Journal of the American College of Cardiology
Vol. 48, No. 6, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.056
Published by Elsevier Inc.

Biomarkers and Coronary Disease

Troponin-T and N-Terminal Pro-B-Type Natriuretic Peptide Predict Mortality Benefit From Coronary Revascularization in Acute Coronary Syndromes

A GUSTO-IV Substudy

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OBJECTIVES This study was designed to evaluate biomarkers for selection of patients with non–ST-segment elevation acute coronary syndromes (ACS) that derive mortality benefit from revascularization.

BACKGROUND Biomarkers are essential for identification of patients at increased risk, which may be reduced by revascularization.

METHODS During the initial 30 days, 2,340 patients of 7,800 (30%) with non–ST-segment elevation ACS in the GUSTO (Global Utilization of Strategies To open Occluded arteries)-IV trial underwent coronary revascularization. The 1-year mortality was calculated in 30-day survivors stratified by status of revascularization and levels of biomarkers. A propensity score for receiving revascularization was constructed and included in a survival analysis that also included the time point of revascularization as a time-dependent covariate.

RESULTS Elevation of troponin-T or N-terminal pro-B-type natriuretic peptide (NT-proBNP) was associated with a high mortality. In patients with either or both of these markers elevated, a lower mortality following revascularization was observed. In contrast, patients without elevation of these markers had low 1-year mortality without any reduction in mortality following revascularization. In fact, in patients with normal levels of both troponin-T and NT-proBNP, a significant increase in 1-year mortality after revascularization was observed. Elevation of C-reactive protein, interleukin-6, creatinine clearance, and ST-segment depression was also related to a higher mortality. However, independent of these markers, mortality was lower after revascularization.

CONCLUSIONS Markers of troponin-T and NT-proBNP not only assist in risk stratification of patients with non–ST-segment elevation ACS but also appear to identify patients who have a reduced mortality associated with early coronary revascularization. (J Am Coll Cardiol 2006;48:1146–54) © 2006 by the American College of Cardiology Foundation

Unstable coronary artery disease, such as unstable angina or non–ST-segment elevation myocardial infarction (MI), is a heterogeneous condition with a variable risk of subsequent cardiac events. Early risk stratification is essential and is usually performed with clinical baseline characteristics, clinical findings, electrocardiogram (ECG) (1), and biochemical markers of myocardial damage (2). During the past few years, it has been proven that markers of reduced renal function, such as creatinine clearance (3), cardiac performance (for example, N-terminal pro-BNP [NT-proBNP]) (4,5), inflammation (e.g., C-reactive protein [CRP]) (6,7), and interleukin (IL)-6 (8) also provide independent prognostic information on mortality.

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Manuscript received November 30, 2005; revised manuscript May 16, 2006, accepted May 23, 2006.

In the overall population, recent studies have convincingly shown that a strategy using early revascularization procedures reduces the risk of death and recurrent MI (9). Revascularization is, however, resource consuming and potentially hazardous. Therefore, clinicians need tools to select patients with the greatest potential benefit from revascularization. It has been shown that patients with troponin elevation or ST-segment depression derive a particular benefit from revascularization procedures (10). Furthermore, one study suggested that IL-6 also provides predictive information regarding benefit from this treatment strategy (8). N-terminal pro-BNP and creatinine clearance are the biochemical markers with the strongest relation to mortality (5,11). However, no consistent results have been published regarding their ability to predict a particular mortality reduction following revascularization therapy (12,13).

The GUSTO (Global Utilization of Strategies To open Occluded arteries)-IV trial included 7,800 patients with non–ST-segment elevation acute coronary syndromes (ACS) (14) for evaluation of abciximab as primary medical treatment.

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CI	= confidence interval
CRP	= C-reactive protein
ECG	= electrocardiogram
GUSTO-IV	= Global Utilization of Strategies To open Occluded arteries-IV trial
IL	= interleukin
MI	= myocardial infarction
NT-proBNP	= N-terminal pro-B-type natriuretic peptide
PCI	= percutaneous coronary intervention
RR	= relative risk

Thirty-day survivors who underwent revascularization had a lower 1-year mortality compared with medically treated patients after correction for patient characteristics in multivariable analyses, including a propensity score that adjusted for covariates that were associated with the likelihood of early revascularization (15).

The aim of the present study was to evaluate whether biochemical markers of myocardial damage, reduced myocardial performance, inflammation, and renal insufficiency are useful for the identification of patient subsets with lowered mortality after revascularization therapies.

METHODS

Patient selection and randomized treatment. The GUSTO-IV trial included 7,800 patients with non–ST-segment elevation ACS from 458 centers in 24 countries during 1999 and 2000 (14). Patients over 21 years of age with 1 or more episodes of angina lasting ≥5 min within 24 h of admission and either a positive cardiac troponin test or ≥0.5mm of ST-segment depression were eligible. The study was conducted in a double-blind fashion, with patients randomly assigned to three groups: abciximab infusion for 24 h, abciximab infusion for 48 h, 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 discouraged until 12 h after the completion of the study agent infusion but was thereafter at the discretion of the treating physician. Myocardial infarction was defined as either a new Q-wave or creatinine kinase-MB fraction ≥3 times the normal upper limit as previously presented in detail (14). At 12 months, data on all-cause mortality were collected. There was no benefit of the randomized abciximab treatment in any subgroup based on clinical characteristics or levels of biomarkers.

Laboratory analyses. Venous blood samples were obtained via a 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 fraction 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, Uppsala, Sweden, for analyses. One batch was unfortunately lost during transportation. The levels of troponin-T were determined in 7,115 patients by a third-generation assay on an Elecsys (Roche Diagnostics, Basel, Switzerland) with a detection limit of 0.01 μg/l. C-reactive protein concentrations were measured in 7,108 patients with a chemiluminescent enzyme-labeled immunometric assay (Immulite CRP, Diagnostic Products Corporation, Los Angeles, California) with a detection limit of 0.1 mg/l. Measurements of plasma levels of IL-6 were performed in 6,857 patients with a commercial enzyme-linked immunosorbent assay (Quantikine, R&D systems, Abingdon, United Kingdom) with a detection limit of 0.7 ng/l. Serum NT-proBNP was determined in 6,809 patients with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). Serum creatinine for 7,703 patients was analyzed at local laboratories. The creatinine clearance rate was calculated with the Cockcroft and Gault equation: $[(140 - \text{age}) \times (\text{weight, kg})]/\text{serum creatinine}$ (μmol/l) (16). Baseline ECG was performed in all 7,800 patients.

Statistical analyses. Patients who underwent revascularization within 30 days after enrollment were compared with those who did not undergo such a procedure. Because patients who underwent revascularization within 30 days were selected and survived at least until their revascularization, which may introduce bias, all univariable analyses regarding potential beneficial effect of revascularization were restricted to 30-day survivors.

However, because the treatment itself causes an early increased risk of death, exclusion of deceased patients may also overestimate the treatment effect. Both these biases were avoided by redefining the risk sets for every time point, allowing patients to move from the non-revascularized to the revascularized group at the time of revascularization. To adjust for baseline differences between the revascularized and non-revascularized patients, a propensity score (17) estimating the probability of revascularization was calculated through a logistic regression model. A selection was done among a large number of the baseline variables, and the final model included the following variables: age, gender, region (Western Europe, Eastern Europe, North America, and others), race, diabetes status, history of heart failure, treatment with beta-blockers, nitroglycerin, digitalis, ST-segment depression at admission, and time from symptom onset to randomization. Age was entered as a quadratic polynomial. Two interactions with region were also included: treatment with nitroglycerin and history of percutaneous coronary intervention.

The revascularization rate was markedly lower in Eastern Europe (11.5%) as compared with the rest of the world (38%), and the procedure-related mortality (within 30 days after revascularization) was substantially higher, 6% versus 4% after percutaneous coronary intervention (PCI) and 18% versus 7% after coronary artery bypass grafting (Fig. 1). The F1
likelihood of revascularization by multivariable analyses was

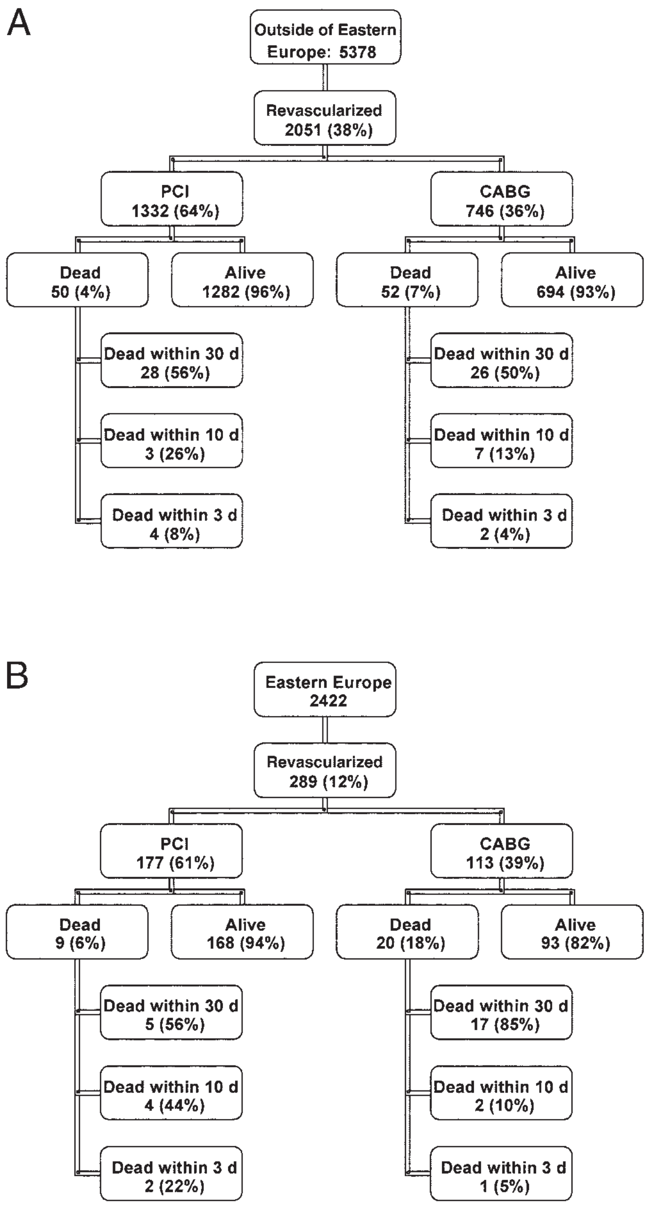

Figure 1. Mortality in subgroups of patients stratified by type of interventional treatment: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). **(A)** Outside of Eastern Europe; **(B)** Eastern Europe.

positively associated with admission outside of Eastern Europe, increasing age, male gender, prior nitroglycerin and beta-blocker therapy, ST-segment depression, absence of diabetes, previous heart failure, and digitalis treatment. Hence, the calculated propensity score for revascularization was strongly dominated by region, making it difficult to include the propensity score for the entire population in the final multivariable analysis. Therefore, patients from Eastern Europe were excluded and the propensity score refitted in the final analyses.

The average risk of death was then calculated as the number of cases per aggregated person-time at risk for each group (revascularized/non-revascularized). To be able to adjust for the propensity score and other variables, a parametric survival model assuming an exponentially distributed survival time was formulated.

Finally, the relative reduction in mortality following revascularization was estimated for subgroups defined by different levels of biochemical markers. Differences between the markers regarding their ability to select subsets of patients with lower mortality following revascularization were tested by inclusion of a multiplicative interaction term in the model. The following cutoff values were used: troponin-T (0.01 μg/l = lowest detection limit and 25th percentile), NT-proBNP (237 ng/l = 25th percentile), IL-6 (10 ng/l = 75th percentile), CRP (10 mg/l = 75th percentile), and creatinine clearance (50.7 ml/min = 25th percentile) based on experience from previous publications (5,18). All calculations were done using the statistical program R (19).

RESULTS

Revascularization. The patient population is well characterized and has been described in detail previously (14). Baseline characteristics for patient strata based on levels of troponin-T and Nt-proBNP are shown in Table 1. In T1 accordance with the protocol, only 147 patients (2%) were revascularized during the 48 h of study drug infusion. However, within 30 days after inclusion, coronary angiography was performed in 3,804 patients (49%), and a total of 2,340 (30%) patients had undergone revascularization on clinical indications. Coronary bypass surgery was performed in 831 patients after a median of 12 days, and 1,481 patients underwent PCI after a median of 7 days. Both coronary artery bypass grafting and PCI were performed in 26 patients. Differences between patients receiving and not receiving revascularization have been described previously (15).

Observed reduction of mortality following revascularization. Among 30-day survivors, patients who underwent revascularization during the initial 30 days after admission had a significantly lower mortality compared with those who did not undergo revascularization, as presented in a previous publication from our group (15). In patients with elevation of troponin-T $\geq$0.01 μg/l, a significantly lower 1-year mortality in patients who underwent revascularization during the initial 30 days, as compared with those who did not undergo revascularization, was observed; 6.9% versus 2.2%, $p < 0.001$ (Table 2, Fig. 2A). Among the troponin-negative T2, F2 patients, there was no statistically significant difference in the crude mortality among those who received or did not receive revascularization (2.6% vs. 3.0%, $p = 0.7$). Similarly, a lower mortality following revascularization was also observed in patients with elevation of NT-proBNP ($\geq$237 ng/l, 7.0% vs. 2.7%, $p < 0.001$). In patients with NT-proBNP <237 ng/l, there was no difference in 1-year mortality between revascularized and non-revascularized patients (1.2% vs. 1.2%, $p = 1.0$) (Fig. 2B). Revascularization was associated with a significantly lower 1-year mor-

Table 1. Baseline Characteristics for Patient-Strata Based on Levels of Troponin-T and NT-proBNP

	TnT, μg/l			NT-proBNP, ng/l		
	≤0.01	>0.01	p	≤237	>237	p
Age (yrs), mean ± SD	64 ± 11	66 ± 11	<0.001	59 ± 10	67 ± 11	<0.001
Weight (kg), mean ± SD	76 ± 13	78 ± 14	<0.001	80 ± 13	76 ± 13	<0.001
Male gender, %	48.3	67.5	<0.001	65.9	60.5	<0.001
Current smoking, %	16.6	24.8	<0.001	28.6	20.7	<0.001
History of stroke, %	1.5	2.5	0.02	1.0	2.7	<0.001
Heart failure, %	7.7	7.3	0.6	2.8	9.0	<0.001
Hypercholesterolemia, %*	35.0	29.7	<0.001	31.9	30.7	0.3
Angina pectoris, %	60.6	42.2	<0.001	42.0	48.8	<0.001
Hypertension, %	57.4	49.8	<0.001	44.5	54.2	<0.001
Diabetes mellitus, %	18.4	22.1	0.01	13.7	23.3	<0.001
Previous MI, %	28.2	32.0	0.02	17.9	34.8	<0.001
Previous revascularization, %	16.4	15.0	0.13	11.3	16.5	<0.001
ST-segment depression	93.2	76.2	<0.001	84.8	79.6	<0.001

*History of hypercholesterolemia requiring medical therapy.
MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TnT = troponin-T.

tality independent of levels of creatinine clearance, although the absolute difference was greater in the high-risk patients with a creatinine clearance below 51 ml/min. Similarly, when stratifying the patients for levels of the inflammatory markers, the mortality was significantly lower following revascularization independent of levels of IL-6 (Fig. 2D) or CRP (data not shown), although the absolute reduction of mortality was larger in patients with higher compared with lower levels of the inflammation markers. Also, when the patients were stratified for the occurrence of ST-segment depression (0.5 mm) at admission, the relative observed improvement in outcome following revascularization was similar among patients with and without ST-segment depression. The absolute improvement, as expected, was larger in patients with ST-segment depression (data not shown). As both troponin-T and NT-proBNP appeared to stratify patients with versus without improvement in outcome following revascularization, the combination of the markers were evaluated in patients surviving 30 days (Fig. 3). Among the 950 patients without elevation of either of the markers, 154 patients underwent revascularization and had a higher crude mortality than patients that did not undergo revascularization (3.2% vs. 0.6%, p = 0.04). For patients with either of the markers positive, 1-year mortality was lower with revascularization (1.3% vs. 3.7%, p < 0.001). Finally, among the 3,914 patients with both markers positive, a clearly lower 1-year mortality after revascularization was observed (2.6% vs. 7.6%, p < 0.001).

Multivariable survival analyses. Among patients with troponin-T elevation (>0.01 μg/l), there was a significantly lower mortality associated with revascularization (relative risk [RR] 0.56, 95% confidence interval [CI] 0.4 to 0.7) (Table 1, Fig. 4). On the contrary, among troponin-negative patients, revascularization tended to be associated with an increase in mortality (RR 1.79, 95% CI 0.96 to 3.8). The difference in risk ratio between troponin-positive

Table 2. One-Year Mortality in Relation to Performed Revascularization in the Initial 30 Days and Levels of Biomarkers

		Univariable			Multivariable Survival Model†		
		Mortality*, % (n)					
Marker	Patients	No Revasc	Revasc	p Value	RR	95% CI	p Value‡
TnT ≤0.01 μg/l	1,779	2.6 (42)	3.0 (11)	0.7	1.79	(0.96, 3.8)	0.004
TnT >0.01 μg/l	5,336	6.9 (222)	2.2 (37)	<0.001	0.56	(0.4, 0.7)	
NT-proBNP ≤237 ng/l	1,702	1.2 (15)	1.2 (5)	1.0	1.91	(0.7, 5.3)	0.04
NT-proBNP >237 ng/l	5,107	7.0 (235)	2.7 (40)	<0.001	0.63	(0.5, 0.8)	
Il-6 ≤10 ng/l	5,143	4.5 (158)	2.0 (30)	<0.001	0.77	(0.6, 1.1)	0.39
Il-6 >10 ng/l	1,714	8.4 (95)	3.6 (17)	0.001	0.61	(0.4, 0.9)	
CRP ≤10 mg/l	5,331	4.2 (155)	1.5 (24)	<0.001	0.54	(0.4, 0.8)	0.03
CRP >10 mg/l	1,777	9.3 (107)	5.5 (25)	0.01	0.94	(0.7, 1.4)	
Creacl >51 ml/min	5,777	3.5 (134)	1.9 (35)	0.01	0.76	(0.5, 1.0)	0.30
Creacl ≤51 ml/min	1,926	11.6 (157)	4.3 (18)	<0.001	0.60	(0.4, 1.8)	

*Patients not surviving 30 days excluded. †Adjusted for a propensity score for revascularization and predictors for increased mortality. The time point of revascularization was entered as a time-dependent covariate. Patients from Eastern Europe were excluded. ‡The p values indicate the test for difference between the marker groups with regard to the relative reduction in mortality following revascularization.
CI = confidence interval; Creacl = creatine clearance; CRP = C-reactive protein; Il-6 = interleukin-6; RR = relative risk; other abbreviations as in Table 1.

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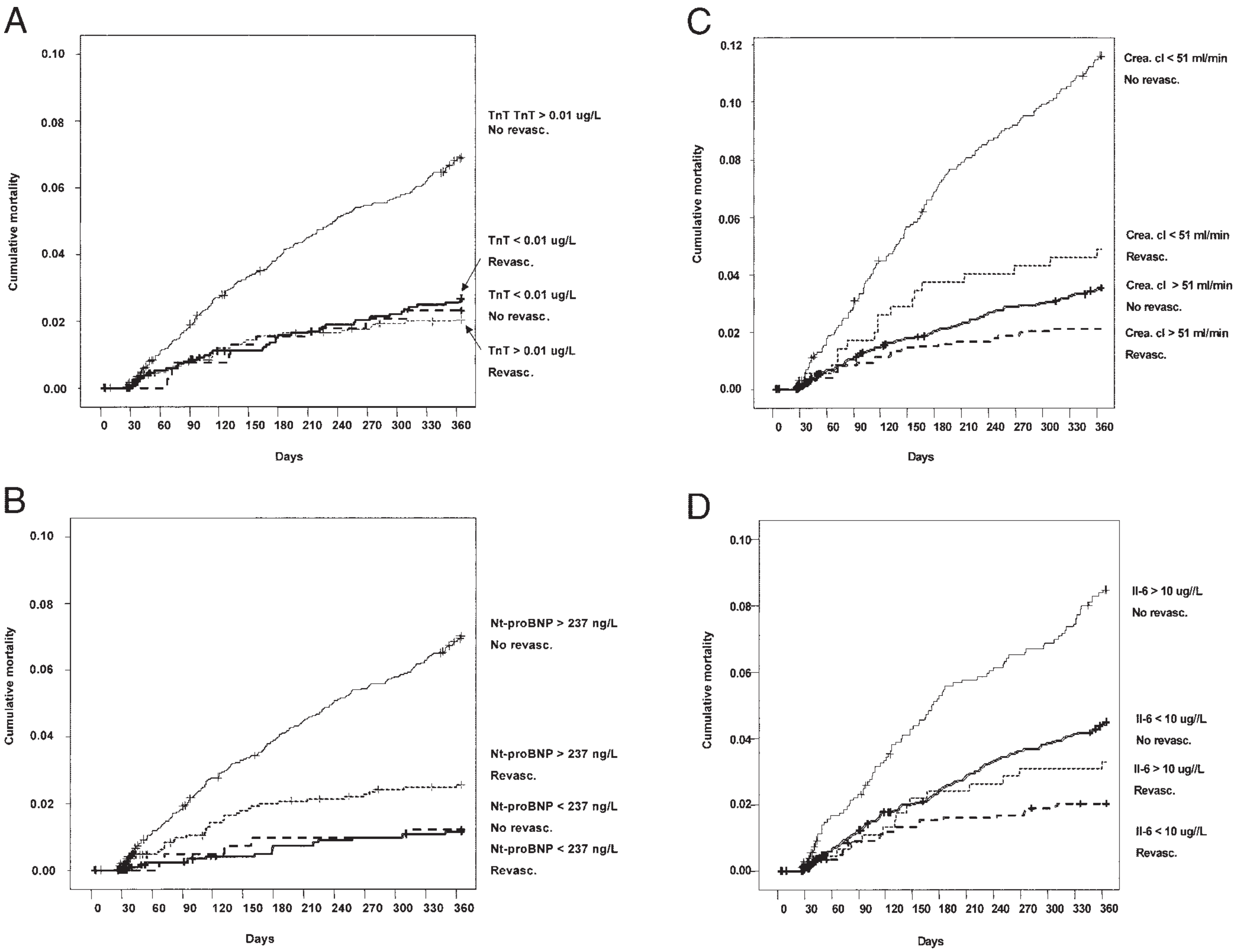

Figure 2. Cumulative mortality estimated by the Kaplan-Meier method of 30-day survivors stratified by revascularization (revasc.) status at 30 days and levels of biochemical markers. **(A)** Troponin-T (TnT) above or below the detection limit of 0.01 μg/l at admission; **(B)** N-terminal pro-B-type natriuretic peptide (Nt-proBNP) above or below the median of 237 ng/l at admission; **(C)** creatinine clearance (Crea. cl) above or below the first quartile limit of 51 ml/min at admission; **(D)** interleukin-6 (Il-6) above or below the third quartile limit of 10 ng/l at admission.

and -negative patients was highly significant (p = 0.003). Similarly, 1-year mortality was significantly lower with revascularization in patients with NT-proBNP above the 25th percentile of 237 ng/l (RR 0.63, 95% CI 0.5 to 0.8). Among patients with Nt-proBNP below 237 ng/l, on the other hand, revascularization tended to be associated with an increase in mortality (RR 1.91, 95% CI 0.7 to 5.3). Thus, there was also a significant interaction between the NT-pro-BNP level and revascularization on 1-year mortality (p = 0.04). For patients with a creatinine clearance below the 25th percentile of 51 ml/min who were at high risk, revascularization was associated with a significantly lower mortality. However, patients with creatinine clearance above the cutoff also tended to have a similar lower mortality following an invasive treatment. Thus, the risk ratios did not differ between the two groups, and the interaction was not significant (p = 0.3). Although elevation of IL-6 was related to increased 1-year mortality, the relative reduction of mortality following invasive therapy was similar in patients with levels above or below the 75th percentile of 10 ng/l. The CRP elevation was associated with a higher mortality, but only patients with CRP levels below the 75th percentile of 10 mg/l had a significant relative reduction of mortality following revascularization in the multivariable model. All results were generally unaltered, with the cut points at the medians of the markers (troponin-T 0.11 μg/l, CRP 4.0 mg/l, IL-6 5 ng/l, NT-proBNP 669 ng/l, and creatinine clearance 66 ml/min).

In patients with elevation of both troponin-T and NT-proBNP, a significantly lower mortality after revascularization was observed, with a relative risk of 0.55 (95% CI 0.4, 0.7) (Fig. 5). On the contrary, revascularization was associated with a significant hazard, with a relative risk of 10.8 (95% CI 2.1 to 56) in patients without elevation of either troponin-T or NT-proBNP. With a cutoff for NT-proBNP at the median of 669 ng/l, the result pointed in the same direction with a narrower CI (relative risk 4.6, 95% CI 1.6 to 13.7).

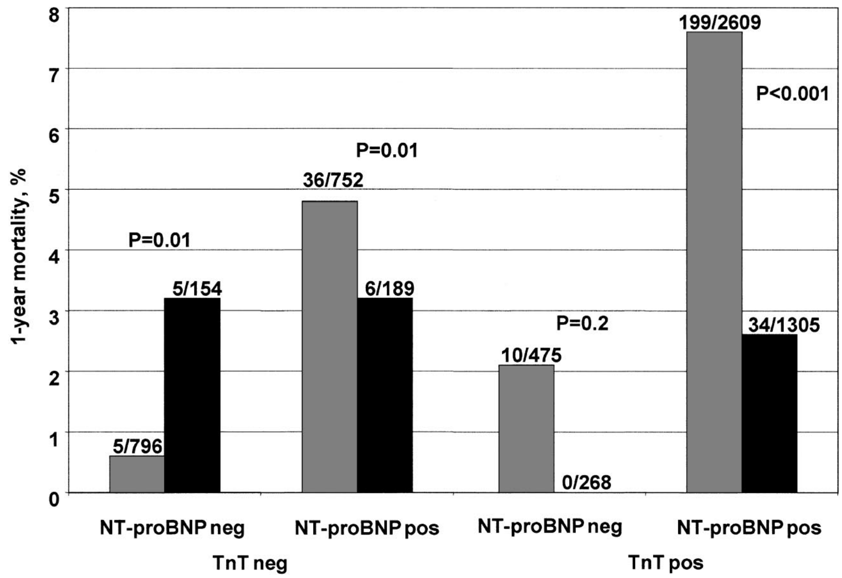

Figure 3. One-year mortality for 30-day survivors stratified by revascularization status and combinations of troponin-T (≤0.01 μg/l and >0.01ug/l) and NT-proBNP (≤237 ng/l and >237 ng/l). **Black bars** represent patients who underwent revascularization and **gray bars**, patients who did not undergo revascularization the initial 30 days. Abbreviations as in Figure 2.

DISCUSSION

Moderate- to high-risk patients with non–ST-segment elevation ACS are recommended to be treated with early revascularization, as this strategy has proven to reduce symptoms of angina, reduce the number of readmissions, shorten the length of hospital stay, and lower the risk of coronary events (9,20,21). Only one randomized trial has shown a reduction of mortality (9), whereas there was an increased mortality with early angiography and revascularization as the standard treatment strategy in one of the early studies (22). An important remaining question is, therefore, how to select patients who may particularly derive a mor-

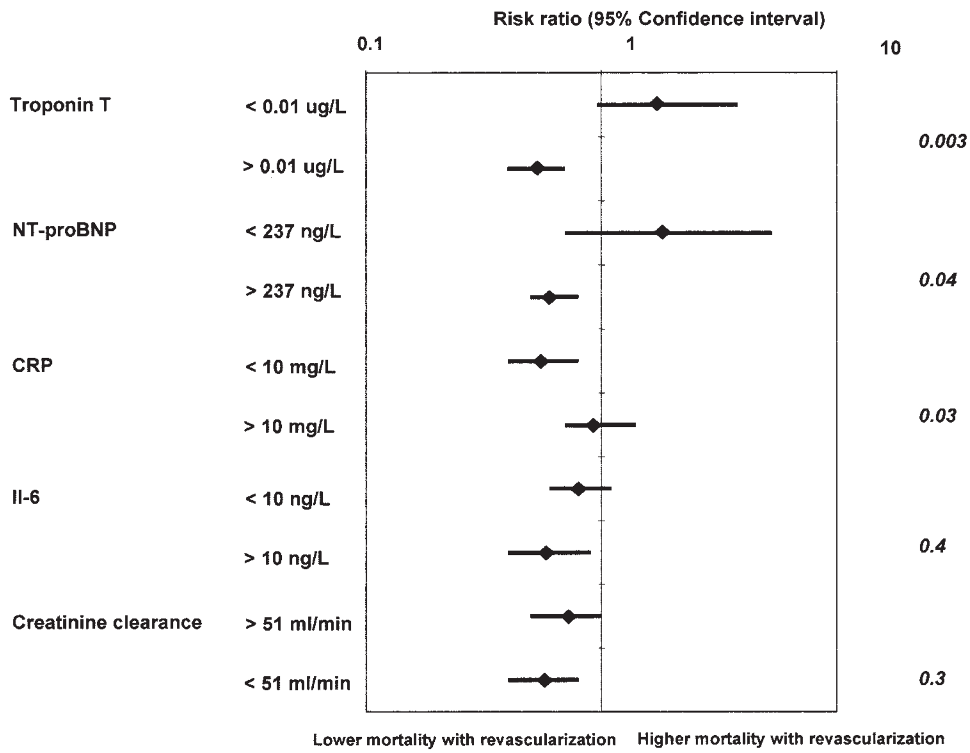

Figure 4. Risk ratios regarding 1-year mortality following revascularization of patients stratified by biomarker status in a parametric survival model, including a propensity score of receiving revascularization and other confounding variables of increased mortality. The p values indicate the significance of difference between the relative risks for positive versus negative markers. A relative risk ratio and 95% confidence intervals <1.0 indicate a lower mortality with revascularization. Patients from Eastern Europe were excluded. CRP = C-reactive protein; other abbreviations as in Figure 2.

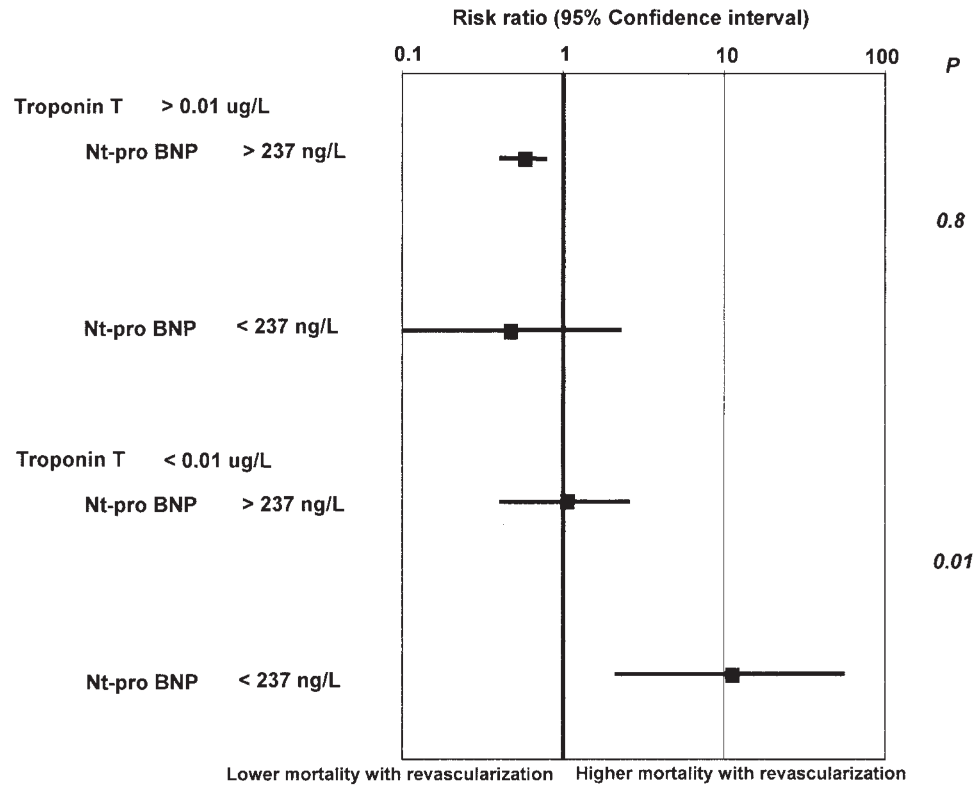

Figure 5. Risk ratios regarding 1-year mortality following revascularization of patients stratified by combinations of biomarkers in a multivariable parametric survival model adjusted for a propensity score of receiving revascularization and other significant variables of increased mortality as well as the time-point of revascularization as a time-dependent variable. The p values indicate the test for difference between the marker groups regarding the reduction of mortality following revascularization. A relative risk ratio and 95% confidence intervals <1.0 indicate a lower mortality with revascularization. Abbreviations as in Figure 2.

tality benefit from early revascularization. In the present study we have shown that biomarkers of myocardial damage and dysfunction are not only useful for prediction of high mortality in patients with non–ST-segment elevation ACS but also for the prediction of a reduced mortality following revascularization. Furthermore, and equally important, normal levels of these markers appear to identify subgroups of patients with a low mortality, which is, in fact, increased by an invasive therapy.

Troponin. In accordance with previous randomized studies regarding the invasive treatment, troponin was shown to be the biomarker with the best ability to predict improvement in outcome following revascularization (10,23). In the GUSTO-IV trial, revascularization was not randomized, which makes is possible that troponin levels biased the selection of patients for angiography and revascularization. However, after correction for the propensity score for revascularization and with the time point of revascularization entered as a time-dependent covariate, all of the observed improvement in survival following coronary revascularization was found among the troponin-positive patients, with a tendency to an increased mortality for the troponin-negative patients. The results of the TACTICS–TIMI-18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy) trial pointed in the same direction, with a significant reduction of the combined end point of death or MI at 6 months only for the troponin-positive patients (10). Similarly, in the FRISC (Fragmin and fast Revascularization during InStability in Coronary artery disease)-II trial, mortality at 12 months was reduced significantly among the troponin-positive patients (24). The relation between levels of troponin-T and extent of coronary disease and the likelihood of embolization of coronary thrombi may explain the reduction of mortality with revascularization in troponin-positive patients (25). On the other hand, the tendency toward an increased mortality with revascularization in troponin-negative patients may be explained by the lower mortality overall in this subgroup.

B-type natriuretic peptide. B-type natriuretic peptide and the N-terminal part of its prohormone, NT-proBNP, are among the most powerful biomarkers for prediction of mortality in patients with non–ST-segment elevation ACS (5). Yet, no previous study has clearly shown that levels of NT-proBNP may be useful for the prediction of benefit or harm of revascularization. In the GUSTO-IV, revascularization was associated with an absolute risk reduction of 4.3% in 30-day survivors with a positive NT-proBNP. A similar tendency was found in the TACTICS–TIMI-18 trial, in which patients with a BNP level above 80 ng/l tended to have a lower mortality after an invasive strategy (7.9% vs. 9.0%). On the contrary, in patients with a BNP level below 80 ng/l, the invasive strategy did not tend to decrease the overall low mortality (1.9% vs. 1.6%) (13).

Similarly, in the FRISC II trial an invasive strategy tended to reduce mortality from 10.8% to 7.2% (absolute risk reduction 3.6%, $p = 0.11$) among patients with NT-proBNP levels in the top tertile (906 ng/l for men and 1,345 ng/l for women). There was, however, no mortality reduction in patients with NT-proBNP in the bottom tertiles (2.6% to 2.0%) (12). In the present study, the 25th percentile of 237 ng/l was chosen as the cut point, which is close to the 97.5th percentile of 290 ng/l in healthy individuals (26). The results pointed in the same direction as other cut points of the markers.

Patients without elevation of NT-proBNP have a low likelihood of other concomitant cardiovascular disorders and are at a very low long-term risk of death (5). The increased short-term risk associated with a coronary intervention in general, and coronary bypass surgery in particular, may not be offset by any long-term mortality reduction in these low-risk patients. Patients with elevated levels of BNP (or NT-proBNP), on the other hand, have been shown to have more concomitant cardiovascular diseases and a greater extent and severity of the ischemic territory during the index event. These factors may explain the observed lower mortality in association with revascularization (27).

Inflammatory markers. Although there was an observed lower mortality with revascularization in IL-6 positive patients after multivariable correction in the present study there was no differential benefit of revascularization based on either of the inflammatory markers in contrast to the substudy results of the FRISC II trial (8). The results did not change if a cut point for IL-6 similar to the one in the FRISC substudy (6 ng/l) was chosen. The reason for the divergent results in the two studies is unclear but may be explained by different methods and sensitivity of the IL-6 analyses. ST-segment depression on admission ECG did not predict any particular reduction in mortality in the present study in contrast to previous studies (23). This may be explained by the low level for the definition of ST-segment depression (0.05 mV) in the GUSTO-IV trial, making the variable rather unspecific for prognostic evaluation.

Combination of markers. Patients without elevation of troponin-T or NT-proBNP in the present study had an extremely low 1-year mortality of 1.6%. Thus, there is a very low potential for improvement in outcome following revascularization (5). Despite the low overall risk in this cohort, 154 of 950 patients (16%) in fact underwent revascularization on clinical grounds during the 30 days after the index event. Our observational data suggest that it may be harmful to revascularize this group of low-risk patients despite an angiographically proven coronary disease.

Study limitations. The present study is post-hoc analysis of non-randomized data. Because of the extensive analysis, statistical power may be limited. However, the large number of included patients with a high event rate and the extensive collection of biomarkers should lend support to our mortality subset analyses. Furthermore, through our propensity score analyses, we have attempted to control for selection bias in the decision to perform coronary revascularization. We also used revascularization as a time-dependent variable among other predictors of increased mortality in the final survival model. Because the propensity score for revascularization was completely dominated by region, patients included in Eastern Europe were excluded in the final multivariable model for statistical reasons. There was, however, no indication that the evaluated biomarkers had different relations to crude mortality for patients in Eastern Europe or in other regions.

Conclusions. Our data show that measurement of troponin-T and NT-proBNP levels improves risk stratification of patients with non–ST-segment elevation ACS. In centers where early revascularization can be performed with low procedural mortality, patients with elevated levels of both markers are at high risk of death that appears to be reduced by coronary revascularization. In addition, patients with low levels of both these markers have a very low 1-year mortality with medical management, and early invasive procedures appear to increase their overall risk of mortality. Measurement of troponin-T and NT-proBNP levels should be included in risk stratification and early management strategy decisions for patients with ACS.

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