoking		0.069	−0.001 to 0.14
Hypertension		0.082	0.022 to 0.14
Hypercholesterolemia†		−0.098	−0.16 to 0.04
Diabetes mellitus		0.08	0.013 to 0.15
Creatinine levels	0.20	0.0013	0.001 to 0.002
Previous cardiovascular disease			
Angina pectoris		0.11	0.05 to 0.17
MI		0.35	0.29 to 0.42
Revascularization		0.099	0.021 to 0.18
Heart failure		0.45	0.34 to 0.55
Stroke		0.14	−0.037 to 0.32
Treatment at randomization			
ACE inhibitor		0.14	0.08 to 0.21
β-Blocker		0.13	0.09 to 0.2
Aspirin		0.002	−0.05 to 0.09
Risk marker			
Heart rate, bpm	0.14	0.07	0.005 to 0.009
ST-segment depression >0.5 mm		0.06	−0.01 to 0.13
Troponin T levels*	0.48	0.35	0.34 to 0.37
CRP levels*	0.34	0.19	0.16 to 0.21

*Logarithmically transformed skewed variables.
†Hypercholesterolmia requiring pharmacological treatment.

calculated with the Cockcroft and Gault equation: {(140−age)×[weight (kg)]}/serum creatinine (μmol/L).[16]

Statistical Methods

The patients were divided into quartiles on the basis of their NT-proBNP levels. Means were expressed with 1 SD for continuous variables, and medians were presented with the 25th to 75th percentiles for skewed variables. Differences in categorical baseline variables between quartiles were evaluated with χ^2 tests for trend. Differences between mean or median values for continuous variables were evaluated with 1-way ANOVA or Kruskal-Wallis tests, as appropriate. Levels of NT-proBNP, CRP, and troponin T were highly skewed and thus, were logarithmically transformed for calculation of independent associations between the markers in a multiple linear regression analysis. Kaplan-Meier estimates were used for evaluation of the occurrence of the individual end points of death and MI after enrollment. Troponin T values <0.01 μg/L (lowest discrimination limit),[5] CRP values >10 mg/L (75th percentile),[2] and a creatinine clearance rate <51 mL/min (25th percentile)[4] were considered abnormal. Logistic regression analyses were performed for evaluation of the significance of predictors of MI at 30 days and mortality at 1 year, with the following variables included: age >65 years; body weight <77 kg (mean); gender; creatinine clearance ≤51 mL/min; heart rate >68 beats/min (bpm; median); time from symptom onset to randomization; randomized abciximab treatment; current smoking; history of hypertension, hypercholesterolemia, diabetes mellitus, and heart failure; previous angina pectoris, MI, and revascularization; treatment with aspirin, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors at baseline; ST-segment depression >0.5 mm; troponin T >0.01 μg/L; CRP>10 mg/L; and quartiles of NT-proBNP. All variables with $P<0.10$ were then forced into the multivariable analyses.

Results

Baseline Characteristics

NT-proBNP analyses from serum samples obtained at randomization were available for 6809 (87.3%) of the patients in the GUSTO-IV trial. The mean age of these patients was 65.0±11.0 years, and 38.1% were women. There was no influence of the randomized abciximab treatment on either NT-proBNP levels or on outcome in any subgroup based on NT-proBNP levels. Therefore, the randomized groups were combined in the present report.

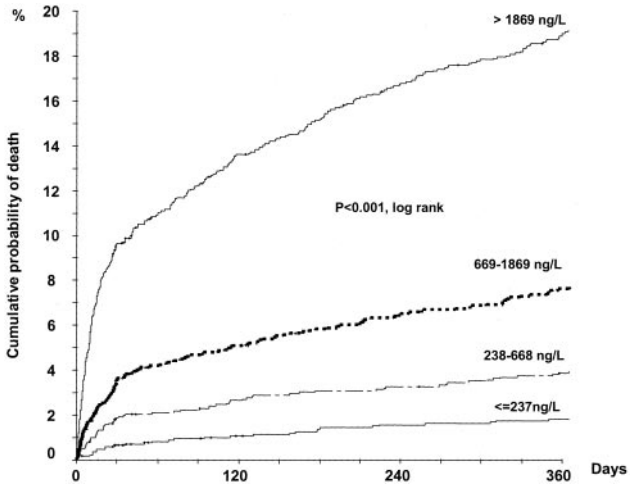

Figure 1. Kaplan-Meier survival curves regarding probability of death during 1 year for patient strata, according to quartiles of NT-proBNP.

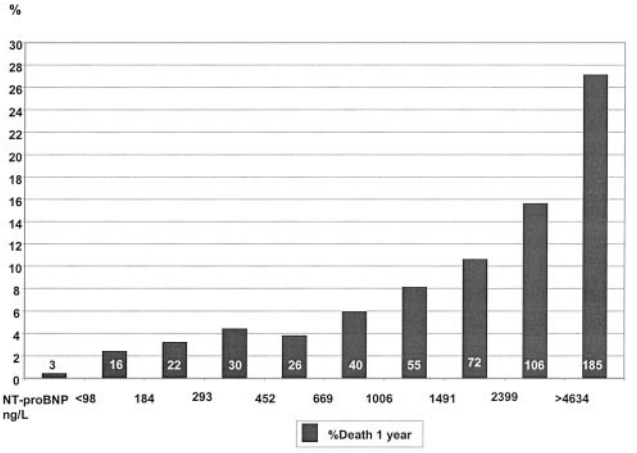

Figure 2. Mortality at 1-year follow-up among strata of patients, according to deciles of NT-proBNP levels. Number of deaths in each decile is given at the bottom of the bars.

Relations to Clinical and Biochemical Factors

The median time from the onset of the qualifying episode of ischemic chest pain to randomization was 9.5 (5.0 to 16.5) hours. NT-proBNP levels ranged from 5.3 to 35 000 ng/L, with a median of 669 ng/L (interquartile range, 237 to 1869 ng/L). Increasing quartiles of NT-proBNP were associated with a large number of baseline clinical factors as well as biochemical markers (Table 1). After logarithmic transformation of skewed variables, the independence of the associations was evaluated in a multiple linear regression analysis (Table 2). Increasing levels of NT-proBNP were independently and positively associated with age, female gender, angina pectoris, diabetes mellitus, hypertension, previous MI, heart failure, heart rate, and ST-segment depression at baseline but negatively with body weight and hypercholesterolemia. NT-proBNP levels were also associated with time from symptom onset and the magnitude of myocardial necrosis ie, troponin elevation, as well as with renal dysfunction and inflammatory activity, as reflected by the elevation of creatinine and CRP.

Outcome

Mortality

There was increased mortality among patients with increasing quartiles of NT-proBNP (Figure 1). The Kaplan-Meier survival curves for the quartiles separated early, and already at 48 hours after randomization, the difference in mortality between the quartiles was statistically significant ($P=0.001$), with a mortality of 0.2% (3), 0.4% (6), 0.4% (7), and 1.4% (23), respectively. The separation of the curves continued through the first year after the index event ($P<0.001$, log rank). Thus, at 1-year follow-up, the mortality was 1.8% (31), 3.9%(66), 7.7%(131), and 19.2% (327) in the respective quartiles. Quartiles of NT-proBNP predicted 1-year mortality in patients enrolled <5 hours (first quartile) after symptom onset (1.8%, 4.6%, 8.6%, 24%; $P<0.001$), as well as patients enrolled for >16.5 hours after symptom onset (2.3%, 3.0%, 6.2%, 15.3%; $P<0.001$). Mortality increased exponentially throughout the entire spectrum of NT-proBNP levels, with a mortality of 0.4% (3) in the lowest decile (≤98 ng/L) and 27.1% (185) in the highest decile (> 4634 ng/L) (Figure 2).

In a multivariable logistic regression analysis adjusting for a large number of predictors of long-term mortality, increasing quartiles of NT-proBNP still independently contributed to the prediction of 1-year mortality (Figure 3). There was a significant interaction only with age, with a greater predictive value of NT-proBNP quartiles for patients below compared with above 65 years of age. Thus, there was an 11-fold increased risk of death for patients <65 years of age in the top versus the bottom quartile of NT-proBNP compared with a 3-fold risk for patients >65 years of age.

Also, heart rate >68 bpm, troponin-T levels >0.01 μg/L, CRP >10 mg/L, ST-segment depression >0.5 mm, and creatinine clearance <51 mL/min. contributed to the prediction of mortality. With NT-proBNP entered into the same equation as a dichotomous variable (> vs ≤669 ng/L), the odds ratio was 1.97 (95% confidence interval, 1.48 to 2.61). The results regarding NT-proBNP were unchanged when other cutoff levels for troponin T, CRP, or creatinine clearance were used or when these or other variables were introduced in a continuous format.

Myocardial Infarction

The risk of subsequent MI after the index event increased with increasing quartiles of NT-proBNP, with an MI rate of 2.7% (46), 5.4% (91), 5.7% (98), and 7.5% (128) ($P<0.001$) for the respective quartile at 30-day follow-up. However, in a multivariable logistic regression analysis, previous MI, creatinine clearance <51 mL/min., angina pectoris, troponin-T elevation (>0.01 μg/L), and ST-segment depression at baseline, but not the level of NT-proBNP, constituted independent predictors of MI at 30 days (Figure 3). The results were unchanged with NT-proBNP as a continuous variable.

Combination of Markers

As levels of NT-proBNP, as well as elevated troponin T, CRP, creatinine clearance, and heart rate were independent predictors of 1-year mortality, the prognostic value of combinations of these markers was also evaluated. A very low mortality

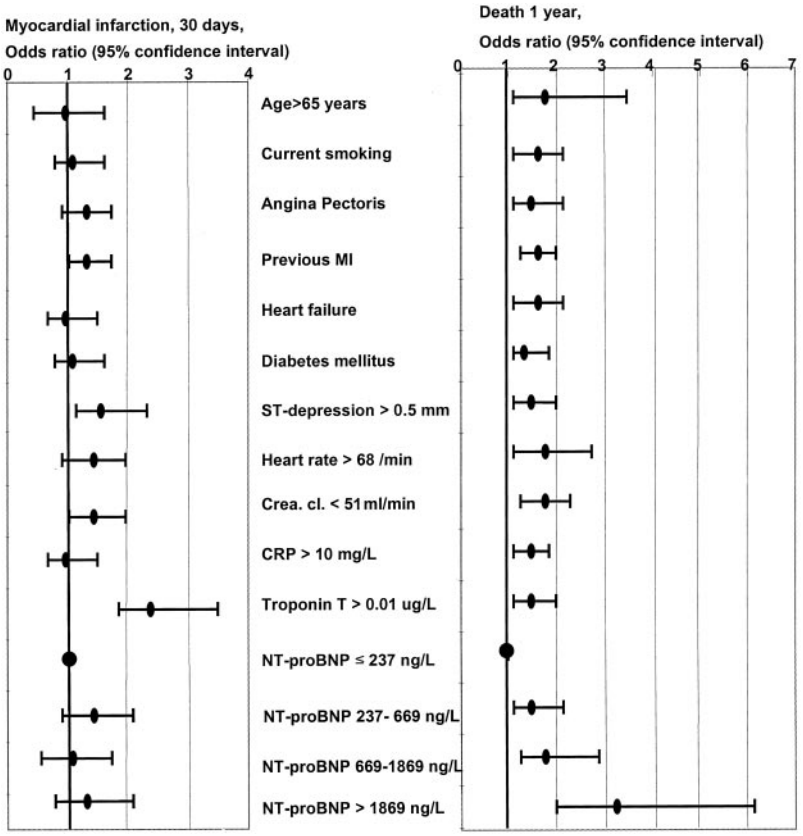

Figure 3. Multiple logistic regression analyses for the prediction of MI at 30 days and death at 1-year follow-up.

was found in patients with NT-proBNP in the bottom quartile in combination with creatinine clearance in the top quartile (0.3%) or in combination with troponin T, CRP, or heart rate in the bottom quartiles: 1.6%, 1.6%, and 1.8%, respectively (Figure 4). The highest 1-year mortality, 25.7%, was found in patients with levels of NT-proBNP in the top quartile and creatinine clearance in the bottom quartile. A similar high mortality was found in patients with NT-proBNP in combination with troponin T, CRP levels, or heart rate in the top quartiles: 22.3%, 23.4%, and 25.6%, respectively.

Discussion

Relations to Baseline Characteristics

It is well recognized that levels of BNP increase with increasing degree of ventricular enlargement and dysfunction in patients with heart failure and after MI.[7] In a population-based cohort, it has recently been shown that BNP increases considerably with age and is higher in women than in men.[17] In the present study, from a large cohort of patients with non–ST-segment-elevation ACS, we demonstrated that baseline levels of NT-proBNP are independently related not only to age and female gender but also to low body weight and renal dysfunction. Part of this relation might be explained by an increased sensitivity to volume overload, as BNP levels have been shown to be secreted in response to raised intracardiac pressure,[18] irrespective of the cause. The present study also demonstrated that levels of NT-proBNP were independently related to clinical factors indicating any kind of cardiovascular damage or dysfunction, supporting the concept that elevation of BNP (or NT-proBNP) is a general indicator of reduced cardiac performance rather than a specific indicator of systolic dysfunction.[19] Moreover, our study demonstrated that ongoing myocardial damage (ie, minimal troponin elevation), time since start of myocardial ischemia and damage, and the inflammatory response (ie, CRP elevation) were related to the magnitude of elevation of NT-proBNP, further supporting the concept of BNP as a sensitive and rapid marker of reduced cardiac performance. This is in accordance with the recent report that BNP levels increase as a result of temporary occlusion of a coronary artery in conjunction with a coronary intervention,[20] even when intracardiac filling pressures remain unchanged.[21]

Prediction of the Individual End Points of Death and MI

Recently, it has been shown that elevation of BNP as well as NT-proBNP levels obtained after the acute phase (median, 40 to 72 hours after symptom onset) in patients with a broad range of ACS independently predicts mortality.[3,13] In the present study, we extended these results in a considerably larger population of non–ST-segment-elevation ACS for NT-proBNP levels already obtained on admission at a median of 9.5 hours after symptom onset, in accordance with a previous study from our group in an unselected chest pain population.[22] Accordingly, we could demonstrate that NT-proBNP predicted 1-year mortality as well in patients with blood samples obtained within 5.0 hours (first quartile) as in those obtained >16.6 hours (fourth quartile) after symptom onset. The present study also demonstrated that any elevation of NT-proBNP >97.5 percentile, 290 ng/L, in a healthy

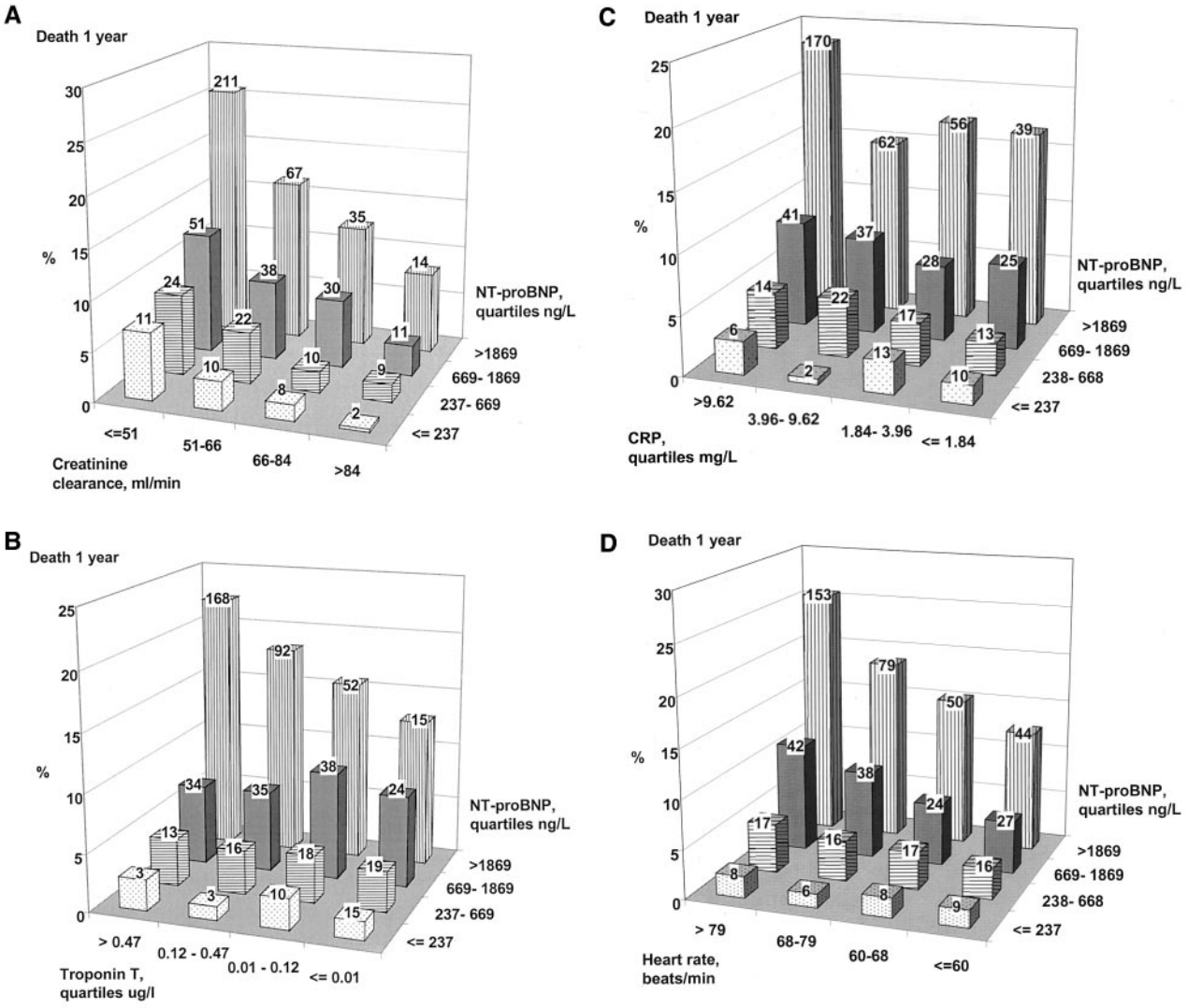

Figure 4. Mortality at 1-year follow-up among strata of patients, according to quartiles of NT-proBNP and quartiles of creatinine clearance (A), troponin T (B), CRP (C), and heart rate (D). The number of deaths is given at the top of each bar.

population matched for age and gender, was associated with an increased risk of death after the index event.

We also extend previous results on the predictive importance of NT-proBNP to include most subgroups of non–ST-segment-elevation ACS patients on the basis of clinical history, creatinine clearance, and biochemical markers of MI and inflammation. Elevation of NT-proBNP was an even stronger prognostic marker in the low- versus high-risk patients on the basis of other risk indicators, as indicated by the interaction with age.

Despite the fact that the level of NT-proBNP was independently related to most of the baseline characteristics and biochemical markers, the NT-proBNP level was still the strongest independent indicator of mortality in the multivariate analysis. Also, elevation of troponin T, CRP, and heart rate and a reduced creatinine clearance rate independently predicted increased mortality. In accordance with a recently published study, the combination of several of these markers allowed a very good stratification of the future risk of fatal events.[23] Unlike BNP, NT-proBNP is not cleaved by neutral endopeptidase and might be more dependent on clearance via the clearance receptor, which is located mainly in the kidney. Therefore, NT-proBNP levels could potentially be less useful in patients with renal insufficiency. However, the combination of quartiles of increasing NT-proBNP levels and quartiles of decreasing creatinine clearance rates provided the strongest prediction of long-term mortality. Among patients in every quartile of creatinine clearance, mortality was increased with increasing quartiles of NT-proBNP. NT-proBNP levels also provided prognostic information beyond a history of and clinical signs of heart failure. The combination of quartiles of NT-proBNP and quartiles of CRP or troponin T provided a similar strong prediction of mortality. Interestingly, however, elevated levels of troponin T seemed to contribute to increased mortality only for patients with NT-proBNP levels in the top quartile. Thus, ACS patients without a large amount of circulating natriuretic peptides seem to tolerate even moderately large MIs with a low risk of lethal outcome.

Identification of high-risk patients with high levels of NT-proBNP might be helpful for selection of more intense pharmacologic or interventional treatment. It has been shown that carvedilol treatment is particularly effective in patients with

heart failure and elevated levels of NT-proBNP.[24] It remains to be investigated whether patients with high levels of NT-proBNP might derive a particular benefit from ACE inhibition, early coronary interventions, implantable cardioverter-defibrillators, or other therapeutic modalities.

In contrast to ST-segment depression and troponin elevation at baseline, the risk of subsequent MI at 30-day follow-up was not independently predicted by increasing levels of NT-proBNP, in accordance with previous studies.[13] The reason for this finding might be that BNP is a regulatory myocardial hormone that is not involved in the processes related to the rupture of coronary plaques or formation of coronary thrombi. In contrast, an elevation of BNP has been shown to predict sudden death in patients with heart failure.[25] Thus, the release of natriuretic peptides from ventricular myocytes, in response to increased wall tension due to ischemia or volume overload, might indicate a propensity to develop ventricular arrhythmias, ventricular rupture, or terminal heart failure rather than MI. Unfortunately, the causes of death were not available in the current trial. Other potential limitations are those inherent in performing a study within a clinical trial. GUSTO-IV included ACS patients with selected risk criteria, such as ST-segment depression and troponin elevation. The results are therefore primarily applicable to a patient population with similar characteristics. However, these characteristics are representative of a more general ACS population and are not likely to affect the results.

Conclusion

Levels of NT-proBNP early after symptom onset in suspected non–ST-segment-elevation ACS are independently associated with age, female gender, and clinical and biochemical factors indicating a history of cardiovascular and renal disease, ongoing myocardial ischemia, time since onset of ischemia, and the inflammatory response to the acute event. Regardless of the presence or absence of these and other baseline risk indicators, elevation of NT-proBNP is an independent, strong predictor of short- and long-term mortality, with a continuous increase in mortality at 1 year in relation to these levels. The combination of NT-proBNP with creatinine clearance rate, heart rate, or levels of troponin T or CRP provides an even better risk stratification concerning mortality in ACS patients.

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