N-terminal pro B type natriuretic peptide is better than TIMI risk score at predicting death following acute myocardial infarction

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Abstract

Background: The TIMI risk score is a well validated scoring system to predict mortality in patients following an ST-segment elevation myocardial infarction (STEMI). N-terminal pro B type natriuretic peptide (NTproBNP) has also been found to be useful in predicting mortality following STEMI. We sought to investigate the utility of TIMI score and NTproBNP levels at predicting risk of death in acute myocardial infarction (AMI) patients. Methods: We studied 473 patients (352 men, mean age 63.7 ± 12.3 years) with AMI. Blood was drawn within 24 hours following the onset of chest pain and the plasma concentration of NTproBNP was determined using an in-house non-competitive immunoassay. Patients were TIMI risk scored and stratified into low (0 to 2), intermediate (3 to 7) and high risk (>8) groups. Results: Mortality was 8.9% and was related to higher TIMI risk scores (p=0.029 for trend). Higher NTproBNP levels were also related to increased mortality (median [range] fmol/ml, survivors 700.2[0.3-11485.3] vs. dead 5781.3[1.4-10835.9], p<0.0001). In a multivariate binary logistic regression model, independent predictors of mortality were NTproBNP levels in the first 24 hours (OR 4.21, 95% CI: 1.96-9.07, p<0.001) along with drug therapies. The receiver-operating curve for NTproBNP in the first 24 hours yielded an area under the curve (AUC) of 0.79 (95% CI: 0.70-0.88, p<0.001), for TIMI risk score the AUC was 0.67 (95% CI: 0.58-0.76, p=0.001). Conclusion: In the first 24 hours following an AMI, NTproBNP is superior to TIMI risk scoring at predicting mortality. A simple NTproBNP blood test is more easily applicable and is more accurate than a clinical risk score.

Keywords Myocardial infarction; peptides, NTproBNP, prognosis
Introduction

There is still mortality associated with an acute ST-segment elevation myocardial infarction (STEMI) despite the use of fibrinolytic therapy and primary percutaneous intervention. Assessment of the patient is important as a means of guiding therapy and also to identify those at highest risk of death so that therapy can be tailored in the future. Scoring systems have been developed to aid the clinician in judgement making, although accurate in predicting mortality they are either cumbersome to use or unweighted. Recently the TIMI risk score for STEMI, a bedside scoring system has been developed and is probably the most widely used scoring system for risk assessment of STEMI. The TIMI risk score was developed by identifying prognostic information from a multivariable analysis of the Intravenous nPA for Treatment of Infarcting Myocardium Early II (InTIME II) trial and found 10 clinical variables, which accounted for 97% of the predictive capacity of the model. The TIMI score has been found to be useful at predicting mortality when investigated in a population of STEMI patients and also in predicting mortality in patients with right ventricular infarction. In parallel with this biomarkers particularly B type natriuretic peptide (BNP) and its more stable counterpart N-terminal pro B type natriuretic peptide (NTproBNP) have been shown to have a vigorous response following an acute myocardial infarction (AMI) and to be useful in predicting mortality following a STEMI. Both of these peptides are easily measured using bedside assays. In this study we investigated whether NTproBNP was better than TIMI risk score at predicting risk of death in ST-segment acute myocardial infarction (AMI) patients.
Methods

Study population

We studied 473 consecutive post ST-segment elevation myocardial infarction (STEMI) patients who were admitted to the Coronary Care Unit of Leicester Royal Infirmary. The study complied with the Declaration of Helsinki, was approved by the local ethics committee and written informed consent was obtained from patients. Myocardial infarction (MI) was diagnosed if a patient had chest pain lasting >20 minutes, diagnostic serial electrocardiographic (ECG) changes consisting of new pathological Q waves or ST-segment changes, and a plasma creatine kinase-MB elevation greater than twice normal or cardiac troponin I level > 0.1 ng/mL. 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 were TIMI risk scored for STEMI as described previously and grouped into low (TIMI score 0-2), intermediate (3 to 7) and high risk (>8) groups.

Plasma samples

Blood measurements were made within 24 hours after onset of chest pain for determination of plasma NTproBNP. A 300 patients cohort also had blood taken between 72 and 96 hours to look at optimal timing of bloods at predicting death. After 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.
Echocardiography

Transthoracic echocardiography was performed in patients using a Sonos 5500 instrument (Philips Medical Systems, Reigate, UK). A 16-segment left ventricular wall motion index (LVWMI) based on the American Society of Echocardiography model was derived by scoring each LV segment (1=normal, 2=hypokinesis, 3=akinesis and 4=dyskinesis (Paradoxical Motion), and dividing the total by the number of segments scored.

NTproBNP assay

Our NTproBNP assay was based on a non-competitive assay as previously described. Sheep antibodies were raised to the N-terminal of human NTproBNP and monoclonal mouse antibodies were raised to the C-terminal. The N-terminal IgG was affinity-purified and biotinylated. Samples or NTproBNP 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 fmol/ml. 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) to those obtained on the NTproBNP assay marketed by Roche Diagnostics Ltd. (Lewes, East Sussex, UK).

End points

We assessed the value of NTproBNP for the prediction of mortality. We used a primary endpoint consisting of death. Endpoints were obtained by reviewing the Office of National Statistics Registry which logs all hospital deaths and review of the
medical notes. There was a minimum 30-day follow-up of all patients. No patient was lost to follow-up.

**Statistical analysis**
Statistical analyses were performed on SPSS Version 12 (SPSS Inc, Chicago, Illinois). The continuous variables in the two independent groups were compared using the Mann Whitney U test. To test the independent predictive power for death of NTproBNP levels above and below the median, binary logistic regression analyses were conducted. We included as variables baseline patient characteristics as part of the TIMI score, gender, prior history of AMI, LVWMI, post-AMI drug therapies, coronary revascularisation and peptide markers (including troponin I and peak CK). NTproBNP was normalised by log transformation. Thus, odds ratios and hazard ratios refer to a tenfold rise in the levels of this marker. Spearman’s correlations were performed for peptide values and continuous variables. To identify the independent predictors of death, Cox proportional hazard analysis was used (we included the same variables as the binary logistic regression model). Kaplan-Meier survival curves were generated to visualise the relationship between the peptides NTproBNP and the composite endpoints. To compare the predictive value of NTproBNP, receiver-operating characteristic (ROC) curves were generated and the area under the curves (AUC) was calculated. A p value below 0.05 was deemed to be statistically significant. Power calculations suggest that 473 patients recruited over 24 months with a follow-up period of at least 1 month would enable median survival probabilities of 0.9 or 0.85 at 12 months in the groups stratified by the biomarker median to be distinguished with a power of 93% at P<0.05 (2-sided test).
Results

Patient characteristics

The demographic features of the patient population are shown in Table 1. Median length of follow-up was 272 days with a range of 0–644 days. Of the patients enrolled, 68.5 % received thrombolysis during the index admission. There were 86 coronary revascularisations. No patient was lost to follow-up. During follow-up, 42 (8.9%) patients died. Echocardiographic data was available for 399 (84.4%) of the 473 patients and performed at a median of 3.5 days (range 2-5) after presentation with AMI. 30 echocardiograms were unanalysable and 44 patients did not receive an echocardiogram.

NTproBNP levels in patients

Median NTproBNP was 811.1 fmol/ml, IQR 257.0-2951.2 fmol/ml. NTproBNP was significantly elevated in patients who died (median [range] fmol/ml, survivors 700.2[0.3-11485.3] vs. dead 5781.3[1.4-10835.9], p<0.0001).

Relationship between NTproBNP and echocardiographic parameters

For the whole population, mean LVWMI was 1.53 (range 1.08-2.83). The LVWMI score was significantly higher in patients who died compared to survivors (median, [range], 1.83 [1.06-2.83] vs. 1.5 [1.0-2.85], p=0.002). The LVWMI score in those subjects with anterior AMI was higher than in those with inferior AMI (1.8 [1.08-2.75] vs. 1.4 [1.00-2.83], p<0.001). NTproBNP correlated with LVWMI (r=0.342, p<0.0001),
**TIMI score and NTproBNP as predictors of death**

Mortality was 8.9% and was related to higher TIMI risk scores (p=0.029 for trend, figure 1). When clinical and demographic characteristics were entered into a multivariate binary logistic model NTproBNP (OR 4.21, 95% CI: 1.96-9.07, p<0.001) and post-AMI treatment with beta blockers (OR 0.24, 95% CI: 0.1-0.56, p=0.001) and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (OR 0.29, 95% CI: 0.12-0.72, p=0.007) were the only independent predictors of death. This was also confirmed on the Cox proportional hazards model with the independent predictors of death being NTproBNP (HR 3.82, 95% CI: 1.89-7.78, p<0.001) and post-AMI treatment with beta blockers (HR 0.27, 95% CI: 0.12-0.57, p=0.001) and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (HR 0.33, 95% CI: 0.16-0.71, p=0.004) The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with NTproBNP below the median compared with those with NTproBNP above the median (log rank 15.06, p=0.0001, figure 2). There was also a grading of mortality on the Kaplan-Meier survival curve related to whether the patients were in low, intermediate or high TIMI risk groups (log rank 29.86, p=0.0001, figure 3). The receiver-operating characteristic curve for NTproBNP in the first 24 hours yielded an area under the curve (AUC) of 0.79 (95% CI: 0.70-0.88, p<0.001), for TIMI risk score the AUC was 0.67 (95% CI: 0.58-0.76, p=0.001, figure 4). The combination of TIMI score and NTproBNP did not significantly improve risk prediction for mortality. When NTproBNP above the median with or without the clinical presence of heart failure post AMI was investigated there was no improvement in the predictive power of the ROC curve. No difference was noted with regards to whether NTproBNP was measured early (within first 24 hours) or late (72-96 hours) after an infarct at predicting death (OR for
Discussion

The aim of this study was to compare the TIMI risk score for STEMI and compare it to NTproBNP in determining the prognosis of AMI patients. The results of this study confirm the previous findings that TIMI risk score is of prognostic value in patients with STEMI. However in multivariate testing NTproBNP is superior to TIMI risk scoring and is of independent prognostic value in determining death in patients who have an acute STEMI. The predictive value of NTproBNP provides risk prediction independent of the TIMI score, which includes known clinical predictors of death. Reperfusion therapy has improved mortality post AMI, however the outcome of patients despite this is still poor;\textsuperscript{16} for this reason risk stratification remains important and may be useful to select treatment regimes in the future. Kaplan-Meier analysis revealed that both raised NTproBNP and higher TIMI scores were predictive of poor outcome. However from ROC curve analysis the AUC for NTproBNP was greater than that for TIMI risk score showing that NTproBNP is more accurate than TIMI score at predicting death. This was also borne out in multivariate binary and Cox regression analyses with NTproBNP but not TIMI score independently predicting mortality.

In Morrow et al’s original paper the c statistic obtained for the prognostic value of the TIMI risk score was 0.779. In our cohort of patients the c statistic for the TIMI risk score (equivalent to the receiver-operating characteristic curve AUC) is 0.67. The reasons for the difference are probably accounted for by the different population...
groups. In our cohort of STEMI patients only 68.5% of the patients received thrombolytic therapy. The TIMI risk score was derived from a population of patients who were all given thrombolytic therapy (lanoteplase or alteplase). When the TIMI risk score was used previously in a real world sample of patients the c statistic was 0.65\textsuperscript{17} similar to what we have found. We would argue that our patient population is more in keeping with the real life situation where not all patients are eligible for thrombolytic therapy and indeed these patients may in fact be at higher risk.\textsuperscript{18} The utility of the TIMI risk score and NTproBNP have been investigated individually at predicting death in numerous studies\textsuperscript{5,6,10,11} however the 2 have never been compared directly. There is now a bedside point of care assay for NTproBNP so results of such tests when taken should be readily available. Moreover, we have shown that there is no difference in risk prediction whether NTproBNP is measured early or late after an acute STEMI. This makes a simple NTproBNP blood test more easily applicable and as we have shown, the NTproBNP level has more predictive accuracy than a clinical risk score in a cohort of unselected STEMI patients.

In conclusion, the present large single centre study reveals that in the first 24 hours following an AMI, NTproBNP is superior to TIMI risk scoring at predicting mortality. A simple blood test may be more easily applicable than a clinical risk score.

\textbf{Acknowledgments}

Dr Sohail Q Khan is supported by a British Heart Foundation Junior Research Fellowship (FS/03/028/15486).
References


Legends

Figure 1 Bar chart showing relationship between higher TIMI score and increased mortality. There were 142, 179 and 152 patients in the low, intermediate and high TIMI risk groups respectively.

Figure 2 Kaplan-Meier Curve: Time to death related to serum NTproBNP

Figure 3 Kaplan-Meier Curve: Time to death related to low, intermediate or high TIMI risk groups

Figure 4 Receiver Operating Characteristic Curve comparing NTproBNP and TIMI score for prediction of mortality
### Table 1  Characteristics of Patients in the Study. Values are means (SD) or numbers (percentage)

<table>
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<th>AMI Patients</th>
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<tr>
<td>Number</td>
<td>473</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>63.7 ± 12.3</td>
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<tr>
<td>Male Sex</td>
<td>352</td>
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<tr>
<td>Previous Medical History</td>
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<tr>
<td>Myocardial infarction</td>
<td>61 (12.9)</td>
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<tr>
<td>Angina Pectoris</td>
<td>64 (13.5)</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes mellitus</td>
<td>95 (20.1)</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>133 (28.1)</td>
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<tr>
<td>Obesity</td>
<td>65 (13.7)</td>
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<tr>
<td>Current/Ex-Smokers</td>
<td>170 (30.9)</td>
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<tr>
<td>Thrombolytic</td>
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<td>Territory of Infarct</td>
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<td>Anterior</td>
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<tr>
<td>Inferior</td>
<td>220 (46.5)</td>
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<tr>
<td>Other/undetermined</td>
<td>73 (15.0)</td>
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<td>Killip Class on Admission</td>
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<tr>
<td>I</td>
<td>255 (53.9)</td>
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<tr>
<td>II</td>
<td>185 (39.1)</td>
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<tr>
<td>III</td>
<td>25 (5.3)</td>
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<tr>
<td>IV</td>
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<td>Metric</td>
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<tr>
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<tr>
<td>Peak CK (I/U)</td>
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<tr>
<td>Peak Troponin I (ng/ml)</td>
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<tr>
<td>Creatinine (µmol/l)</td>
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<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>99.1 ± 29.1</td>
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Figure 1
Figure 2
Figure 3
Figure 4