

Admission NT-proBNP and its interaction with admission Troponin T and ST-segment resolution for early risk stratification in ST-elevation myocardial infarction.

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Abstract

Objective: To assess the long-term prognostic value of N-terminal pro brain natriuretic peptide (NT-proBNP) on admission and its prognostic interaction with both admission troponin T (tnT) levels and the resolution of the ST-segment elevation in fibrinolytic treated ST-elevation myocardial infarction (STEMI).

Design and setting: Substudy of the ASSENT-2 and ASSENT-PLUS trials.

Patients: NT-proBNP and tnT levels were determined on admission in 782 patients.

According to NT-pro-BNP levels, patients were divided into three groups: 1) normal level (≤ 65 years, ≤ 184 ng/L and ≤ 268 ng/L, and in those >65 years, ≤ 269 ng/L and ≤ 391 ng/L, for men and women, respectively) 2) $>$ normal, but below median level (742 ng/L) and 3) above the median level. For tnT, a cut-off value of 0.1 μ g/L was used. Out of the 782 patients, 456 had the ST-segment resolution at 60 minutes calculated from ST-monitoring ($<50\%$ or $\geq 50\%$).

Main outcome measures: All cause one-year mortality.

Results: There was a stepwise increase in one-year mortality according to increasing levels of NT-proBNP, 3.4%, 6.5% and 23.5% ($p < 0.001$), respectively. In ROC analysis, NT-proBNP showed a strong trend to be more strongly associated with mortality than tnT and time to 50% ST-resolution, AUC 0.81 (0.72-0.9), 0.67 (0.56-0.79) and 0.66 (0.56-0.77), respectively. In a multivariable analysis adjusting for baseline risk factors and tnT, both elevated NT-proBNP and ST-resolution $<50\%$ were independently associated with higher one-year mortality, whereas elevated tnT only contributed independently prior to including information on ST-resolution in the model.

Conclusion: Admission NT-pro-BNP is a strong independent predictor of mortality and gives together with 50% ST-resolution at 60 minutes important prognostic information even after adjusting for tnT and baseline characteristics in STEMI.

Introduction

The mortality risk is quite variable among patients with fibrinolytic treated ST-elevation myocardial infarction (STEMI)¹. A careful and early risk evaluation of each patient is therefore important. Several clinical baseline variables have been identified as important predictors of outcome, especially age, heart rate and blood pressure². In recent years, interest has been focused on cardiac biomarkers and the early resolution of the ST-segment elevation^{3, 4} for risk stratification in STEMI. Until now, the most evaluated biomarker has been Troponin T (or I) on admission which gives strong prognostic information,⁵ also in combination with ST-resolution⁶.

Brain natriuretic peptide (BNP) and the N-terminal part of its prohormone, NT-proBNP, are released from the cardiac ventricles in response to increased wall stress,⁷ and also to ischemia per se⁸. A few previous smaller studies have shown that NT-proBNP and BNP levels have been independent predictors of mortality day 2 to 5 after STEMI^{9, 10}. Also, elevated levels of NT-proBNP and BNP on admission in STEMI have been related to adverse outcome in two recent studies^{11, 12}. These studies however only evaluated short-term mortality. Furthermore, the prognostic interaction of NT-proBNP and the early resolution of the ST-segment elevation have previously not been investigated. We therefore evaluated admission NT-proBNP levels and its prognostic interaction with admission troponin T (tnT) and ST-segment resolution for early risk stratification in STEMI patients with long-term follow up.

Methods

Patients and study design

This study was a substudy of the ASSENT-2¹³ (ASSESSment of Safety and Efficacy of a New Thrombolytic) trial and the ASSENT-PLUS¹⁴ trial. In brief, the ASSENT-2 trial was a multicenter study comparing tenecteplase with front loaded alteplase. In the ASSENT-PLUS trial 434 patients were recruited in Scandinavia and USA during 1999 and 2000, evaluating the efficacy and safety of the low molecular weight heparin dalteparin compared to unfractionated heparin as an adjunct to alteplase.

In both studies inclusion criteria were symptoms of acute myocardial infarction within 6 hours of onset, ST-elevation ≥ 0.1 mV in 2 or more limb leads, or ≥ 0.2 mV in 2 or more contiguous precordial leads, or left bundle branch block and age ≥ 18 years. Exclusion criteria in both trials were the regular ones for thrombolytic treatment and have been described in detail previously^{13, 14}. In addition, known renal dysfunction (S-creatinine > 1.7 mg/dl) was an exclusion criterion in the ASSENT-PLUS trial. Out of 1456 patients enrolled in the ASSENT-2 and ASSENT-PLUS trials at Swedish hospitals, 782 (with 8.4% one-year mortality) had an admission NT-proBNP sample available and constituted the study population for the present substudy (568 from the ASSENT-2 and 214 from the ASSENT-PLUS trial).

Blood samples for biochemical markers

Venous blood samples were collected immediately before start of thrombolytic and anti-coagulation therapy at selected Swedish sites. After centrifugation the EDTA-plasma samples were stored frozen at -70 C for central analysis. NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostics). The analytical range extends from 20 to 35000 ng/L. At our laboratory, the total CV was 3.3% at a level of 209 ng/L and 3% at a level of 7431 ng/L. A normal level of NT-proBNP ($\leq 97.5^{\text{th}}$ percentile in a healthy population) according to age and gender has been shown to be: ≤ 65 years, ≤ 184 ng/L and ≤ 268 ng/L, and in those > 65 years, ≤ 269 ng/L and ≤ 391 ng/L, in men and women, respectively¹⁵. TnT was analyzed with the third-generation tnt assay on an Elecsys 2010 with a detection limit of 0.01 $\mu\text{g/L}$. A prospectively defined cut-off level of ≤ 0.1 $\mu\text{g/L}$ was used based on previous evaluations of admission tnt in STEMI for risk stratification^{6, 11, 16}, which should not be confused with the cut-off level used for diagnosis of myocardial infarction¹⁷.

ST-segment resolution

A subgroup of 456 patients were monitored for 24 h after admission by continuous vectorcardiography (VCG) (n=334) and continuous 12-lead ECG (n=122), respectively. The one-year mortality was 6.3% in this subgroup and thus similar to the whole ST-monitoring substudy population^{4, 6}.

These two ST-monitoring methods have previously been shown to identify the same risk-groups among patients with STEMI^{4, 6}. Inclusion and exclusion criteria for ST-monitoring, methods for acquirement of continuous VCG and ECG recordings and for assessment of ST-segment measurements have previously been described^{4, 6}. A cut-off level of $\leq 50\%$ ST-segment resolution from the maximal ST-elevation, measured at 60 minutes after start of recording was used^{4, 6}. We also assessed time to 50% ST-segment resolution to evaluate its relation to admission NT-proBNP levels.

Coronary Angiography

A predischarge coronary angiogram was scheduled at day 4 to 7 and performed in 179 of the 214 patients from the ASSENT-PLUS cohort¹⁴. The coronary vessels were divided in 15 segments¹⁸ and degree of stenosis was analysed. A CASS score was computed to determine the severity of coronary artery disease^{19, 20}. By adding the regional scores, a CASS score with a possible range of 0-3 was obtained. When calculating the CASS score, the culprit lesion was considered occluded in order to imitate the situation on admission.

Clinical end points

The outcome event in this substudy was all-cause one-year mortality. The one-year mortality was evaluated by patient records and telephone contacts.

Statistical analysis

Baseline characteristics were expressed as medians (with 25th-75th percentile) or percentages. Differences in categorical baseline variables between groups according NT-proBNP level were evaluated with chi-square tests for trend. Differences between median values for continuous variables were evaluated with Kruskal-Wallis tests or Mann-Whitney U tests. Correlations were assessed by the Spearman's rank statistics. To compare the predictive capacity of NT-proBNP, tnT and time to 50% ST-resolution, receiver operating characteristic (ROC) curves were used. Kaplan-Meier curves were constructed to illustrate the risk for death during the one year of follow-up and log-rank tests were done to compare the risk between strata.

Independent predictors of one-year mortality were identified with stepwise multiple logistic regression analyses including age, sex, heart rate, systolic blood pressure (SBP), Killip class, previous MI, time to therapy, anterior infarction, tnT and NT-proBNP (log-transformed (base 10) due to its skewed distribution) in the whole study population. The independent predictors of mortality as well as Killip class which tended to be independent were then evaluated in two models, model 1 included tnT and NT-proBNP and in model 2, information on ST-resolution at 60 minutes was added (Table 2). Additional logistic regression analyses were performed to adjust for study (ASSENT-2 or ASSENT-PLUS) and to test for the interaction between NT-proBNP and ST-resolution. In all statistical analyses, a p-value of less than 0.05 was considered significant. All statistics were calculated with SPSS software (version 12.0, Statistical Package for the Social Sciences).

Results

General findings

During one year follow-up 66 (8.4%) deaths occurred in the whole study population. More than half of the study population (n=443) had normal levels of NT-proBNP on admission according to age and gender. The remaining patients had a median level of 742 ng/L (395-1894). Clinical characteristics in relation to 1) normal, 2) above normal, but below median (intermediate) and 3) above the median (high) level of NT-proBNP are listed in Table 1. There was a stepwise increase in age, heart rate, Killip class, the rate of previous MI and time from symptom onset to therapy in relation to higher levels of NT-proBNP. However, the correlation between NT-proBNP and symptom duration was weak ($r=0.17$, $p<0.001$). The distribution of NT-proBNP levels and baseline characteristics according to NT-proBNP were similar in the subgroup of patients with ST-monitoring.

The prevalence of more severe coronary artery disease tended to increase with increasing NT-proBNP levels.

NT-proBNP in relation to tnT and ST-resolution

Patients with $\text{tnT} \geq 0.1 \mu\text{g/L}$ (n=177, 23%) had markedly higher levels of NT-proBNP than those with $\text{tnT} < 0.1 \mu\text{g/L}$ (678 ng/L (215-2230) vs. 167 ng/L (69-382), $p<0.001$), respectively. There was a moderate positive correlation between levels of tnT and NT-proBNP ($r=0.43$, $p<0.001$). In the subgroup (n=456) of patients with ST-monitoring, those without 50% ST-resolution at 60 min. (n=262, 60%) had slightly higher levels of NT-proBNP compared to those with 50% ST-resolution (249 ng/L (109-721) vs. 174 ng/L (70-504), $p=0.009$), respectively, although there was only a weak positive correlation between time to 50% ST-resolution and levels of NT-proBNP ($r=0.13$, $p=0.005$).

Table 1. Clinical characteristics according to NT-proBNP levels on admission.

	NT-proBNP normal*	NT-proBNP >normal & <median <742 ng/L	NT-proBNP ≥median ≥742 ng/L	p-value
Variable (%)	(n=443)	(n=169)	(n=170)	
Age (years) [†]	63 (55-71)	68 (59-75)	74 (67-79)	NA
Male gender	71.6	77.5	62.9	NA
Time to therapy (min) [‡]	135 (95-200)	160 (110-225)	172 (110-239)	<0.001
Current smoker	37.6	23.1	22.5	<0.001
Diabetes mellitus	9.7	10.7	12.4	0.34
Hypertension	25.1	29.6	32.4	0.06
Previous MI	8.8	18.9	27.1	<0.001
Anterior MI	40.9	50.9	50.9	0.01
SBP (mmHg) [†]	140 (125-156)	145 (130-160)	140 (125-160)	0.26
Heart rate (b.p.m.) [†]	68 (59-78)	68 (59-78)	78 (66-90)	<0.001
Killip class >1	9.5	15.9	25.0	<0.001
tnT ≥0.1 µg/L	11.7	23.7	50.0	<0.001
≥50% ST-resolution [‡]	47.4	37.7	35.6	0.03
Coronary angiography [§]				
CASS-score 0	8.0	0	0	} 0.03
CASS-score 1	56.3	73.3	72.7	
CASS-score 2	33.0	20.0	13.6	
CASS-score 3	2.7	6.7	13.6	

Footnotes: NA=not applicable; MI=myocardial infarction; SBP=systolic blood pressure.

*≤/≥65 years, ≤184/≥269 ng/L in men, ≤/≥65 years, ≤268/≥391 ng/L in women;

[†]median (25th-75th percentile); [‡]assessed in 249/106/101; [§]assessed in 112/30/22**Table 2.** Univariable and multivariable logistic regression analysis for one-year mortality.

	Univariable	Multivariable		
	OR (95% CI)	Model 1 (n=782) OR (95% CI)	Model 2 (n=456) OR (95% CI)	M2 with interaction OR (95% CI)
Age (years)	1.13 (1.10-1.17)	1.11 (1.06-1.15)	1.08 (1.02-1.14)	1.09 (1.03-1.15)
Heart rate (b.p.m.)	1.04 (1.03-1.05)	1.02 (1.01-1.04)	1.02 (1.0-1.05)	1.03 (1.0-1.05)
SBP (mmHg)	0.98 (0.97-0.99)	0.98 (0.96-0.99)	0.98 (0.96-0.99)	0.98 (0.96-0.99)
Killip class >1	3.28 (1.86-5.76)	1.74 (0.89-3.40)	1.11 (0.38-3.26)	1.09 (0.37-3.20)
Log(NT-proBNP)*	3.04 (2.33-3.97)	1.69 (1.20-2.37)	2.27 (1.33-3.87)	
ST-resolution <50% [†]	NA	NA	NA	2.97 (1.58-5.59)
ST-resolution ≥50% [†]	NA	NA	NA	1.15 (0.50-2.63)
ST-resolution <50% [‡]	3.02 (1.20-7.56)	NA	3.06 (1.07-8.76)	1.42 (0.41-4.90) [‡]
Troponin T ≥0.1 (µg/L)	4.56 (2.72-7.65)	2.25 (1.21-4.19)	1.35 (0.52-3.48)	1.30 (0.49-3.50)

Footnotes: M2= Model 2; SBP=systolic blood pressure; NA=not applicable

* log(NT-proBNP) standardised to have mean=0 and SD=1; [†]at 60 minutes; [‡]OR for patient with mean log(NT-proBNP) representing a value of NT-proBNP of 256 ng/L.

Prognostic value of NT-proBNP

There was a stepwise increase in one-year mortality according to increasing levels of NT-proBNP (3.4%, 6.5% and 23.5%, respectively) (Fig 1). Accordingly, there was a striking mortality difference between patients with high and those with normal level of NT-proBNP (O.R. 8.8; 4.7-16.4, $p<0.001$). There was also significantly higher mortality in those with high compared to intermediate level of NT-proBNP (O.R. 4.4; 2.2-9.0, $p<0.001$).

Fig 2 illustrates the univariable association between levels of NT-proBNP, tnT and time to 50% ST-resolution and one-year mortality by ROC-curves. Notably, the areas under the curves (AUC) showed a strong trend for NT-proBNP to be more strongly associated with mortality than the other variables (NT-proBNP vs. tnT, $p=0.056$ and NT-proBNP vs. time to 50% ST-resolution, $p=0.052$, respectively). Moreover, when evaluated in the whole study population the AUC for NT-proBNP (0.79) and tnT (0.71) were unaltered and NT-proBNP was significantly more strongly related to mortality than tnT ($p=0.026$). The AUC for NT-proBNP (0.76, $n=574$) was also similar for patients without previous MI and in Killip class I on admission.

A high NT-proBNP level (>742 ng/L) yielded a sensitivity and specificity in the whole study population of 61% and 82%, respectively. The corresponding positive and negative predictive values were 24% and 96%, respectively.

In a multivariable analysis including all patients in this study and thus not including information on early ST-resolution in the model; age, heart rate, SBP, “elevated” tnT and $\log(\text{NT-proBNP})$ were independently associated with one-year mortality (Table 2, model 1). In a restricted version of model 1 that only included patients with data on ST-resolution ($n=456$), NT-proBNP but not tnT (O.R. 1.52; 0.60-3.85) contributed independently. When 50% ST-resolution at 60 minutes was added to the model, both $\log(\text{NT-proBNP})$ and $<50\%$ ST-resolution were independently associated with mortality in contrast to tnT (Table 2, model 2). The results were similar when NT-proBNP was entered as a categorical variable in model 2 (O.R. for high NT-proBNP vs. normal NT-proBNP=3.34; 1.06-10.54, $p=0.03$). Also, the results were unchanged when tnT and ST-resolution (log-transformed) were entered in a continuous format and when adjusting for study (ASSENT-2 or ASSENT-PLUS).

Combination of NT-proBNP with tnT and ST-resolution

When stratification was based on the level of tnT, there was a gradual increase in mortality according to increasing levels of NT-proBNP in both patients with and without tnT elevation (Fig 3a).

There was a profound difference in mortality between the group with high NT-proBNP and without ST-resolution and the group with normal NT-proBNP and with ST-resolution (O.R. 20.5; 4.6-92.4, $p<0.001$) (Fig 3b). Notably, the difference in mortality between patients with and without ST-resolution was mainly restricted to those with high levels of NT-proBNP. The result was similar using other classifications of NT-proBNP and ST-resolution. Accordingly, there was a significant interaction between NT-proBNP and 50% ST-resolution at 60 minutes ($p=0.04$) (Table 2).

Discussion

NT-proBNP and prognosis

Our study demonstrates that admission NT-proBNP is a strong independent predictor of long-term mortality in STEMI in accordance with previous evaluations of NT-proBNP (and BNP) and short-term mortality^{11, 12}. For the first time, NT-proBNP was evaluated together with ST-resolution, tnT and other well known risk factors, and still independently predicted mortality. As in a previous trial¹¹, NT-proBNP were equally predictive in patients without previous MI and signs of heart failure on admission. Accordingly, Killip class provided no independent prognostic information when NT-proBNP was added to the multivariable model (Table 2).

Although more than half of the study population had normal levels of NT-proBNP in contrast to STEMI studies with later sample time points^{9, 10}, the predictive capacity seen in these trials was maintained also with admission sample acquisition. This is in line with a previous small study²¹ in which there was no difference in predictive capacity according to NT-proBNP levels on admission or after 2 days following STEMI.

We found only a weak correlation between symptom duration and NT-proBNP, which was somewhat unexpected considering the time dependent rise of BNP in the early phase after STEMI^{22, 23}. One explanation for this might be that a patient's recollection of the symptom duration is highly subjective. Thus, admission tnt, which is believed to be a more objective marker of ischemic time^{5, 6} had a stronger correlation to NT-proBNP.

As shown in previous acute coronary syndromes studies²⁴, increased levels of NT-proBNP were associated with more severe coronary artery disease also in patients with STEMI.

Combination of NT-proBNP with tnt and ST-resolution

When testing NT-proBNP in multivariable analysis including well known predictors of outcome and tnt but not ST-resolution (model 1, Table 2), both NT-proBNP and tnt contributed independently to mortality prediction in contrast to previous studies^{11, 12}.

However, when model 1 was restricted to patients with data on ST-resolution, tnt no longer contributed independently, which probably is explained by the smaller sample size and fewer events in this subgroup of patients. Finally, when information on ST-resolution at 60 minutes was added, NT-proBNP and ST-resolution predicted mortality independently in contrast to tnt (model 2, Table 2). Thus, these results suggest that NT-proBNP and 50% ST-resolution at 60 minutes are complementary concerning their pathophysiological mechanisms in relation to mortality. There was a significant interaction between NT-proBNP and ST-resolution and the benefit of an early ST-resolution was mainly restricted to patients with high levels of NT-proBNP (Table 2 and Fig 3b). In contrast, NT-proBNP and tnt seemed to reflect more similar mechanisms in relation to mortality as indicated by a moderate correlation. The fact that NT-proBNP has been shown to be an indicator of myocardial ischemia per se⁸ and tnt of myocardial necrosis, might to some extent explain why NT-proBNP has greater prognostic accuracy on admission in STEMI than tnt as discussed by Galvani et.al.¹¹, but also why they in part seem to be markers of similar pathophysiology in the early phase of STEMI.

However, the knowledge of tnt level in addition to NT-proBNP provided further risk stratification on admission (Fig 3a) especially before information on ST-resolution at 60 minutes was obtained.

The combination of NT-proBNP and early ST-resolution improved risk prediction. Hence, one third of the high risk patients with high NT-proBNP, who achieved early ST-resolution could be stratified into a moderate to low risk group, which might be explained by subsequent early tissue level reperfusion²⁵. It might be hypothesized that the patients with high levels of NT-proBNP on admission either have a large ongoing MI or a previously established left ventricular dysfunction with subsequent raised risk of adverse outcome unless there is an early tissue level reperfusion. On the other hand, patients with normal admission NT-proBNP (more than half of the population) were at low risk almost regardless of 50% ST-resolution or not.

Identification of high risk patients with high NT-proBNP already on admission in STEMI may be helpful for selection of more intense interventional or pharmacological treatment strategies. Our study suggests that an early tissue level reperfusion is especially important in patients with elevated NT-proBNP level and could alter the adverse outcome for this high risk group. Thus, one might speculate that primary angioplasty could be valuable for these high risk patients since tissue level reperfusion is achieved more frequently with primary angioplasty compared to thrombolysis²⁶. However, this and other new treatment strategies according to admission NT-proBNP levels need to be tested in prospective trials.

Limitations

One limitation is that the prognostic interaction of NT-proBNP and ST-resolution could only be studied in a subgroup of the study population which has a lower one-year mortality compared to the other patients, although baseline characteristics were similar. The mortality among the patients with a blood sample (NT-proBNP) was similar to the entire ASSENT-2 study population in contrast to the lower mortality in the patients with ST-monitoring as reported in a previous study⁶. This lower mortality is in accordance with previous trials that evaluated ST-resolution³ and is probably explained by the time criteria for ST-monitoring⁴ which excluded some of the patients with fatal early events. Also, patients with left bundle branch, a high risk group¹, were prospectively excluded from ST-monitoring.

Another limitation is that we had no information on renal function which has been shown to be independently associated with both NT-proBNP levels and mortality in a large population with unstable coronary artery disease²⁷. However, in a previous smaller study that evaluated admission NT-proBNP in STEMI in which information on renal failure was present, renal dysfunction was not independently associated with mortality¹¹. Thus, it is not likely that information on renal dysfunction would alter our results that much.

Conclusion

NT-proBNP on admission is a strong independent predictor of long-term mortality in STEMI patients treated with fibrinolytics. When evaluated together with admission tnT and ST-resolution at 60 minutes, both NT-proBNP and early ST-resolution remain independently associated with mortality in contrast to tnT. The combination of NT-proBNP and ST-resolution at 60 minutes gives complementary early information on prognosis and provides an even better risk stratification in STEMI patients.

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Disclosure

No conflict of interest in the manuscript.

Legends to figures

Figure 1: Cumulative probability of death during one year according to the level of NT-proBNP (n=782).

Figure 2: Receiver operator characteristic curve concerning death at one year for NT-proBNP, Troponin T and time to 50% ST-segment resolution with an area under the curve (95% confidence interval) of 0.81 (0.72-0.90), 0.67 (0.56-0.79) and 0.66 (0.56-0.77), respectively (n=456).

Figure 3a: One year mortality according to the combination of NT-proBNP (ng/L) and tnT (μ g/L) (n=782).

Figure 3b: One year mortality according to the combination of NT-proBNP (ng/L) and ST-segment resolution (%) at 60 min (n=456).

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Figure 1

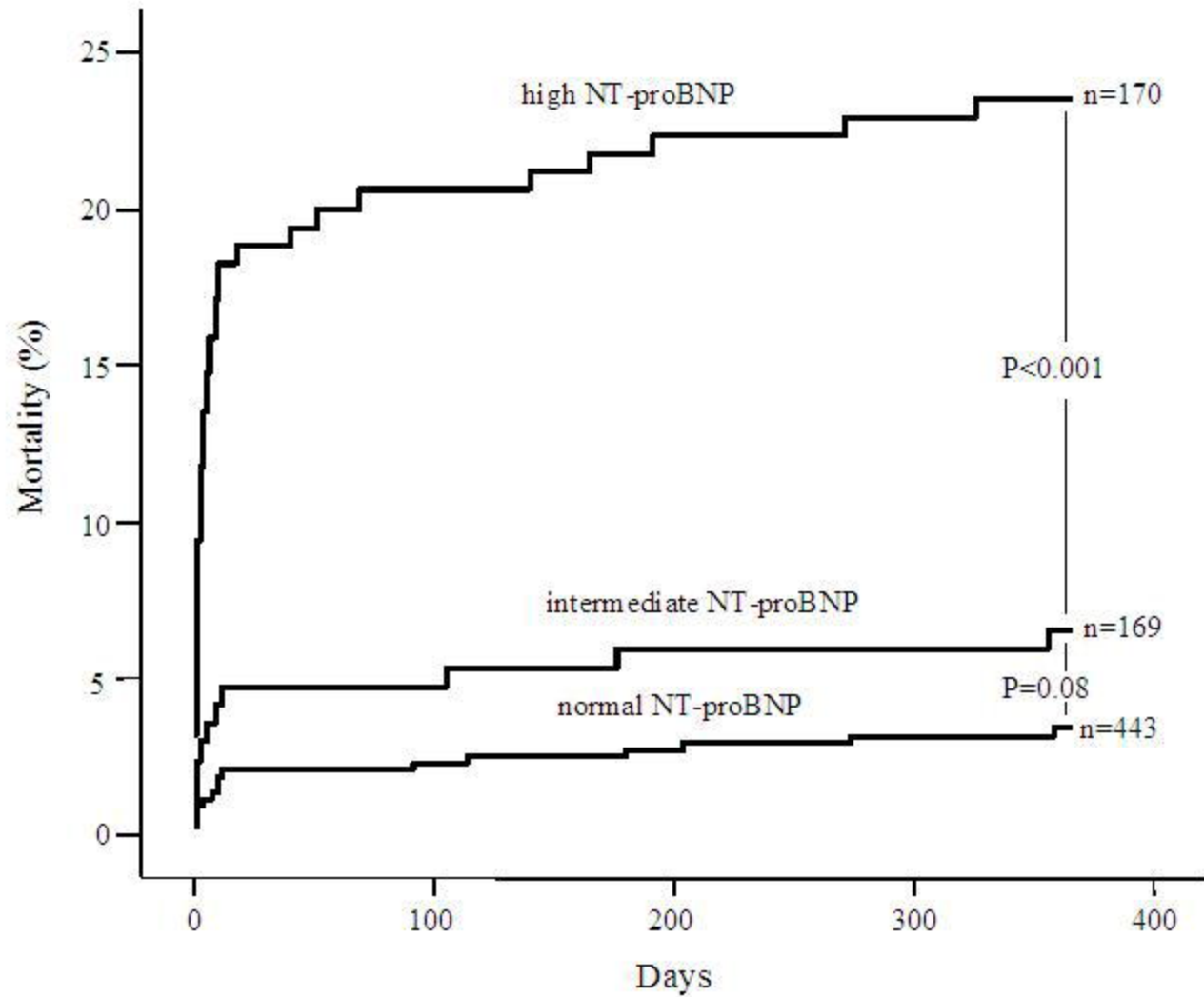


Figure 2

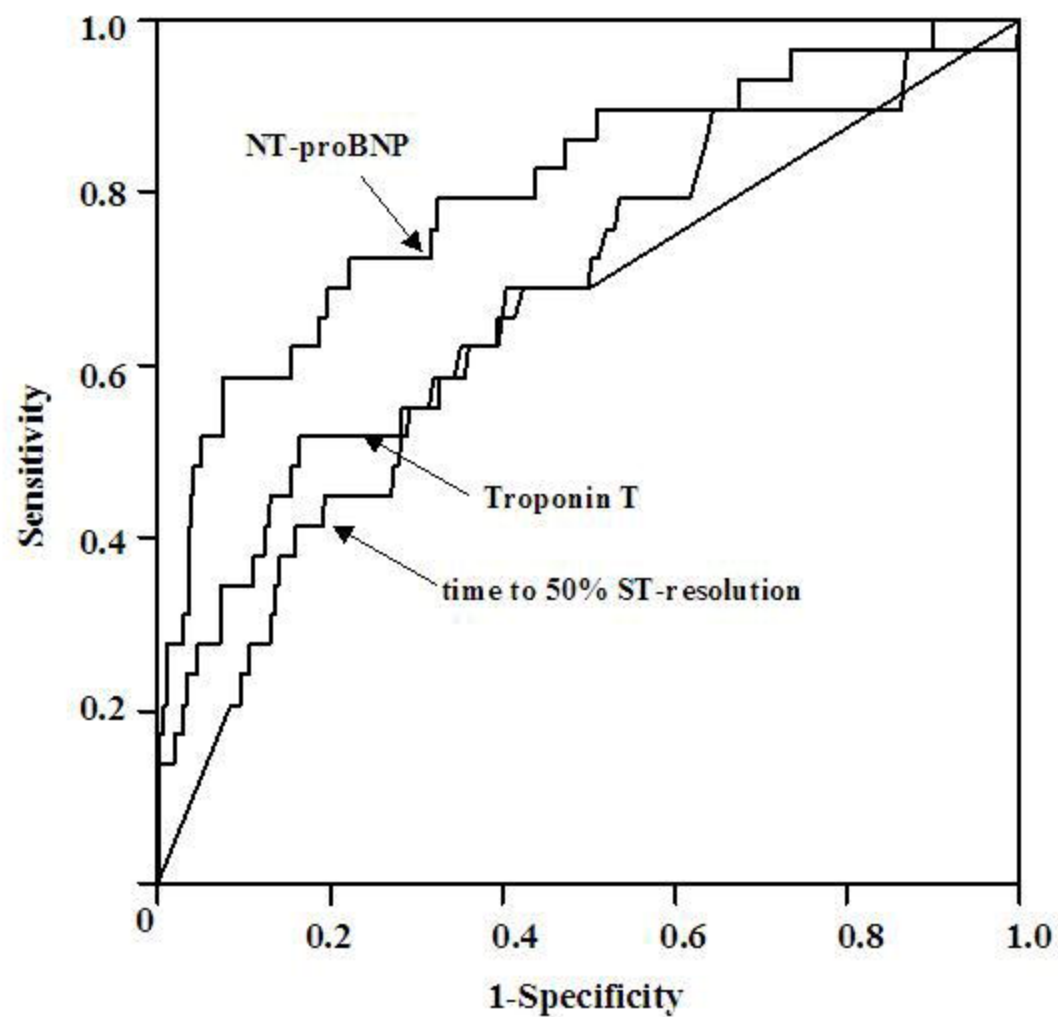


Figure 3a

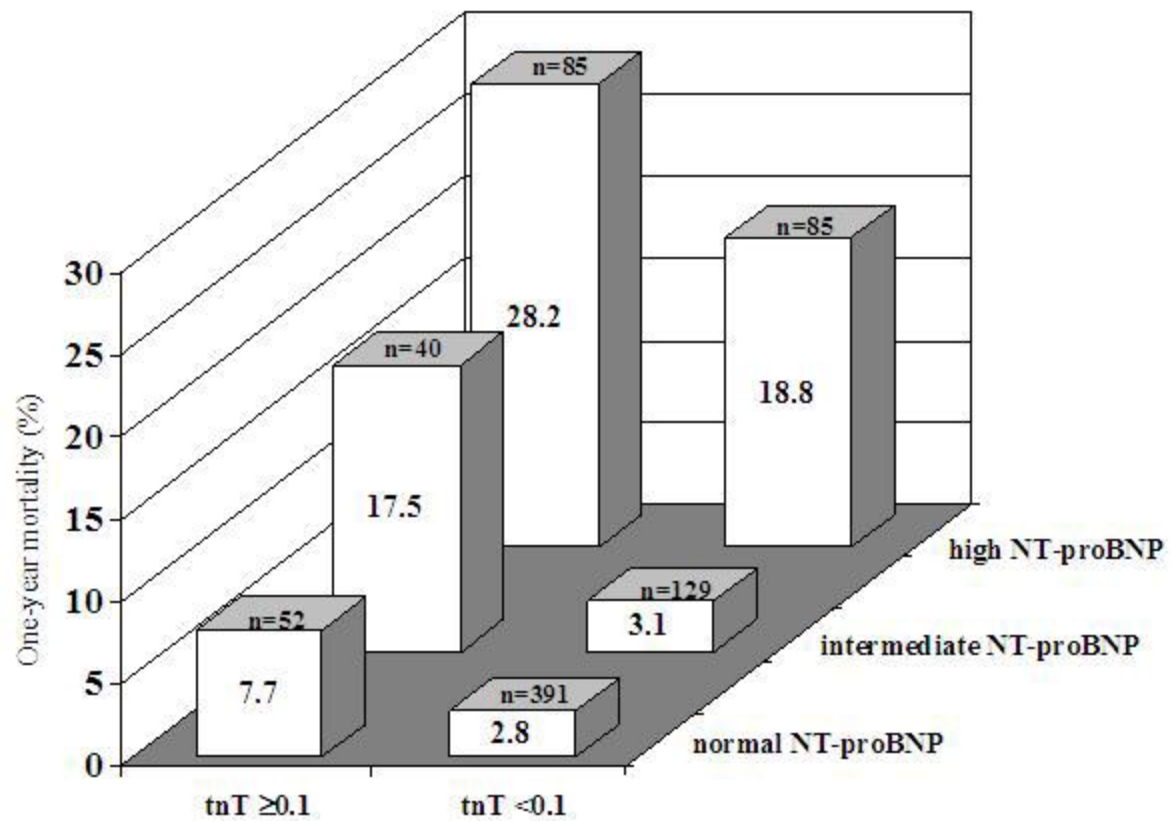
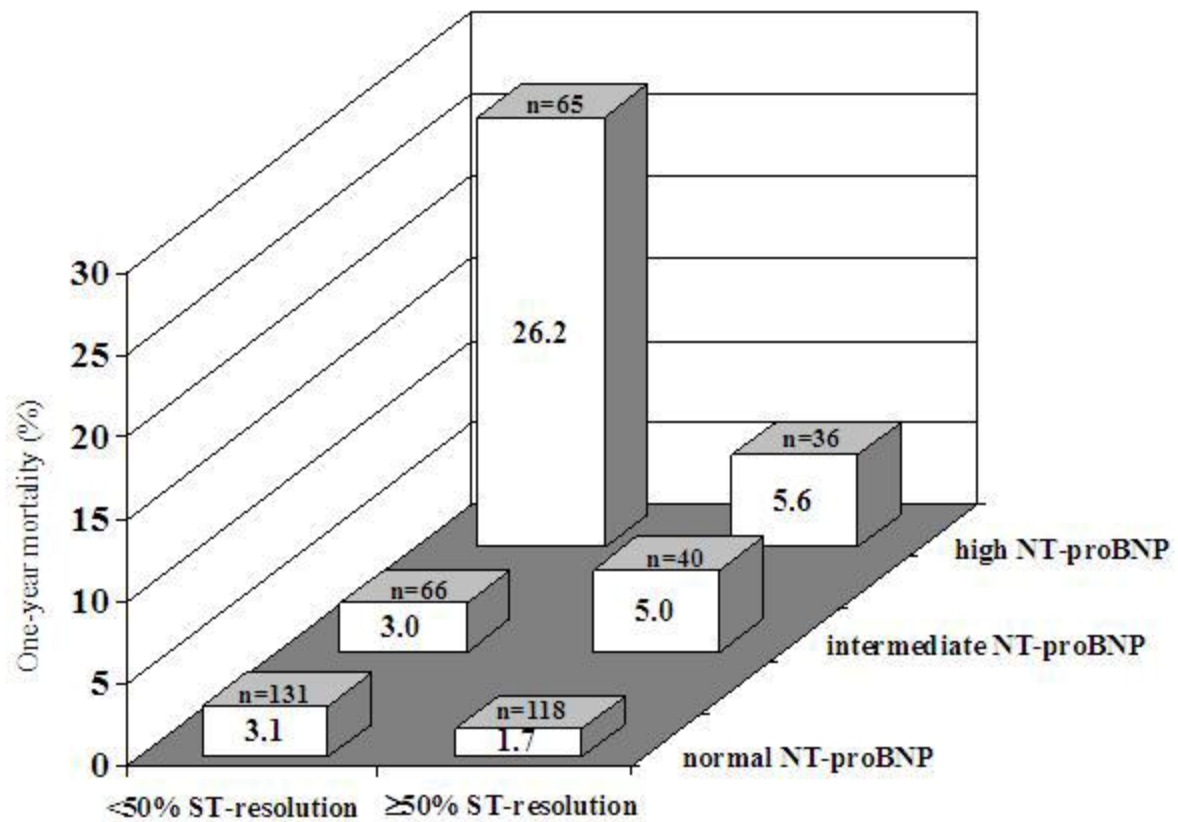


Figure 3b





Admission NT-proBNP and its interaction with admission Troponin T and ST-segment resolution for early risk stratification in ST-elevation myocardial infarction

Erik Björklund, Tomas Jernberg, Per Johanson, Per Venge, Mikael Dellborg, Lars Wallentin and Bertil Lindahl

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