N-terminal pro B type natriuretic peptide complements the GRACE risk score in predicting early and late mortality following acute coronary syndrome

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Abstract

Background: The GRACE risk score has been shown to offer predictive power with regards to death and myocardial infarction (AMI) in patients with acute coronary syndromes (ACS). N-terminal pro-B type natriuretic peptide (NT-proBNP) has also been found to be useful in predicting mortality following ACS.
Aim: We sought to investigate the utility of GRACE score and NT-proBNP levels at predicting risk of early and late deaths following ACS.
Method: We studied 1033 patients (740 men, mean age 66.5 ± 12.7years) with AMI. Blood was drawn once within 24 hours following the onset of chest pain. The plasma concentration of NT-proBNP was determined using an in-house non-competitive immunoassay.
Results: Patients were GRACE risk scored as described. 30-day mortality was 3.7%, 6-month mortality was 7.8%, all were related to higher GRACE risk scores ($p=0.001$ for trend). Higher NT-proBNP levels were also related to increased mortality ($p<0.0001$). In a Cox proportional hazards model, independent predictors of 30-day and 6-month mortality included NT-proBNP levels and GRACE risk score. The receiver-operating curve for GRACE risk score was complemented by NT-proBNP levels for prediction of 30-day mortality (AUC 0.85) and 6-month mortality (AUC 0.81).
Conclusion: NT-proBNP gives complementary information to GRACE risk score for predicting early and late mortality. The inclusion of the NT-proBNP blood test is useful in risk stratifying patients after an acute coronary syndrome.
Keywords Myocardial infarction; acute coronary syndromes, NT-proBNP, prognosis, GRACE score

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Introduction

Risk stratification is an important and integral part of the management of patients following an acute coronary syndrome (ACS). A number of models have been developed to help the clinician in risk stratification such as the TIMI, PURSUIT and GRACE scores [1,2]. Of these, the GRACE scoring system is probably the most robust clinical risk stratification tool as it has was based on patients seen in routine clinical practice as opposed to selected patients who were enrolled in clinical trials [3]. A GRACE score has been developed predicting in-hospital mortality and 6-month mortality and recently, variables have been defined that predict death or AMI at 6 months [4,5,6]. The three major scoring systems that have been developed have been shown to have prognostic power at predicting early adverse events. However all three have been shown to have prognostic value at predicting adverse events out to 1 year [7]. The GRACE score had better predictive power than TIMI and PURSUIT. The GRACE score also has good predictive capacity out to 4 years [8].

In parallel with this, biomarkers particularly B type natriuretic peptide (BNP) and its more stable counterpart N-terminal pro-B type natriuretic peptide (NT-proBNP) [9] have been shown to have a vigorous response following an acute myocardial infarction (AMI) [10] and plasma levels are related to short and long-term mortality [11-15]. BNP is able to provide additional prognostic information over and above that provided by left ventricular dysfunction following an acute myocardial infarction [12]. NT-proBNP also has similar prognostic power and levels measured in the sub-acute phase, between days 2 and 4 have prognostic power to predict left ventricular function and 2 year survival [14]. This has been shown across the entire acute coronary syndrome spectrum [16]. There are some data to suggest that the natriuretic peptides may also have prognostic power at predicting future myocardial infarction [13,17]. The aim of this study was to compare the performance of the GRACE score with NT-proBNP and to investigate whether a combination of NT-proBNP with GRACE score would give increased predictive power of short-term (30-day) and long term (6-month) mortality.

Methods

Study population

We studied 1033 consecutive admitted to the Coronary Care Unit of Leicester Royal Infirmary with ACS. The study complied with the Declaration of Helsinki, was approved by the local ethics committee and written informed consent was obtained from patients.

AMI was diagnosed if a patient had a plasma creatine kinase-MB elevation greater than twice normal or cardiac troponin I level >0.1 ng/mL with at least one of the following, symptoms of ischaemia, electrocardiographic (ECG) changes indicative of ischaemia or development of Q-waves on the ECG [18]. AMI was sub-categorised into ST segment elevation myocardial infarction (STEMI) or non-ST segment myocardial infarction (NSTEMI).

Exclusion criteria were known malignancy, or surgery in the previous month. Patients with ST-segment elevation of >0.1 mV in two contiguous ECG leads received thrombolytic therapy (tissue plasminogen activator or streptokinase) if they presented within a suitable time frame. Patients underwent assessment for GRACE risk score for ACS as described previously [4,5] and grouped into tertiles, low, intermediate and high risk groups.

Plasma samples

Blood samples were drawn on 1 occasion within 24 hours after onset of chest pain for determination of plasma NT-proBNP. After at least 15 minutes bed rest, 20mL blood was collected into tubes containing EDTA and aprotinin. All plasma was stored at -70°C until assayed in a single batch.

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Calculating the GRACE score

We used the GRACE score derived by Granger et al [4] for analysis of in-hospital mortality and the GRACE score developed by Eagle et al [5] for analysis of 6-month mortality. The variables in the 2 GRACE scores are detailed in Table 1.

NT-proBNP assay

Our NT-proBNP assay was based on a non-competitive assay as previously described [16]. Sheep antibodies were raised to the N-terminal of human NT-proBNP and monoclonal mouse antibodies were raised to the C- terminal. The N-terminal IgG was affinity-purified and biotinylated. Samples or NT-proBNP standards were incubated in C-terminal IgG–coated wells with the biotinylated antibody for 24 hours at 4°C. Detection was with methyl-acridinium ester (MAE)–labelled streptavidin. The lower limit of detection was 0.3 pmol/L. There was no cross reactivity with atrial natriuretic peptide, BNP, or C-type natriuretic peptide. Inter and intra coefficients of variation were 2.3% and 4.8% respectively. The results from this in-house assay are highly correlated ($r=0.90$, $P<0.0001$, $n=86$; kappa=0.80) to those obtained on the NT-proBNP assay marketed by Roche Diagnostics Ltd. (Lewes, East Sussex, UK).

End points

We assessed the value of NT-proBNP for the prediction of early (1-month) and late (6 month) mortality. Endpoints were identified through routine data provided to the hospital from the Office of National Statistics Registry, and review of the medical notes. There was a minimum 6 month follow-up of all surviving patients. No patient was lost to follow-up.

Statistical analysis

Statistical analyses were performed on SPSS Version 14 (SPSS Inc, Chicago, Illinois) and Stata version 10 (Texas, USA). Comparisons of continuous variables were made using the Mann Whitney U test. The relationship of baseline variables with death was assessed using Cox proportional hazards analysis by multivariable analysis. An epidemiological approach was taken and factors thought to be important for the endpoint was entered in multivariable analyses. The factors entered into the model for predicting 30-day mortality were baseline patient characteristics as part of the GRACE score, gender, past history of AMI, territory of infarction, STEMI or NSTEMI, therapy with ACE inhibitors, angiotensin receptor blockers and beta-blockers and the peptide marker NT-proBNP. The factors entered into the model for predicting 6-month mortality were baseline patient characteristics as part of the GRACE score, gender, territory of infarction, STEMI or NSTEMI, Killip class, therapy with ACE inhibitors, angiotensin receptor blockers and beta-blockers and the peptide marker NT-proBNP. Kaplan-Meier cumulative survival curves were constructed and compared by the log-rank test and the log-rank test for trend. To compare the accuracy of NT-proBNP and GRACE score, receiver-operating characteristic (ROC) curves were generated and the area under the curves (AUC) was calculated. Comparisons between ROC curves was by the method of Hanley and McNeil [19]. Reclassification tables were constructed as a further measure to assess any incremental value for NTproBNP in improving the risk classification afforded by the GRACE score [20]. Levels of NT-proBNP were normalised by $\log_{10}$ transformation. Thus, hazard ratios refer to a tenfold rise in the levels of these markers. A p value below 0.05 was deemed to be statistically significant.

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Results

Patient characteristics

The demographic features of the patient population are shown in Table 2. Median length of follow-up was 503 days with a range of 1–1059 days. No patient was lost to follow-up. During follow-up, 122 (11.6%) patients died. There were 151 (14.4%) readmissions with AMI.

NT-proBNP levels in patients

Median NT-proBNP was 1106.6 pmol/L (range 0.3-34135 pmol/L). NT-proBNP was higher in patients who died (median [range] pmol/L, survivors 782.5[0.3-14109.1] vs. dead 4159.1[9.0-34135], p<0.0001).

GRACE score and NT-proBNP as predictors of early mortality (30-days)

30-day mortality was 3.7% (38 patients) and was related to higher GRACE risk scores (p<0.001 for trend, Figure 1). When clinical and demographic characteristics (as listed in statistical analysis) were entered into a multivariable Cox proportional hazards model the independent predictors of death included NT-proBNP (HR 2.24, 95% CI: 1.07-4.71, p=0.034) and GRACE risk score (HR 1.02, 95% CI: 1.01-1.03, p<0.001), Table 3. When NT-proBNP was added to the individual components of the GRACE score, NT-proBNP displaced many of the factors in the GRACE score, Table 4.

The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with NT-proBNP below the median compared with those with NT-proBNP above the median (log rank 27.10, p=0.0001). Kaplan-Meier curves for quartiles of GRACE score and NT-proBNP are shown (Figure 2 and 3 respectively). The combined Kaplan-Meier survival curve related to whether the patients had a below or above median GRACE score and below or above median NT-proBNP level showed an improved risk prediction (pooled over strata, log rank 98.72, p=0.0001, Figure 4).

The receiver-operating characteristic curve for NT-proBNP yielded an area under the curve (AUC) of 0.79 (95% CI: 0.72-0.86, p<0.001), for GRACE risk score the AUC was 0.84 (95% CI: 0.78-0.89, p<0.001). The combination of GRACE risk score and NT-proBNP improved risk prediction for mortality 0.85 (95% CI: 0.85-0.90, p<0.001), which significantly exceeded that of NT-proBNP (p=0.007) but not GRACE score (p=0.20). Patients who had an NT-proBNP level above median (above 1100 pmol/L) and GRACE score above 149 were at especially high-risk of death.

GRACE score and NT-proBNP as predictors of 6-month mortality

6-month mortality was 7.8% (82 patients) and was related to higher GRACE risk scores (p<0.001 for trend). When clinical and demographic characteristics were entered into a multivariable Cox proportional hazards model the independent predictors of death included NT-proBNP (HR 1.84, 95% CI: 1.09-3.13, p=0.023) and GRACE risk score (HR 1.02, 95% CI: 1.02-1.03, p<0.001), Table 5. When NT-proBNP was added to the individual components of the GRACE score, NT-proBNP displaced many of the factors in the GRACE score, Table 6.

The Kaplan-Meier survival curve revealed a grading of mortality related to whether the patients had a below or above median GRACE score and below or above median NT-proBNP level (pooled over strata, log rank 103.0, p=0.0001). The receiver-operating characteristic curve for NT-proBNP yielded an area under the curve (AUC) of 0.76 (95% CI: 0.70-0.82, p<0.001), for GRACE risk score the AUC was 0.79 (95% CI: 0.74-0.83, p<0.001). The combination of GRACE risk score and NT-proBNP improved risk prediction for mortality 0.81 (95% CI: 0.86-0.86, p<0.001), which significantly exceeded that of NT-proBNP (p<0.001) and GRACE score (p=0.035).

Patients who had an NT-proBNP above 1100 pmol/L and GRACE score above 120 were at especially high-risk of death.

Reclassification analysis for added predictive ability of NT-proBNP over the GRACE score

Net reclassification improvement [20] was used to assess the incremental prediction improvement afforded by NTproBNP over the GRACE score for both 30 day and 6 month mortality. Individuals were categorised according to their GRACE risk scores (as low, intermediate and high risk as described on the GRACE net site (http://www.outcomes-umassmed.org/grace/grace_risk_table.cfm). Table 7 shows the net reclassification improvement of adding NTproBNP to the GRACE model, for both 30 day and 6 month mortality. The improvement for predicting 30 day mortality was 24.4% ($P<0.0001$) whereas at 6 months, it was 10.4% ($P<0.04$).

Discussion

The aim of this study was to compare the prognostic utility after ACS of the GRACE risk score to that of NT-proBNP. The results of our study show that the GRACE risk score and NT-proBNP are good predictors of adverse events in our unselected cohort of patients. We have shown that using a combination of GRACE risk score with NT-proBNP can give further prognostic information with regard to both short term and long term mortality.

GRACE score and NT-proBNP – 30-day mortality

The Grace score predicting in-hospital mortality considers 8 independent factors. In Granger et al's paper [4] the GRACE score had an area under the ROC curve of 0.83 at predicting in-hospital death. In our cohort of patients the area under the ROC curve for GRACE was 0.84. The similarities are probably because of our unselected patient population similar to that from which the GRACE database is derived. We have recruited consecutive patients with no restriction or overt exclusion criteria (mean age of our cohort of patients was 65 compared to 66 in the GRACE study).

The additive value of NT-proBNP is over and above the factors of the GRACE score which include robust factors such as Killip class and serum cardiac markers. Indeed we have shown that when NT-proBNP is included with the standard GRACE variables it outperforms many of the variables as a strong independent predictor of 30-day mortality. Using net reclassification improvement analysis, the contribution of NT-proBNP to improving risk prediction from the GRACE score alone was also very significant.

GRACE score and NT-proBNP – 6-month mortality

The GRACE score for predicting late mortality has 9 factors [5]. The 6-month mortality in our cohort was greater than that of the GRACE study (7.8% vs. 4.8% in GRACE). In our cohort the main reperfusion strategy employed was thrombolysis which could well account for some of the differences in mortality seen. Having said this, the AUC of the ROC curve showed that NT-proBNP had similar predictive power to GRACE score and both were similar to that found in the GRACE study (0.81). NTproBNP improved upon the accuracy of mortality prediction of the GRACE score on both ROC AUC analysis and net reclassification improvement analysis. The mortality at 12 months was similar to that seen in the OPERA study a large French registry [21]. When NT-proBNP is added to the standard GRACE variables in a multivariable Cox model it remains a strong independent predictor of mortality. The outcome of patients following an AMI is still poor; [5,21] for this reason risk stratification is important as it can select patients who are at risk of adverse events including mortality. Also those at greatest risk are more likely to derive benefit from pharmacological or reperfusion strategies [22]. This is

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the first study comparing GRACE scoring with NT-proBNP both of which have strong prognostic potential [4,5,6,14,15,23,24]. We have shown that there is equivalence of the GRACE risk score and measurement of NT-proBNP levels. The GRACE risk score is the most accurate risk score available for predicting outcomes after an acute coronary syndrome. However it is a complicated scoring system. As NT-proBNP is equivalent in terms of prognosis it may in the future be possible to replace this with the GRACE score.
The two combined however give additional prognostic information as shown by the Kaplan-Meier curve. A raised NT-proBNP above the median and a high GRACE score identify a particularly high-risk cohort of patients following an acute coronary syndrome.
Other studies have investigated the natriuretic peptides and compared them to GRACE and even the TIMI score. When the GRACE score was compared with BNP the two were found to provide complementary information [25]. BNP also provides incremental prognostic information over and above the TIMI score in STEMI patients treated with primary angioplasty [26,27]. Similarly NT-proBNP is able to provide prognostic information in NSTEMI patients over and above the TIMI score [28]. Our study however has a larger population than the other studies which have investigated natriuretic peptides and clinical scores.
Prognostic information may help guide treatment in the future a study which utilized NT-proBNP for risk stratification showed that patients with raised levels of the peptide derived more benefit from an invasive treatment strategy than a conservative treatment strategy [29]. With the availability of rapid point of care assays for NT-proBNP this marker could easily be part of the armamentarium of the clinician and could readily be combined with the GRACE score to identify individuals at high risk of adverse events.

Limitations and Strengths:
A major strength of our data set is that it has an approximately equal weighting of STEMI and NSTEMI patients. We have to acknowledge that we have not included patients with unstable angina, this is due to the admission policies in place. We also utilised plasma samples in the acute phase of the AMI. A limitation is that the reperfusion strategy that was used for STEMI patients was predominantly thrombolysis; however this is still the major reperfusion strategy in many parts of the world. We have a smaller number of females than males in our cohort. We have also utilised an in-house assay for measuring NT-proBNP but this is a well published robust assay. It would be necessary to confirm our findings with the Roche Elecys NT-proBNP assay in an independent population before appropriate cut-offs can be implemented for risk scoring. One of the overwhelming strengths of the study is the inclusion of consecutive patients with no restrictions on age. Our cohort of patients is similar to that which is encountered by clinicians around the world.

Conclusion:
The present large single centre study reveals that following ACS, NT-proBNP gives complementary and independent information to the GRACE risk score for predicting early and late mortality. The inclusion of the NT-proBNP blood test is useful in risk stratifying patients after an acute coronary syndrome. A simple blood test has the ability to enhance a well validated a clinical risk score.

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Legends

Figure 1 Bar chart showing relationship between higher GRACE score and increased 30-day mortality. Patients in tertiles of low, intermediate and high GRACE risk groups

Figure 2 Kaplan-Meier analysis for GRACE quartiles

Figure 3 Kaplan-Meier analysis for NT-proBNP quartiles

Figure 4 Kaplan-Meier analysis for NT-proBNP levels (< or >median) predicting the endpoint of death in patients stratified by GRACE score < or >median. Group 1= NT-proBNP <median, GRACE <median, Group 2= NT-proBNP >median, GRACE <median, Group 3= NT-proBNP <median, GRACE >median, Group 4= NT-proBNP >median, GRACE >median

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Table 1 Details of the GRACE risk score for calculating 30-day and 6-month mortality

GRACE score for 30-day mortality (2-258)		GRACE score for 6-month mortality (1-263)	
Age (years)		Age (years)	
<40	0		
40–49	18	<29	0
50–59	36	30–39	0
60–69	55	40–49	18
70–79	73	50–59	36
>80	91	60–69	55
		70–79	73
		80–89	91
		>90	100
Heart rate (bpm)		Heart rate (bpm)	
<70	0	<49.9	0
70–89	7	50–69.9	3
90–109	13	70–89.9	9
110–149	23	90–109.9	14
150–199	36	110–149.9	23
>200	46	150–199.9	35
		>200	43
Systolic BP (mmHg)		Systolic BP (mmHg)	
<80	63	<79.9	24
80–99	58	80–99.9	22
100–119	47	100–119.9	18
120–139	37	120–139.9	14
140–159	26	140–159.9	10
160–199	11	160–199.9	4
>200	0	>200	0
Creatinine (mg/dL)		Creatinine (mg/dL)	
0–0.39	2	0–0.39	1
0.4–0.79	5	0.4–0.79	3
0.8–1.19	8	0.8–1.19	5
1.2–1.59	11	1.2–1.59	7
1.6–1.99	14	1.6–1.99	9
2–3.99	23	2–3.99	15
>4	31	>4	20
Killip class		History of Congestive Heart Failure	24
Class I	0		
Class II	21		
Class III	43		
Class IV	64		
Cardiac arrest at admission	43	History of Myocardial Infarction	12
Elevated cardiac markers	15	ST-Segment Depression	11

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ST-segment deviation 30	Elevated Cardiac Enzymes 15
	No In-Hospital Percutaneous Coronary Invervention 14

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Table 2 Characteristics of Patients in the Study. Values are means (SD) or numbers (%).

	AMI Patients
Number	1033
Age (in years)	66.5 ± 12.7
Male Sex	740
Previous Medical History	
Myocardial infarction	245 (23.7)
Hypertension	544 (52.7)
Diabetes mellitus	252 (23.9)
Hypercholesterolaemia	360 (34.8)
Current/Ex-Smokers	441 (42.7)
Killip Class on Admission	
I	608 (58.9)
II	320 (31.0)
III	94 (9.1)
IV	7 (1.0)
Peak CK (I/U)	1261 ± 1385
Peak Troponin I (ng/ml)	12.6 ± 24.7
Creatinine (µmol/l)	106.3 ± 36.8
STEMI	476 (46.1)
NSTEMI	557 (53.9)
Systolic BP	136 .9 ± 24.8
Beta-blockers	826 (80.0)
ACEi/ARB	842 (81.5)

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Table 3. Cox regression analysis for 30-day mortality

	Multivariable Analysis	
	Hazard Ratio [95% CI]	P value
GRACE score	1.02 [1.01-1.03]	<0.001
Male Gender	0.64 [0.35-1.17]	0.14
Previous History of AMI	1.17 [0.60-2.30]	0.64
ST-elevation AMI	2.39 [1.27-4.50]	0.007
Log NT-proBNP	2.24 [1.07-4.71]	0.034
ACEi/ARB	0.25 [0.13-0.48]	<0.001
beta-blockers	0.31 [0.16-0.31]	0.001

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Table 4. Cox regression analysis for 30-day mortality using GRACE predictors and NT-proBNP

	Multivariable Analysis	
	Hazard Ratio [95% CI]	P value
Age	1.07 [1.03-1.11]	<0.001
Heart Rate	1.00 [0.00-1.01]	0.80
Systolic Blood Pressure	0.99 [0.98-1.01]	0.32
Creatinine	1.00 [1.00-1.01]	0.72
Killip Class	0.96 [0.47-1.95]	0.91
Cardiac arrest	8.72 [4.02-18.89]	<0.001
Elevated cardiac enzymes	0.33 [0.04-2.56]	0.29
ST-segment deviation	2.20 [0.97-4.97]	0.06
Log NT-proBNP	2.77 [1.20-6.41]	0.017

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Table 5. Cox regression analysis for 6-month mortality

	Multivariable Analysis	
	Hazard Ratio [95% CI]	P value
GRACE score	1.02 [1.01-1.03]	<0.001
Male Gender	0.68 [0.43-1.08]	0.10
ST-elevation AMI	2.32 [1.45-3.70]	<0.001
Log NT-proBNP	1.84 [1.09-3.13]	0.023
ACEi/ARB	0.36 [0.22-0.60]	<0.001
beta-blockers	0.45 [0.27-0.73]	0.001
Killip class >1	1.57 [0.93-2.65]	0.093

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Table 6. Cox regression analysis for 6-month mortality using GRACE predictors and NT-proBNP

	Multivariable Analysis	
	Hazard Ratio [95% CI]	P value
Age	1.06 [1.03-1.09]	<0.001
Heart Rate	1.00 [0.99-1.01]	0.87
Systolic Blood Pressure	0.99 [0.98-1.00]	0.09
Creatinine	1.00 [1.00-1.01]	0.06
History of Congestive Heart Failure	0.71 [0.22-2.29]	0.56
History of Myocardial Infarction	1.16 [0.70-1.93]	0.57
ST-segment depression	1.66 [1.01-2.75]	0.05
Elevated cardiac enzymes	0.80 [0.11-5.94]	0.83
In-hospital PCI	0.89 [0.43-1.84]	0.75
Log NT-proBNP	2.45 [1.38-4.35]	0.002

(NT-proBNP, N-terminal pro-B-type natriuretic peptide, ACEi, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker)

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Table 7. Net reclassification improvement of mortality risk using GRACE model alone and GRACE model with NTproBNP

	GRACE model with NT-proBNP					
Grace Model	Number of Individuals			Reclassification		% Correctly
alone	Low	Intermediate	High	Up	Down	Reclassified
Individuals without Endpoint at 30 days *n = 995*						
Low	205	2	0			
Intermediate	217	94	2	4	420	41.4
High	75	128	272			
Individuals with Endpoint at 30 days *n = 38*						
Low	1	0	0			
Intermediate	1	1	0	0	8	-17.0
High	1	6	28			
			Net Reclassification Improvement %			24.4
					95% C.I.	12.0 to 36.9
					P	0.0001

6 Month Mortality Risk ACS

	GRACE model with NT-proBNP					
Grace Model	Number of Individuals			Reclassification		% Correctly
alone	Low	Intermediate	High	Up	Down	Reclassified
Individuals without Endpoint at 6 months *n = 951*						
Low	361	36	0			
Intermediate	109	179	64	100	129	3.0
High	4	16	182			
Individuals with Endpoint at 6 months *n = 82*						
Low	6	3	0			
Intermediate	2	8	8	11	5	7.4
High	0	3	52			
			Net Reclassification Improvement %			10.4
					95% C.I.	0.3 to 20.4
					P	0.04

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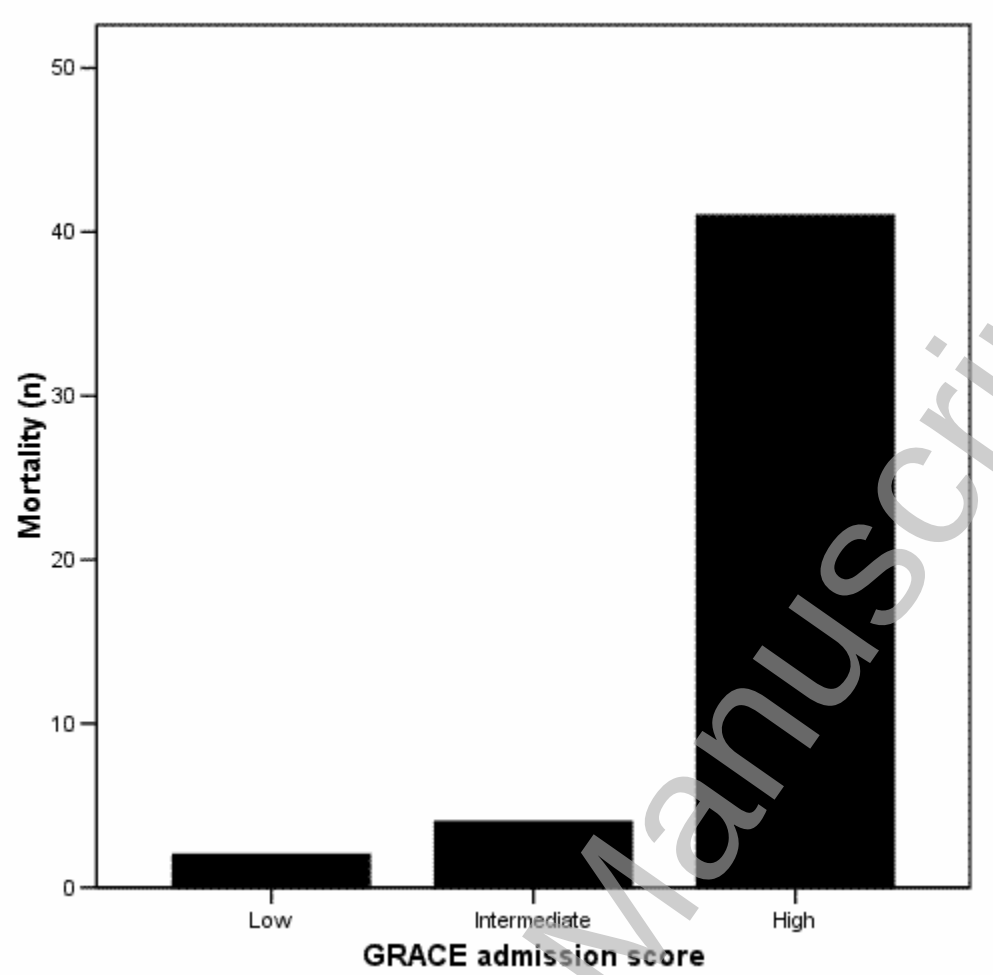

Figure 1

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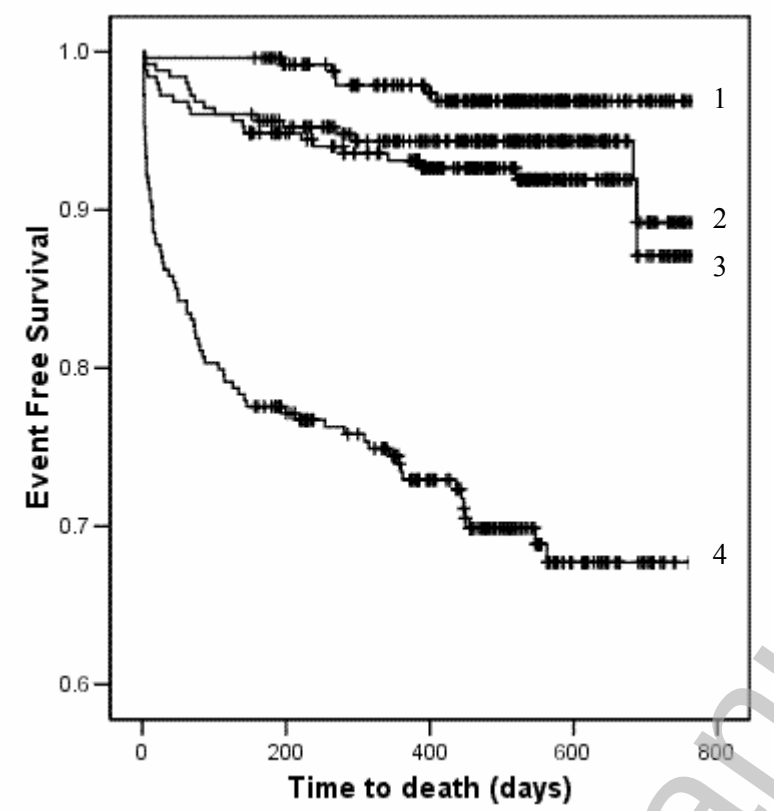

Figure 2

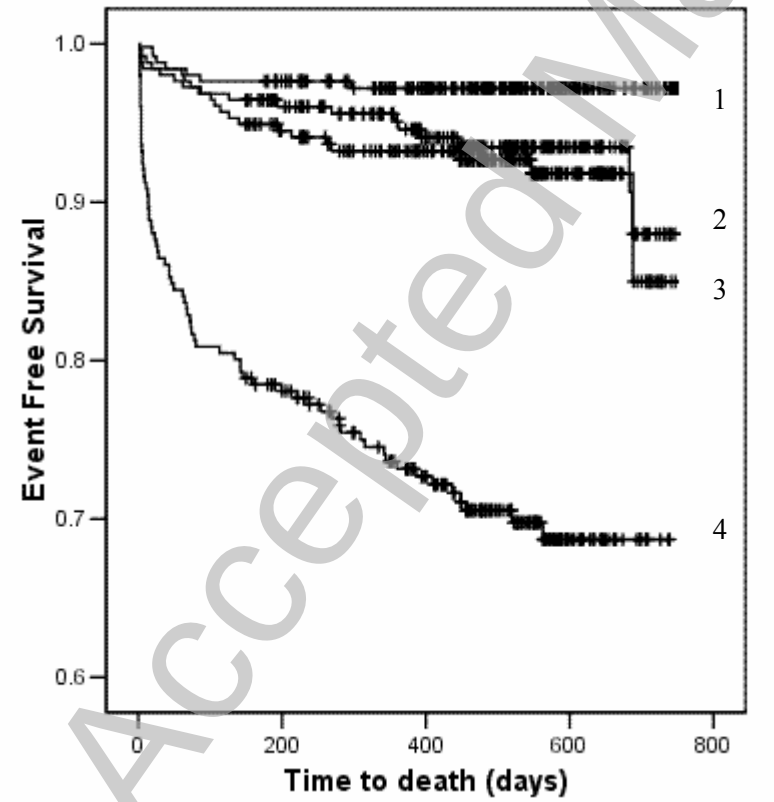

Figure 3

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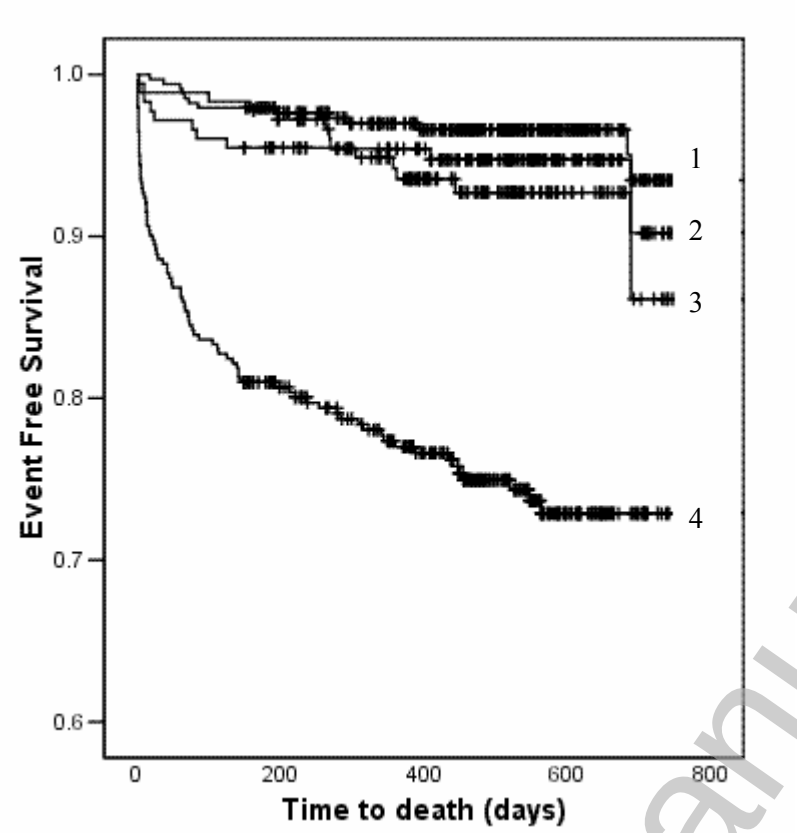

Figure 4

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