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Chapter 7

N-terminal pro–brain natriuretic peptide for additional risk stratification in patients with non–ST-elevation acute coronary syndrome and an elevated troponin T: An Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) substudy

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ABSTRACT

Background New evidence has emerged that the assessment of multiple biomarkers such as cardiac troponin T (cTnT) and N-terminal pro–brain natriuretic peptide (NT-proBNP) in patients with non–ST-elevation acute coronary syndrome (nSTE-ACS) provides unique prognostic information. The purpose of this study was to assess the association between baseline NT-proBNP levels and outcome in patients who have nSTE-ACS with an elevated cTnT and to determine whether patients with elevated NT-proBNP levels benefit from an early invasive treatment strategy.

Methods Baseline samples for NT-proBNP measurements were available in 1141 patients who have nSTE-ACS with an elevated cTnT randomized to an early or a selective invasive strategy. Patients were followed-up for the occurrence of death, myocardial infarction (MI), and rehospitalization for angina.

Results We showed that increased levels of NT-proBNP were associated with several indicators of risk and severe coronary artery disease. Mortality by 1 year was 7.3% in the highest quartile (≥1170 ng/L for men, ≥2150 ng/L for women) compared with 1.1% of patients in the lower 3 quartiles ($P < 0.0001$). N-terminal pro–brain natriuretic peptide (highest quartile vs lower 3 quartiles) was a strong independent predictor of mortality (hazard ratio 5.0, 95% CI 2.1-11.6, $P = 0.0002$). However, NT-proBNP levels were not associated with the incidence of recurrent MI by 1 year. Furthermore, we could not demonstrate a benefit of an early invasive strategy compared with a selective invasive strategy in patients with an elevated NT-proBNP level.

Conclusions We confirmed that NT-proBNP is a strong independent predictor of mortality by 1 year but not of recurrent MI in patients who have nSTE-ACS with an elevated cTnT. We could not demonstrate a benefit of an early invasive strategy compared with a selective invasive strategy.

INTRODUCTION

Patients presenting with non–ST-elevation acute coronary syndrome (nSTE-ACS) represent a heterogeneous population in terms of short- and long-term prognosis. Among the powerful independent predictors of adverse outcome in these patients are elevated plasma levels of natriuretic peptides.

Persistent or transient thrombotic occlusion at the site of plaque rupture or erosion may lead to episodes of myocardial ischemia, which, in turn, may lead to irreversible myocardial damage.[1] Ischemia and myocardial damage can cause transient and permanent increase in wall tension and myocardial stretch, which stimulates B-type natriuretic peptide (BNP) neurohormone synthesis in the ventricular myocardium.[2] Furthermore, it has been shown that myocardial ischemia by itself can stimulate BNP synthesis and release.[3,4]

Several studies have shown that there is a strong association between plasma levels of BNP and N-terminal pro–brain natriuretic peptide (NT-proBNP) and adverse outcomes in patients with nSTE-ACS.[5-9] However, it is unclear whether a routine early invasive or a noninvasive treatment strategy among patients with high levels of BNP or NT-proBNP may improve outcome.[7,10-13] New evidence has emerged that simultaneous assessment of multiple biomarkers such as cardiac troponin T (cTnT) and NT-proBNP in patients with nSTE-ACS provides unique prognostic information.[6,14,15] We assessed the association between baseline NT-proBNP levels and outcome in a well-defined patient population with nSTE-ACS and an elevated cTnT.

METHODS

Between July 2001 and August 2003, a total of 1200 patients from 42 Dutch hospitals, 12 of which were high-volume centers with percutaneous intervention and on-site cardiac surgery, were enrolled in the ICTUS trial. Patients were randomly assigned to an early invasive strategy or a selective invasive strategy. The details of the design and the main results of the randomized ICTUS trial have been published previously.[16] Briefly, eligible patients had to meet 3 criteria: (1) symptoms of ischemia that were increasing or occurring at rest, with the last episode occurring no longer than 24 hours before randomization; (2) an elevated serum cTnT (≥0.03 μg/L) (Roche Diagnostics GmbH, Mannheim, Germany); and (3) either ischemic changes on the electrocardiogram (defined as ST depression, or transient ST elevation ≥0.05 mV, or T-wave inversion ≥0.2 mV in 2 contiguous leads) or a documented history of coronary artery disease (CAD). Main exclusion criteria were age <18 years or >80 years, ST-elevation myocardial infarction (MI) in the last 48 hours, an indication for reperfusion therapy, hemodynamic instability or overt congestive heart failure, and increased risk of bleeding.

Patients assigned to the early invasive strategy were scheduled to undergo angiography within 24 to 48 hours after randomization and percutaneous revascularization when appropriate based on the coronary anatomy. Cardiac surgery was recommended in case of extensive 3-vessel disease or significant left main stem disease and was to be performed as soon as possible during initial hospitalization. Patients assigned to the selective invasive strategy were managed medically. These patients were to undergo angiography and subsequent revascularization only in case of refractory unstable angina despite optimal medical treatment, hemodynamic or rhythmical instability, or significant ischemia on the predischarge exercise test.

This study complied with the principles in the Declaration of Helsinki and was approved by all the local institutional review boards. All patients gave written informed consent.

N-terminal pro–brain natriuretic peptide study

Baseline samples were obtained at admission and were stored for central analyses of cTnT, NT-proBNP, and creatinine. Blood samples were collected in tubes without anticoagulant. The samples were then centrifuged, and serum was stored frozen in aliquots at –20°C to –80°C at the enrolling site until shipped to the clinical chemistry core laboratory at the AMC in Amsterdam, where they were maintained at –80°C.

Serum cTnT (third-generation assay) and serum NT-proBNP (sandwich immunoassay) were determined using an Elecsys 2010 (Roche Diagnostics GmbH). The analytic range of NT-proBNP assay extends from 5 to 35 000 ng/L. The total coefficient of variation was 2.1% at a level of 181 ng/L and 1.8% at a level of 572 ng/L.

Other examinations

Echocardiograms were obtained before discharge, and the left ventricular ejection fraction was visually assessed. In patients randomized to the early invasive strategy, the extent of CAD was assessed on the first coronary angiogram. A ≥70% diameter stenosis in at least 1 of the segments in the respective vessel area (right coronary artery, left anterior descending artery, and diagonal and circumflex artery) was considered significant with respect to the traditional 1-vessel, 2-vessel, and 3-vessel disease classification. Left main was considered significant in the event of a diameter stenosis exceeding 50%.

End-point definitions

The primary end point of the ICTUS trial was a composite of death, recurrent MI, or rehospitalization for angina within 1 year after randomization. Myocardial infarction was defined as documented myocardial necrosis either in the setting of myocardial ischemia or in the setting of percutaneous revascularization following the recommendations of the consensus committee for the definition of MI.[17] All end points were adjudicated by members of an independent clinical end-point committee who were unaware of patients' treatment assignments.

Statistical analyses

Men and women were classified separately into quartiles according to NT-proBNP level. Continuous baseline variables with normal distribution are expressed as mean ± SD, and data with a nonnormal distribution are given as median value (25th-75th percentile). A comparison of the baseline characteristics was done using analysis of variance or the Kruskall-Wallis analysis of variance median test (continuous variables) or the Pearson χ^2 test (categorical variables), as appropriate. χ^2 Test for trend was used for the association between NT-proBNP levels and severity of CAD and left ventricular function at discharge.

Cox regression analysis was performed to identify the predictive value of NT-proBNP on mortality and MI. Hazard ratios comparing the highest quartile of NT-proBNP with

the lower 3 quartiles were calculated. Three different Cox regression models were constructed. Model 1 describes the predictive value of NT-proBNP for death or MI without any adjustments for other covariates. Model 2 includes adjustment for all baseline characteristics that were statistically significantly ($P < 0.05$) associated with death or MI, whereas model 3 includes adjustment for all baseline variables mentioned in table 1 with the exception of variables indicating drug therapy other than aspirin at admission.

Although this study was not powered to assess the association between treatment strategy and mortality, we performed an exploratory survival analysis for illustrative purposes. Event rates at 1 year were estimated from the Kaplan-Meier curve. The relative risk and the 95% CI were calculated with the Kaplan-Meier mortality estimates at 1 year. The significance of differences in event rates between treatment groups was assessed with the use of the log-rank test. All statistical tests were 2-tailed, and a P value of < 0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 12.0 for Windows, SPSS Inc, Chicago, IL).

Table 1. Baseline clinical characteristics according to the quartile of NT-proBNP

	NT-proBNP				
	First quartile ≤217 ng/L (men) ≤407 ng/L (women) (n = 285)	**Second quartile** 218-512 ng/L (men) 408-928 ng/L (women) (n = 285)	**Third quartile** 513-1169 ng/L (men) 929-2149 ng/L (women) (n = 285)	**Fourth quartile** ≥1170 ng/L (men) ≥2150 ng/L (women) (n = 286)	**p-value**
Age (years)	57 (10)	61 (10)	64 (9)	67 (10)	<0.001
Females,	77 (27%)	77 (27%)	77 (27%)	77 (27%)	
Clinical history					
Myocardial infarction	57 (20%)	46 (16%)	75 (26%)	86 (30%)	<0.001
Percutaneous coronary intervention	34 (12%)	28 (10%)	39 (14%)	33 (12%)	0.56
Coronary-artery bypass grafting	15 (5%)	24 (8%)	31 (11%)	31 (11%)	0.06
Risk factors					
Hypertension	86 (30%)	111 (39%)	123 (43%)	125 (44%)	0.003
Diabetes Mellitus	30 (11%)	46 (16%)	45 (16%)	41 (14%)	0.20
Hypercholesterolemia	103 (36%)	94 (33%)	102 (36%)	98 (34%)	0.85
Current cigarette smoking	140 (49%)	116 (41%)	114 (40%)	96 (34%)	0.002
Family history of CAD	132 (46%)	123 (43%)	119 (42%)	112 (39%)	0.38
Drug therapy prior to admission					
Aspirin	80 (28%)	93 (33%)	124 (44%)	139(49%)	<0.001
Ace-inhibitors	27 (10%)	28 (10%)	49 (17%)	56 (20%)	<0.001
Beta-blockers	66 (23%)	90 (32%)	118 (41%)	127 (44%)	<0.001
Calcium-channel antagonists	40 (14%)	43 (15%)	51 (18%)	48 (17%)	0.60
Nitrates	22 (8%)	26 (9%)	36 (13%)	48 (17%)	0.003
Statins	74 (26%)	76 (27%)	86 (30%)	80 (28%)	0.69
Anginal symptoms within 30 days before qualifying episode	124 (44%)	145 (51%)	153 (54%)	169 (59%)	0.002
Abnormalities on the admission EKG					
ST-segment deviation ≥ 0.1mV	129 (45%)	142 (50%)	138 (48%)	160 (56%)	0.04
EKG missing or unreadable	6 (2%)	8 (3%)	8 (3%)	11 (4%)	
Cardiac troponin T ≥ 0.30 μg/L	109 (38%)	139 (49%)	155 (54%)	166 (58%)	<0.001
Creatinine clearance (ml/min)*	114 (90 – 136)	99 (82 – 121)	95 (75 – 112)	79 (63 – 103)	<0.001

Men and women were separately classified according to the NT-proBNP level at baseline. Data are number of patients (%), means (SD) or median (25th and 75th percentile)
CAD = coronary artery disease, ECG = electrocardiogram.
* The creatinine clearance rate was calculated from the equation of Cockcroft and Gault, as follows: [[140-age (years)] x body weight (kg)] ÷ [0.815 x plasma creatinine (μmol/L)]. For women, the correction factor of 0.85 was used.

Results

Serum samples for determination of NT-proBNP concentrations were available for 1141 (95%) of 1200 patients. The clinical characteristics of these patients were similar to those of the 59 patients without samples for baseline NT-proBNP measurements. N-terminal pro–brain natriuretic peptide levels ranged from 5 to 35 000 ng/L, with a median of 595 ng/L (262-1436 ng/L) for the entire population (513 ng/L [218-1170 ng/L] for men and 929 ng/L [408-2150 ng/L] for women). The median time from the last episode of chest pain to sampling was 13 hours (8-20 hours) in the early-invasive group versus 13 hours (7-19 hours) in the selective-invasive group.

Association with baseline characteristics

Higher baseline levels of NT-proBNP were associated with female sex; older age; a history of MI and hypertension; and the use of aspirin, angiotensin-converting enzyme inhibitors, β-blockers, and nitrates before admission. Patients with higher NT-proBNP levels were more likely to have electrocardiographic changes at baseline, more likely to have higher levels of cTnT, more often had anginal symptoms within 30 days before the index event, and more likely to have impaired renal function compared with those with lower levels of NT-proBNP. The level of NT-proBNP was inversely associated with current smoking (Table 1).

N-terminal pro–brain natriuretic peptide in relation to severity of CAD and invasive procedures

In the early-invasive group, coronary angiography was performed in 99% of patients. The angiographic findings in relation to baseline NT-proBNP levels in patients randomized to the early invasive treatment strategy are shown in figure 1. High levels of NT-proBNP were associated with severe CAD ($\chi 2$ for trend $P = 0.01$).

Cardiac procedures within 1 year stratified by quartiles of NT-proBNP and treatment strategy are illustrated in figure 2 The overall revascularization rate in the highest quartile was 77% for the early invasive strategy versus 56% for the selective invasive strategy ($P < 0.001$). For the early invasive strategy, no significant differences were found for the rate of angiography or revascularization between the highest and the lower 3 quartiles. In patients randomized to the selective invasive strategy, coronary angiography was performed in 64% of patients in the lower 3 quartiles of NT-proBNP versus 72% in the highest quartile ($P = 0.08$). The incidence of coronary artery bypass

grafting was 24% among patients in the highest quartile compared with 11% in the lower 3 quartiles (P < 0.001), and the incidence of percutaneous coronary intervention was 32% compared with 43%, respectively (P = 0.02) (Figure 2).

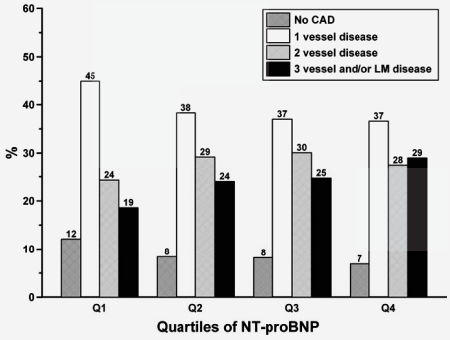

Figure 1. Severity of CAD at angiography in relation to baseline NT-proBNP levels in patients randomized to the early invasive treatment strategy. LM, Left main.

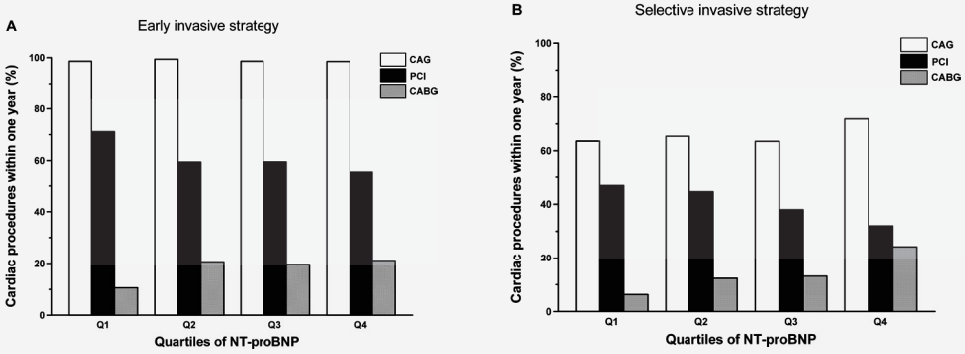

Figure 2. Cardiac procedures within 1 year stratified by quartiles of NTproBNP in patients randomized to (A) early invasive treatment strategy and (B) selective invasive treatment strategy. CAG, Coronary angiogram; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Left ventricular function at discharge in relation to NT-proBNP

In 836 of 1141 patients, an echocardiogram for the assessment of left ventricular function was made at discharge. Impaired systolic left ventricular function was associated with high levels of NT-proBNP ($\chi 2$ for trend P < 0.0001) (Figure 3).

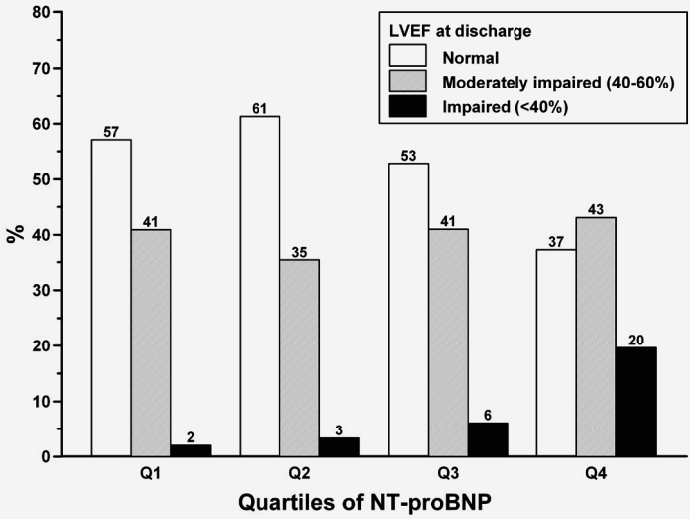

Figure 3. Levels of NT-proBNP in relation to left ventricular ejection fraction at discharge measured by echocardiogram (n = 836). LV, Left ventricular; EF, ejection fraction.

Table 2. Incidence of the composite primary end point and its components by one year according to the quartile of NT-proBNP

	NT-proBNP				
	First quartile n = 285	**Second quartile** n = 285	**Third quartile** n = 285	**Fourth quartile** n = 286	**p-value**
Death	3 (1.1%)	1 (0.4%)	5 (1.8%)	21 (7.3%)	<0.0001
Myocardial infarction	43 (15.1%)	32 (11.2%)	41 (14.4%)	29 (10.1%)	0.19
Spontaneous	12 (4.2%)	11 (3.9%)	11 (3.9%)	14 (4.9%)	0.70
Procedural related	31 (10.9%)	21 (7.4%)	30 (10.5%)	15 (5.2%)	0.06
Rehospitalization for anginal symptoms	24 (8.4%)	23 (8.1%)	26 (9.1%)	25 (8.7%)	0.79
Primary end point	63 (22.1%)	54 (18.9%)	64 (22.5%)	68 (23.8%)	0.44

Data are number of patients (%)

Clinical outcomes

Five patients were lost to follow-up at 12 months. Of these, 3 patients were known to be alive at 6 months, 1 at 1 month, and 1 at discharge from the initial hospitalization. The incidence of the composite primary end point and its components by 1 year according to the quartile of NT-proBNP are shown in table 2.

Mortality at 1 year was 7.3% in the highest quartile compared with 1.1% in the lower 3 quartiles (P < 0.0001). The cause of death in relation to NT-proBNP, treatment strategy, and indicators of risk is shown in table 3.

The incidence of MI after randomization did not differ between increasing quartiles of NT-proBNP (Table 2). Furthermore, no association was found between NT-proBNP levels and the incidence of rehospitalization for angina. In summary, no association was found between NT-proBNP levels and the incidence of the primary end point by 1 year. N-terminal pro–brain natriuretic peptide levels and the risk for death or MI were studied by Cox regression analyses. High NT-proBNP levels were strongly associated with death, if not adjusted for baseline characteristics (model 1). In a Cox regression analysis adjusting for statistically significant predictors of 1-year mortality (model 2) and for

Table 4. NT-proBNP levels and the risk for death and myocardial infarction at 1 year

	Death			Myocardial infarction			Spontaneous MI		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Model 1									
NT-proBNP Q4 vs. Q1-Q3	7.2	3.3 – 15.8	<0.0001	0.7	0.5 – 1.1	0.14	1.3	0.7 – 2.4	0.46
Model 2									
NT-proBNP Q4 vs. Q1-Q3	5.0	2.2 – 11.5	0.0001	0.7	0.5 – 1.1	0.14	1.1	0.6 – 2.0	0.80
Model 3									
NT-proBNP Q4 vs. Q1-Q3	5.0	2.1 – 11.6	0.0002	0.7	0.5 – 1.1	0.18	1.0	0.5 – 2.0	0.95

Cox regression analysis. HR = hazard ratio; Q = quartile; CI = confidence interval; MI = myocardial infarction
Model 1 describes the predictive value of NT-proBNP for death or myocardial infarction without any adjustments for other co-variates. Model 2 includes adjustment for all baseline characteristics that were statistically significantly (p<0.05) associated with death or myocardial infarction (in the model for death: age ≥ 65 years, previous myocardial infarction, hypertension, diabetes mellitus, prior aspirin use, ST segment deviation ≥ 1 mm, and creatinine clearance <75 ml/min; in the model for myocardial infarction: early invasive strategy and ST segment deviation ≥ 1 mm; in the model for spontaneous myocardial infarction: previous myocardial infarction, diabetes mellitus, prior aspirin use, ST segment deviation ≥ 1 mm and family history of CAD). Model 3 includes adjustment for all baseline variables mentioned in Table 1 with the exception of variables indicating drug therapy at admission other than aspirin.

Table 3. Cause of death in relation to NT-proBNP, treatment strategy and indicators of risk

Patient (no.)	NT-proBNP quartile	cTnT at randomization (µg/L)	Treatment strategy	CAD	LVEF (%)	Time to first PCI/CABG (days)	Time to death (days)	Cause of death
1	1	1.70	EI	1-VD	-	0	244	Leukaemia
2	1	1.74	SI	-	<40	-	5	Lethal pericardial effusion
3	1	0.42	SI	3-VD/LM	>60	-	71	Sudden / unobserved death
4	2	1.36	EI	3-VD/LM	-	30	33	Hemorrhagic stroke
5	3	0.57	EI	2-VD	>60	29	308	Thrombosis of arteria mesenterica
6	3	0.08	SI	3-VD/LM	<40	5	69	Sudden / unobserved death
7	3	1.09	SI	1-VD	>60	6	64	Traffic accident
8	3	0.08	SI	-	40-60	-	223	Sudden / unobserved death
9	3	0.40	SI	-	<40	-	76	Myocardial infarction
10	4	0.88	EI	1-VD	-	-	238	Sudden/ unobserved death
11	4	0.78	EI	2-VD	>60	8	15	Cardiogenic shock and intestinal ischemia
12	4	2.58	EI	3-VD/LM	-	0	185	Myocardial infarction
13	4	0.29	EI	2-VD	40-60	-	20	Sudden / unobserved death
14	4	0.71	EI	3-VD/LM	-	1	2	Lethal pericardial effusion caused by PCI
15	4	0.72	EI	2-VD	<40	20	74	Ruptured aortic abdominal aneurysm
16	4	3.19	EI	1-VD	<40	1	87	CABG related septic shock
17	4	0.29	EI	2-VD	-	21	60	Myocardial infarction
18	4	0.05	EI	2-VD	-	2	3	Brady-arrhythmia
19	4	0.19	EI	No CAD	-	-	6	Ischemic stroke caused by CAG
20	4	0.15	EI	1-VD	40-60	-	247	Heart failure
21	4	0.13	EI	2-VD	>60	-	10	Major bleeding
22	4	0.36	SI	-	>60	-	4	Lethal pericardial effusion caused by free wall rupture
23	4	0.33	SI	1-VD	-	85	87	Sudden / unobserved death
24	4	0.13	SI	1-VD	40-60	-	31	Ischemic stroke
25	4	0.68	SI	3-VD/LM	<40	-	8	Heart failure
26	4	2.31	SI	3-VD/LM	<40	-	11	AF followed by cardiogenic shock prior to CABG
27	4	0.27	SI	-	-	-	76	Heart failure
28	4	2.00	SI	-	<40	-	3	Heart failure
29	4	1.86	SI	1-VD	<40	-	163	Sudden / unobserved death
30	4	0.07	SI	2-VD	-	-	120	Sudden / unobserved death

CAD = coronary artery disease; CAG = coronary angiogram; CABG = coronary-artery bypass graft; EI = early invasive treatment strategy; LM = left main; PCI = percutaneous coronary intervention; SI = selective invasive treatment strategy; VD = vessel disease

all baseline characteristics (model 3), the highest quartile of NT-proBNP remained a strong independent predictor of 1-year mortality (Table 4).

There was remarkable association between a high level of NT-proBNP in combination with an impaired renal function (creatinine clearance <75 mL/min) and death within 1 year. Mortality among patients in the highest quartile of NT-proBNP with an impaired renal function was 13.8% versus 2.5% among patients with normal renal function.
There was no association between high NT-proBNP levels and recurrent MI (model 1). In addition, if adjusted for all baseline characteristics that were statistically significantly associated with recurrent MI (model 2) or for all baseline characteristics with the exception of antianginal medication (model 3), the highest quartile of NT-proBNP was not associated with recurrent MI at 1 year (Table 4). Furthermore, there was no association between NT-proBNP and recurrent spontaneous MI.
The mortality over time for patients in the highest quartile and lower 3 quartiles, stratified by treatment strategy, is illustrated in figure 4. An early invasive strategy provided no mortality reduction, irrespective of NT-proBNP (highest quartile: RR 1.5, 95% CI 0.7-3.5, P = 0.32; lower quartiles: RR 0.5, 95% CI 0.1-1.8, P = 0.26).

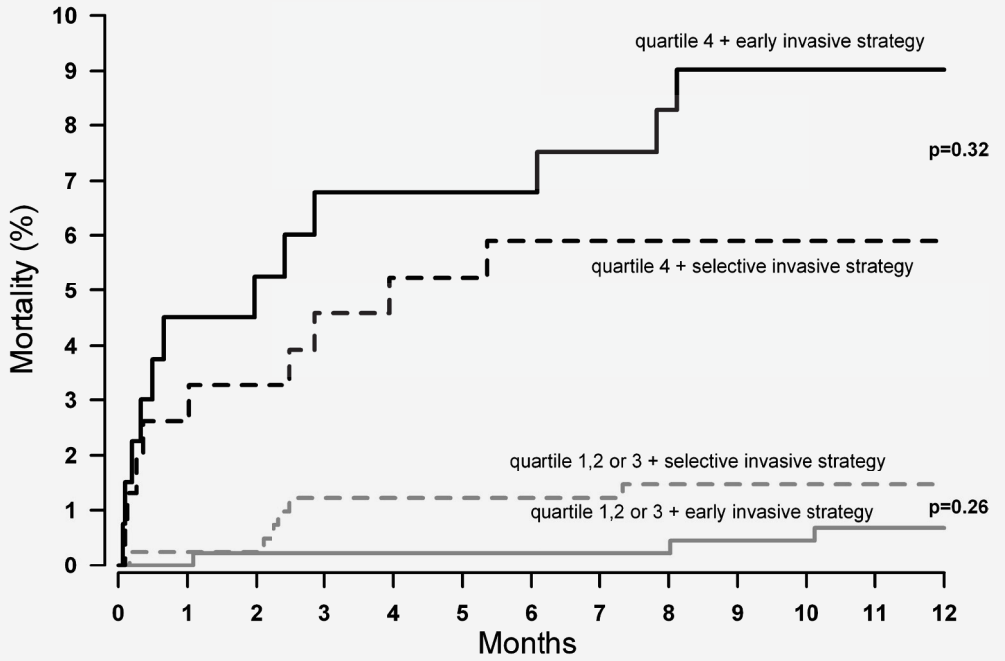

Figure 4. Kaplan-Meier estimates of death in relation to treatment strategy and the level of NT-proBNP.

DISCUSSION

This study confirmed that there was a strong association between the concentration of NT-proBNP at admission and mortality at 1 year in patients who have nSTE-ACS with an elevated cTnT.[13] We demonstrated that increased levels of NT-proBNP at baseline were associated with several indicators of risk and severe CAD, which is in accordance with previous studies.[9,12,18] Furthermore, we found a very strong association between mortality and the combination of a high NT-proBNP and impaired renal function. However, NT-proBNP levels were not associated with the rate of MI by 1 year.

Current guidelines recommend an early invasive treatment strategy for high-risk patients with nSTE-ACS, particularly because prior studies demonstrated a reduction in recurrent MI. In this study, no association between NT-proBNP concentrations at baseline and MI by 1 year was found. These results confirm other reports in which BNPs appear to be a stronger predictor of mortality than of recurrent MI.[6, 13] In addition, BNP levels in the TACTICS TIMI 18 trial and NT-proBNP levels in the FRISC-II trial were not associated with recurrent MI.[7,13]

Several mechanisms have been reported to be responsible for NT-proBNP elevation in acute coronary syndromes. According to present data, acute myocardial ischemia seems to be responsible for only a modest elevation (1-5 times the upper limit of normal) of NT-proBNP levels.[3,4] In our study, high NT-proBNP levels were associated with high cTnT concentrations, indicating that the NT-proBNP is associated with the size of new myocardial damage of the index event. However, it is unclear whether a 10- to 20-fold increase in NT-proBNP (upper quartile) is entirely due to myocardial ischemia of the index event. We showed that high levels of NT-proBNP are associated with anginal symptoms within 30 days before the index event, the use of antianginal medication before randomization, and 3-vessel disease. Therefore, it could be speculated that high levels of NT-proBNP at admission are the result of both myocardial ischemia before the index event and the index event itself. Another mechanism for NT-proBNP elevation in acute coronary syndromes is permanently elevated levels of NT-proBNP reflecting ventricular dysfunction or heart failure before the index event. Unfortunately, there was no information regarding left ventricular function at randomization. However, there was a strong association between high levels of NT-proBNP and an impaired left ventricular function at discharge.

The cause of death in relation to NT-proBNP, treatment strategy, and indicators of risk is shown is table 3. In the highest quartile of NT-proBNP, almost 50% of patients died

because of progression of heart failure or sudden/unobserved death, further stressing that the natriuretic peptides do not predict ischemic events. Whether prognosis in these patients can be improved with other therapies besides revascularization, perhaps with more intensive antiarrhythmic therapy, ICD implantation, or more intensive monitoring of heart failure, remains to be elucidated.

We performed an exploratory analysis for the association between mortality and treatment strategy for different levels of NT-proBNP. We observed no reduction in mortality with the use of an early invasive strategy compared with a selective invasive strategy, regardless of the NT-proBNP level at baseline. The prognostic value and the effect of treatment strategy have previously been studied in 2 major strategy trials, the FRISC-II trial and the TACTICS-TIMI 18 trial.[7,13] In both trials, plasma levels of BNP at baseline were independently associated with mortality, but both trials failed to show a reduction in mortality with the use of an early invasive strategy. However, in the FRISC-II trial, a reduction in mortality was observed with the use of an invasive strategy in patients with an elevated NT-proBNP level in combination with an elevated interleukin 6 level.[7]

When comparing strategy trials, differences in the rate of revascularization should be taken in to account. In the FRISC-II trial, there was a large difference in the rate of revascularization between the invasive and conservative strategies in the trial, 13% and 76%, respectively. Interestingly, this is the only strategy trial showing a reduction of mortality with the use of an invasive strategy at 2-year follow up.

The revascularization rate during initial hospitalization in the noninvasive and invasive treatment arms in the ICTUS study was 40% and 76%, in the TACTICS-TIMI 18 trial 36% and 60%, and in the RITA-3 study 10% and 44%. There was no significant difference in mortality observed in any of these strategy trials.

In conclusion, we confirmed that NT-proBNP is a strong independent predictor of mortality by 1 year, but we found no association between NT-proBNP and recurrent MI. Sudden death and progression of congestive heart failure are important causes of death in the highest quartile of NT-proBNP. We could not demonstrate a benefit of an early invasive strategy in patients who have nSTE-ACS with both an elevated NT-proBNP and cTnT. Therefore, based on our findings and on findings in the FRISC-II and TACTICS TIMI 18 trials, an NT-proBNP measurement may not be useful for the identification of patients with nSTE-ACS who will benefit from an early invasive treatment strategy within 1 year.

REFERENCES

1. E. Falk, P.K. Shah and V. Fuster, Coronary plaque disruption, Circulation 92 (1995), pp. 657–671.

2. E.R. Levin, D.G. Gardner and W.K. Samson, Natriuretic peptides, N Engl J Med 339 (1998), pp. 321–328.

3. J.P. Goetze, C. Christoffersen and M. Perko et al., Increased cardiac BNP expression associated with myocardial ischemia, FASEB J 17 (2003), pp. 1105–1107.

4. J.P. Goetze, A. Gore and C.H. Moller et al., Acute myocardial hypoxia increases BNP gene expression, FASEB J 18 (2004), pp. 1928–1930.

5. C.W. Hamm and E. Braunwald, A classification of unstable angina revisited, Circulation 102 (2000), pp. 118–122.

6. S.K. James, B. Lindahl and A. Siegbahn et al., 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, Circulation 108 (2003), pp. 275–281.

7. T. Jernberg, B. Lindahl and A. Siegbahn et al., N-terminal pro–brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease, J Am Coll Cardiol 42 (2003), pp. 1909–1916.

8. B. Lindahl, J. Lindback and T. Jernberg et al., Serial analyses of N-terminal pro–B-type natriuretic peptide in patients with non–ST-segment elevation acute coronary syndromes: a Fragmin and fast Revascularisation during In Stability in Coronary artery disease (FRISC)-II substudy, J Am Coll Cardiol 45 (2005), pp. 533–541.

9. T. Omland, A. Persson and L. Ng et al., N-terminal pro–B-type natriuretic peptide and long-term mortality in acute coronary syndromes, Circulation 106 (2002), pp. 2913–2918.

10. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators, Lancet 354 (1999), pp. 708–715.

11. C.P. Cannon, W.S. Weintraub and L.A. Demopoulos et al., Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban, N Engl J Med 344 (2001), pp. 1879–1887.

12. J.A. de Lemos, D.A. Morrow and J.H. Bentley et al., The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes, N Engl J Med 345 (2001), pp. 1014–1021.

13. D.A. Morrow, J.A. de Lemos and M.S. Sabatine et al., Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non–ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18, J Am Coll Cardiol 41 (2003), pp. 1264–1272.

14. C. Heeschen, C.W. Hamm and V. Mitrovic et al., N-terminal pro-B–type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes, Circulation 110 (2004), pp. 3206–3212.

15. M.S. Sabatine, D.A. Morrow and J.A. de Lemos et al., Multimarker approach to risk stratification in non–ST-elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide, Circulation 105 (2002), pp. 1760–1763.

16. R.J. de Winter, F. Windhausen and J.H. Cornel et al., Early invasive versus selectively invasive management for acute coronary syndromes, N Engl J Med 353 (2005), pp. 1095–1104.

17. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, Eur Heart J 21 (2000), pp. 1502–1513.

18. M. Galvani, F. Ottani and L. Oltrona et al., N-terminal pro–brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes, Circulation 110 (2004), pp. 128–134.