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Plasma N-Terminal B-Type Natriuretic Peptide as an Indicator of Long-Term Survival After Acute Myocardial Infarction: Comparison With Plasma Midregional Pro-Atrial Natriuretic Peptide

The LAMP (Leicester Acute Myocardial Infarction Peptide) Study

Sohail Q. Khan, MB,* Onkar Dhillon, MB,* Dominic Kelly, MB,* Iain B. Squire, MD,* Joachim Struck, PHD,† Paulene Quinn, MPHIL,* Nils G. Morgenthaler, MD,† Andreas Bergmann, PHD,† Joan E. Davies, PHD,* Leong L. Ng, MD*

Leicester, United Kingdom; and Hennigsdorf, Germany

Objectives Our aim was to assess the prognostic value of midregional proatrial natriuretic peptide (MR-proANP) in patients after acute myocardial infarction (AMI).

Background Multimarker strategies may assist risk stratification after AMI. Midregional proatrial natriuretic peptide is a newly described stable fragment of N-terminal proatrial natriuretic peptide. We compared the prognostic value of MR-proANP and an established marker, N-terminal pro-B-type natriuretic peptide (NT-proBNP), after AMI.

Methods We recruited 983 consecutive post-AMI patients (720 men, median age 65 [range 24 to 95] years) in a prospective study with follow-up over 343 (range 0 to 764) days.

Results Plasma MR-proANP was raised in patients who died ($n = 101$) compared with that seen in survivors (median 310 [range 48 to 1,150] pmol/l vs. 108 [range 4.9 to 1,210] pmol/l, $p < 0.0001$). Using Cox modeling, $\log_{10}$MR-proANP (hazard ratio 3.87) and $\log_{10}$NT-proBNP (hazard ratio 3.25) were significant independent predictors of death. In patients stratified by NT-proBNP in the highest quartile ($>\sim$5,900 pmol/l), MR-proANP in the top quartile ($\sim$330 pmol/l) was associated with poorer outcome ($p < 0.0001$). Findings were similar for heart failure as an individual end point. However, neither marker predicted recurrent AMI.

Conclusions The A- and B-type natriuretic systems are activated after AMI. Midregional proatrial natriuretic peptide is a powerful predictor of adverse outcome, especially in those with an elevated NT-proBNP. Midregional proatrial natriuretic peptide may represent a clinically useful marker of prognosis after an AMI as part of a multimarker strategy targeting the natriuretic neurohormonal pathway. (J Am Coll Cardiol 2008;51:1857–64) © 2008 by the American College of Cardiology Foundation

Acute myocardial infarction (AMI) results as a consequence of plaque rupture and superimposed thrombus formation. This acute event leads to acute disruption of myocardial contractility and neurohormonal activation triggering the release of the natriuretic peptide hormones from the myocardial tissues (1). The natriuretic peptide hormones atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) and the amino-terminal fragments of their prohormones (N-terminal [NT]-proANP and NT-proBNP, respectively) have now been well established as predictors of poor outcome in patients after AMI and in patients with heart failure (HF) (2–7). The prognostic information provided by these hormones is over and above that of impaired left ventricular function, Killip class, and renal impairment

From the *University of Leicester, Department of Cardiovascular Sciences, Clinical Sciences Building, Leicester Royal Infirmary, Leicester, United Kingdom; and the †Research Department, BRAHMS Aktiengesellschaft, Hennigsdorf, Germany. Dr. Khan was supported by a Junior Fellowship from the British Heart Foundation (FS/03/028/15486). Dr. Ng has submitted patents on behalf of the University of Leicester on biomarkers of cardiac disease. Dr. Bergmann holds ownership in BRAHMS AG, patent rights to the midregional proatrial natriuretic peptide (MR-proANP) assay, and is a member of the board of directors of BRAHMS AG. Dr. Struck holds patent rights to the MR-proANP assay and is an employee of BRAHMS AG. Dr. Morgenthaler is an employee of BRAHMS AG. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis. All authors have read and agree to the article as written.

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Abbreviations and Acronyms

AMI = acute myocardial infarction
ANP = atrial natriuretic peptide
AUC = area under the curve(s)
BNP = B-type natriuretic peptide
CI = confidence interval
CV = coefficient of variation
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
MI = myocardial infarction
MR-proANP = midregional proatrial natriuretic peptide
NSTEMI = non–ST-segment elevation myocardial infarction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
STEMI = ST-segment elevation myocardial infarction

(6). Both hormones promote natriuresis and diuresis and have vasodilator properties. The prohormones have a larger molecular weight, lack binding interactions with cells or other proteins and receptors, and have longer half-lives as there are no active excretion pathways and may, therefore, be easier to measure in plasma. B-type natriuretic peptide and its more stable counterpart NT-proBNP have shown the greatest promise in this area (1) as their use covers a range of acute coronary syndromes (8). A multimarker approach looking specifically at the natriuretic neurohormones, however, may be more beneficial. Previous studies have investigated combinations of BNP, NT-proBNP, ANP, and N-terminal atrial natriuretic peptide (N-ANP). Richards et al. (5) proposed NT-proBNP as the strongest independent marker for death or HF, with no additional contribution from N-ANP. In the study of Omland et al. (9) it was found that only BNP gave additional prognostic information on mortality over and above left ventricular systolic function. Our group has previously directly compared N-ANP and NT-proBNP and found N-ANP may be of benefit in predicting late mortality and NT-proBNP at predicting early mortality (10). Here we investigate midregional proatrial natriuretic peptide (MR-proANP) in a multimarker approach. Epitopes of the antibodies used in the assay for MR-proANP cover amino acids 53 to 90 of N-terminal proatrial natriuretic peptide proANP (11). Midregional epitopes of prohormones may be more stable to degradation by exoproteases, unlike epitopes in the N- or C-terminals of proANP used in previous immunoassays. Previous studies may, therefore, have underestimated the utility of proANP as a biomarker. The diagnostic use of MR-proANP has recently been described in the differential diagnosis of acute decompensated HF, where it has been shown to be comparable to that of BNP and NT-proBNP (12). Our aim was to investigate whether MR-proANP alone or in combination with NT-proBNP would be of benefit in determining the prognosis after AMI, particularly for death and HF. We were particularly interested to see if a multimarker approach using combined information from 2 natriuretic markers could give prognostic information over and above just NT-proBNP, a peptide of established prognostic value benefit in this group of patients (5,10,13).

Methods

Study population. We studied 983 consecutive AMI patients admitted to the Coronary Care Unit of the Leicester Royal Infirmary. Acute myocardial infarction was diagnosed if a patient had a plasma creatine kinase-MB elevation greater than twice normal or a cardiac troponin I level >0.1 ng/ml with at least 1 of the following: chest pain lasting >20 min or diagnostic serial electrocardiographic changes consisting of new pathological Q waves or ST-segment and T-wave changes. Acute myocardial infarction was subcategorized into ST-segment elevation myocardial infarction (STEMI) or non–ST-segment myocardial infarction (NSTEMI). The study complied with the Declaration of Helsinki and was approved by the local ethics committee; written informed consent was obtained from all patients. Exclusion criteria were known malignancy, or surgery in the previous month. The estimated glomerular filtration rate (eGFR) was calculated from the simplified formula derived from the MDRD (Modification of Diet in Renal Disease) study, recently validated in patients with HF (14).

Plasma samples. Blood samples were drawn on 1 occasion 3 to 5 days after the onset of chest pain for determination of plasma MR-proANP and NT-proBNP. After 15-min bed rest, 20 ml blood was collected into tubes containing ethylenediaminetetraacetic acid and aprotinin. All plasma was stored at −70°C until assayed in a blinded fashion in a single batch. In a subgroup of 132 patients from the original 983-patient cohort, blood sampling was performed daily for 5 days from admission to discharge.

Echocardiography. Transthoracic echocardiography was performed in patients using a Sonos 5500 instrument (Philips Medical Systems, Reigate, United Kingdom). Left ventricular ejection fraction was calculated using the biplane method of discs formula (15).

NT-proBNP assay. Our NT-proBNP assay was based on a noncompetitive assay as previously published (8). Sheep antibodies were raised to the N-terminus of human NT-proBNP, and monoclonal mouse antibodies were raised to the C-terminus. Samples or NT-proBNP standards were incubated in C-terminal immunoglobulin G–coated wells with the biotinylated N-terminal antibody for 24 h at 4°C. Detection was with methyl-acridinium-ester-labelled streptavidin on a MLX plate luminometer (Dynex Technologies Ltd., Worthing, United Kingdom). The lower limit of detection was 0.3 pmol/l. There was no cross reactivity with ANP, BNP, or C-type natriuretic peptide.

MR-proANP assay. Midregional proatrial natriuretic peptide was detected using a novel commercial sandwich immunoassay in the chemiluminescence-coated tube-format (BRAHMS AG) as described (11). Briefly, patient samples (1:40 dilution of 5 μl plasma in incubation buffer) or standards were added in duplicate to antibody-coated tubes (affinity purified sheep polyclonal antibodies directed against proANP peptide 73 to 90) and incubated for 30 min at room temperature. After 5 washes with 1 ml washing

buffer, 200 μl tracer was added, containing acridinium ester-labelled anti-proANP antibody (affinity purified sheep polyclonal antibodies directed against proANP peptide 53 to 72), followed by 30 min incubation at room temperature. Tubes were washed 3 times with 1 ml washing buffer, and detection was performed in a LB952T luminometer (Berthold, Bad Wildbad, Germany; 1 s detection time per sample). Relative light units of the chemiluminescence assay were expressed in pmol/l MR-proANP, as calculated from a calibration curve (4 to 1,800 pmol/l) that was included in every analytical run. The lower detection limit of the assay is 4.3 pmol/l, and the functional sensitivity of the assay is 11 pmol/l MR-proANP. The interassay coefficient of variation (CV) within the range of plasma measurements was under 10% (8.0% CV at 100 pmol/l; 6.5% CV at 400 pmol/l).

End points. Our primary end point was death. We also investigated hospitalization for HF and recurrent AMI as individual secondary end points. Hospitalization for HF was defined as a hospital readmission for which HF was the primary reason. Myocardial infarction (MI) was diagnosed on established criteria as described in the preceding text (16). End points were obtained by reviewing the Office of National Statistics Registry and by contacting each patient. There was a minimum 60-day follow-up of all surviving patients.

Statistical analysis. Statistical analyses were performed on SPSS Version 14 (SPSS Inc., Chicago, Illinois). Comparisons of continuous variables were made using the Mann-Whitney *U* test. Comparisons in the daily sampling study were performed using the general linear model with repeated measures, with correction for multiple comparisons using the Bonferroni method. The general linear model repeated measures procedure in SPSS provides analysis of variance when the same measurement is made several times on each subject or case. Spearman's correlations were performed. The relationship of baseline variables with death and HF was assessed using Cox proportional hazards analysis by univariate and multivariate analysis. Factors with univariate significance of a value of $p < 0.1$ were included in multivariate analyses. Echocardiographic data were analyzed in a substudy (see the following text). The Kaplan-Meier cumulative survival curves were constructed and compared by the log-rank test and the log-rank test for trend. Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Levels of NT-proBNP and MR-proANP were normalized by $\log_{10}$ transformation. Thus, odds ratios and hazard ratios (HRs) refer to a 10-fold rise in the levels of these markers. Hazard ratio and 95% confidence intervals (CIs) for risk factors and significance level for chi-square (likelihood ratio test) are given.

To compare the accuracy of NT-proBNP and MR-proANP, receiver-operator characteristic curves were generated, and the area under the curve (AUC) was calculated. A 2-tailed p value of <0.05 was deemed to be statistically significant. The study size of 980 patients had a 90% power at a value of $p < 0.01$ to detect a difference of 0.63 in the HR between the top quartile of the biomarker compared with the other quartiles.

Results

Patient characteristics. Patient details are recorded in Table 1. Median length of follow-up was 343 (range 0 to 764) days. The minimum length of follow-up for survivors was 60 days. During follow-up 101 (10.3%) patients died, 49 (5.0%) were readmitted with HF, and there were 79 (8.0%) recurrent AMIs. One-year mortality was 18.1%. There were 783 STEMI patients. No patient was lost to follow-up.

Plasma profile of MR-proANP and NT-proBNP. In a subgroup of 132 patients (102 men, median age 64 [range 32 to 90] years), daily blood samples were obtained for 5 days post-admission. Seven patients in the subgroup experienced the primary end point of death. The time course of plasma NT-proBNP is shown in Figure 1. This shows significant changes with day of sampling ($p < 0.001$, Bonferroni corrected for 4 comparisons in 132 patients), with peak levels on Day 2 ($p < 0.001$ and 0.02 compared with Day 1 and Day 3, respectively, using the Bonferroni correction for 4 comparisons in 132 patients). For plasma MR-proANP, the peak was most evident on Day 1 (significantly elevated compared with Day 2, $p = 0.001$ using the Bonferroni correction for 4 comparisons in 132 patients), falling on Day 2 before significantly rising again on Day 3 ($p < 0.001$, Bonferroni corrected for 4 comparisons in 132 patients).

MR-proANP levels. Midregional proatrial natriuretic peptide was raised in patients who died compared with that in event-free survivors. There was no significant difference

Table 1 Characteristics of Patients in the Study*

	AMI Patients
Number	983
Age (yrs)	66 (24–95)
Male gender	720
eGFR (ml/min/1.73 m^2 surface area)	68.4 (14.9–166.1)
NT-proBNP (pmol/l)	907.4 (0.3–28,886.8)
MR-proANP (pmol/l)	117.0 (4.9–1,210)
Previous medical history (%)	
Angina pectoris	251 (25.5)
Myocardial infarction	165 (16.8)
Hypertension	430 (43.7)
Diabetes mellitus	213 (21.7)
Heart failure	57 (5.8)
Hypercholesterolemia	227 (23.1)
STEMI (%)	783 (79.7)
Revascularization (fibrinolysis)	580/783 (79.1)
Revascularization (PCI)	122 (12.4)
Cardiogenic shock	10 (1.0)
Current smokers/ex-smokers	617 (62.8)

*Values are medians (range) or numbers (percentage).

AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; MR-proANP = midregional proatrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

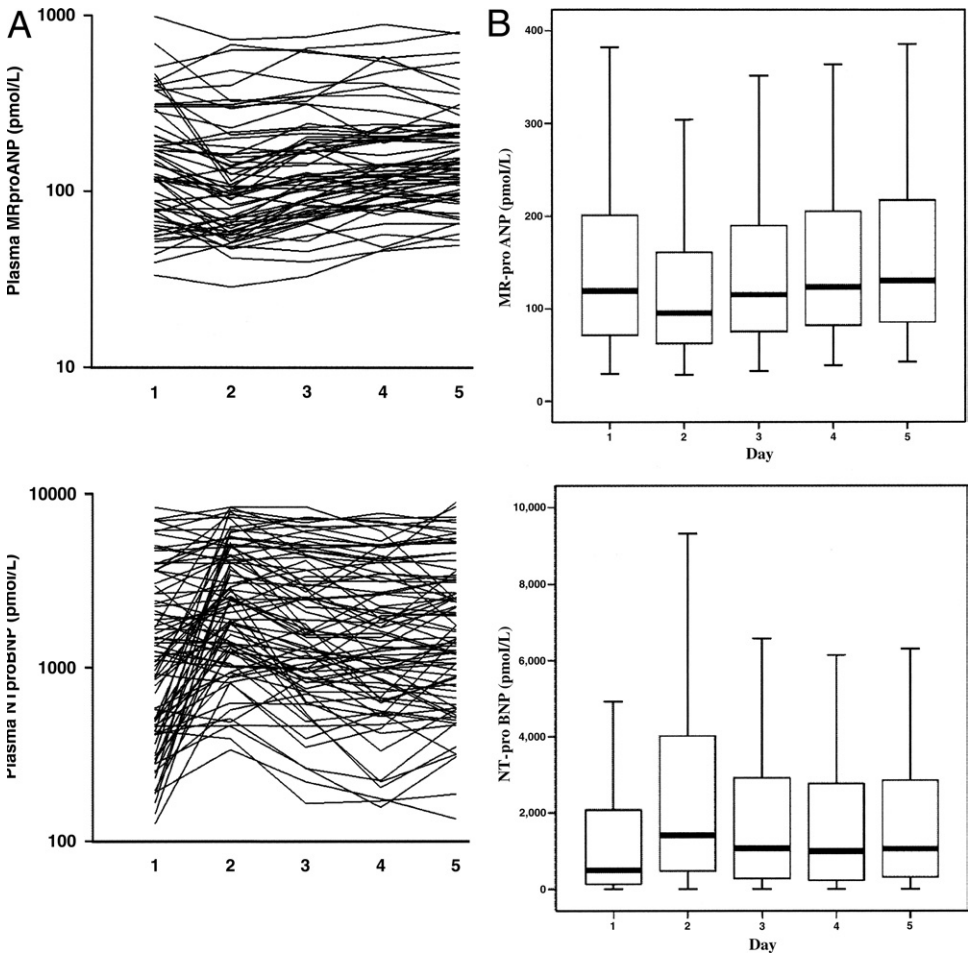


Figure 1 Daily Peptide Sampling and Box Plots

(A) Patient plot for 60 patients. Changes in plasma midregional proatrial natriuretic peptide (MR-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in 60 individual patients within the first 5 days after acute myocardial infarction. **(B)** Midregional proatrial natriuretic peptide and NT-proBNP box plots. Median and interquartile range of plasma peptide levels in the 132 patients with serial sampling data.

in MR-proANP levels between anterior or other site of AMI, STEMI, versus NSTEMI. However, there was a significantly higher level in female versus male patients, patients with a prior history of AMI, patients with a prior history of hypertension, and patients who had a prior history of HF or diabetes, and higher levels in patients who were not thrombolyzed. Midregional proatrial natriuretic peptide levels were higher in patients with Killip class above 1. Plasma MR-proANP correlated with age ($r_s = 0.59$, $p < 0.0005$), eGFR ($r_s = -0.54$, $p < 0.0005$), Killip class ($r_s = 0.25$, $p < 0.0005$), and NT-proBNP ($r_s = 0.63$, $p < 0.0005$) (Fig. 2). There were some patients with markedly raised MR-proANP but low NT-proBNP levels. These patients had the same demographic characteristics as the main cohort of patients described but a significantly better eGFR. No difference in outcomes was noted.

NT-proBNP levels. Significant differences in NT-proBNP levels were noted between male and female patients; those with a Killip class above 1; and in patients with a prior history of HF, hypertension, AMI, or diabetes. Plasma NT-proBNP levels were also higher in STEMI versus NSTEMI patients, and those with anterior site of AMI. Plasma NT-proBNP was correlated with age, eGFR, and Killip class. There were some patients with markedly raised NT-proBNP but low MR-proANP levels. These patients had the same demographic characteristics as the main cohort of patients described but a significantly worse eGFR. No difference in outcomes was noted.

Primary end points: MR-proANP and NT-proBNP as predictors of death. When clinical characteristics were entered into a Cox proportional hazards model (Table 2), MR-proANP (HR 3.87) and NT-proBNP (HR 3.25) together with use of beta-blockers and angiotensin-converting enzyme/angiotensin receptor blockers and age independently predicted the primary end point. Past history of hypertension or diabetes, Killip class, and eGFR were not predictors.

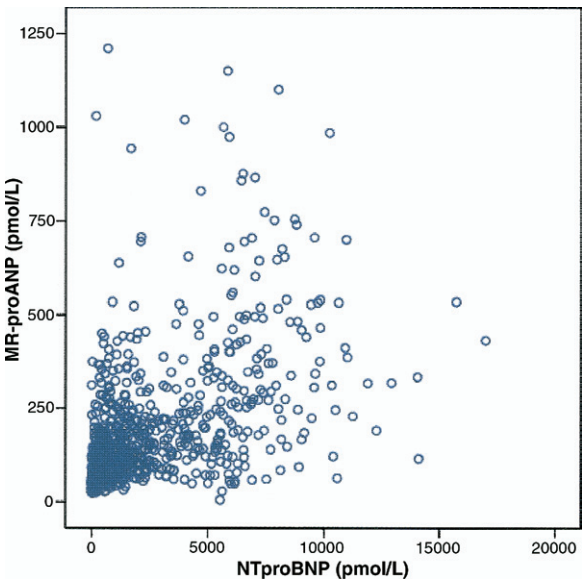


Figure 2 Scatter Diagram

Spearman correlation between MR-proANP and NT-proBNP, r_s = 0.63. Abbreviations as in Figure 1.

The area under the receiver-operating characteristic curve for MR-proANP (0.83 [95% CI 0.78 to 0.87]) and NT-proBNP (0.83 [95% CI 0.78 to 0.87]) were similar. The AUC for troponin was 0.42 (95% CI 0.32 to 0.51, p = NS) and for peak creatine kinase 0.40 (95% CI 0.29 to 0.50, p = NS).

For prediction of mortality, stratification by NT-proBNP (< or > median) correctly identified 83 end points, with an additional 10 identified using stratification by MR-proANP (< or > median). Using MR-proANP levels for risk stratification, 87 end points were correctly identified, with an additional 8 identified using stratification by NT-proBNP. Thus, only 6 end points were incorrectly identified using both markers.

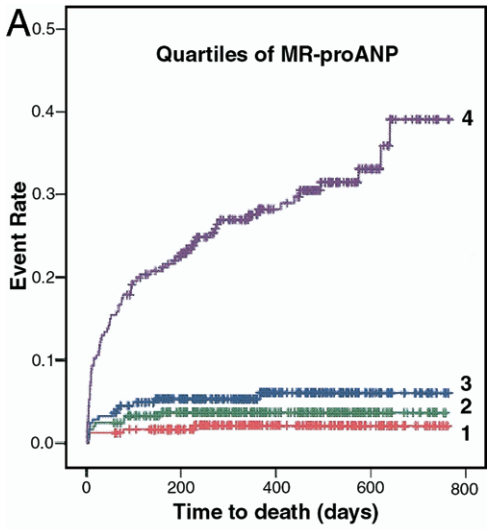
The Kaplan-Meier survival curves plotting quartiles of MR-proANP or NT-proBNP (Fig. 3) show that both MR-proANP and NT-proBNP are useful predictors of death post-AMI.

Patients in the top quartile for MR-proANP (above 331 pmol/l) had a significantly higher mortality than those in quartiles 1 to 3 (p < 0.0001 for all). In patients stratified by NT-proBNP in the highest quartile (median 5,934 pmol/l), MR-proANP in the highest quartile gave additional information on death in those patients who had NT-proBNP levels above the highest quartile (log-rank test chi-square for linear trend of factor levels pooled over NT-proBNP strata, 14.47, p = 0.0001) (Fig. 4). Midregional proatrial natriuretic peptide in the top quartile had predictive value in those patients in the lower 3 quartiles of NT-proBNP (log-rank test chi-square 39.28, p < 0.0001). For NT-proBNP in the lower 3 quartiles, those patients in the top quartile of MR-proANP had higher event rates than those

Table 2 Cox Regression Analysis for Death After AMI*

	Univariate Analysis		Multivariate Analysis (Whole Group)		Multivariate Analysis (Echocardiography Subgroup)	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age	1.10 (1.08–1.12)	<0.0005	1.04 (1.02–1.07)	0.002	1.05 (1.01–1.09)	0.009
Male gender	0.47 (0.32–0.70)	<0.0005	0.69 (0.44–1.08)	0.11	0.75 (0.41–1.38)	0.35
Previous history of						
AMI	2.52 (1.66–3.80)	<0.0005	1.44 (0.93–2.44)	0.10	1.02 (0.56–1.87)	0.94
Heart failure	1.64 (0.85–3.15)	0.14	NA	NA	NA	NA
Hypertension	1.57 (1.06–2.32)	0.024	1.17 (0.77–1.77)	0.46	1.54 (0.87–2.72)	0.13
Diabetes mellitus	1.74 (0.95–2.26)	0.082	1.16 (0.73–1.85)	0.52	0.95 (0.50–1.82)	0.87
Hypercholesterolemia	0.91 (0.57–1.48)	0.716	NA	NA	NA	NA
Smoking	0.69 (0.46–1.02)	0.063	1.19 (0.75–1.88)	0.46	1.01 (0.54–1.87)	0.99
Anterior AMI	1.01 (0.78–1.31)	0.93	NA	NA	NA	NA
ST-segment elevation AMI	1.06 (0.66–1.70)	0.82	NA	NA	NA	NA
Thrombolytic use	0.58 (0.39–0.86)	0.007	1.11 (0.72–1.71)	0.63	1.04 (0.58–1.86)	0.91
Killip class >1	2.50 (1.63–3.83)	<0.0005	0.93 (0.58–1.48)	0.75	1.44 (0.74–2.93)	0.32
Use of beta-blockers	0.29 (0.20–0.43)	<0.0005	0.44 (0.49–0.67)	0.001	0.46 (0.20–0.80)	0.006
Use of ACE/angiotensin receptor blockers	0.62 (0.41–0.92)	0.016	0.63 (0.41–0.96)	0.034	0.77 (0.42–1.42)	0.40
Log NT-proBNP	8.45 (5.35–13.35)	<0.0005	3.25 (1.89–5.89)	<0.0005	3.28 (1.49–7.25)	0.003
Log MR-proANP	22.54 (12.82–69.81)	<0.0005	3.87 (1.51–9.93)	0.005	3.34 (1.03–10.84)	0.044
eGFR	0.95 (0.94–0.96)	<0.0005	0.99 (0.98–1.01)	0.65	1.00 (0.98–1.02)	0.95
Peak CK	1.01 (0.97–1.03)	0.87	NA	NA	NA	NA
Ejection fraction	2.83 (1.89–4.22)	<0.0005			1.99 (1.10–3.59)	0.023

*Multivariate analysis results are reported for the whole group and for the subgroup with echocardiography data (n = 584).
ACE = angiotensin-converting enzyme; CI = confidence interval; CK = creatine kinase; NA = not applicable; other abbreviations as in Table 1.



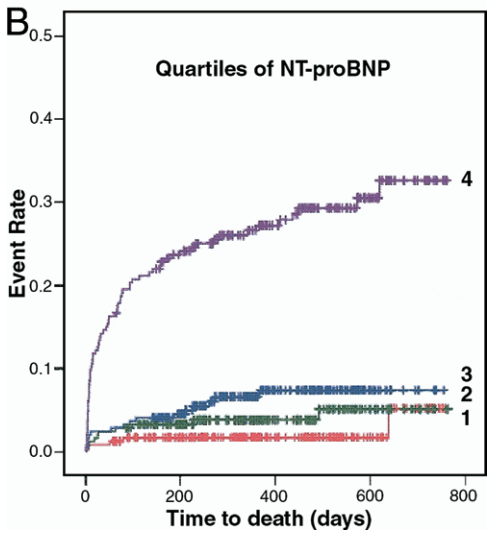


Figure 3 Kaplan-Meier Survival Curves

Event rate (death) in patients grouped according to quartiles of plasma MR-proANP or NT-proBNP (1 = lowest quartile, 4 = highest quartile). Abbreviations as in Figure 1.

in quartile 1 ($p < 0.0001$), 2 ($p < 0.0001$), and 3 ($p = 0.0004$). Patients can, therefore, be classified into low- (both markers < lowest quartile), intermediate- (either marker > highest quartile), or high-risk (both markers > highest quartile) groups (log-rank for trend, $p < 0.0005$).

Echocardiographic substudy. Echocardiographic parameters were available for 584 subjects (59.4%) for the index admission. Plasma MR-proANP and NT-proBNP were elevated in patients with impaired left ventricular systolic function. In this subgroup, there were 54 deaths. Cox modeling analysis of clinical and biomarker variables with echocardiographic presence of impaired left ventricular systolic function (biplanar ejection fraction as a continuous variable) revealed both biomarkers MR-proANP and NT-proBNP along with use of beta-blockers, age, and ejection fraction as significant independent predictors of death (Table 2).

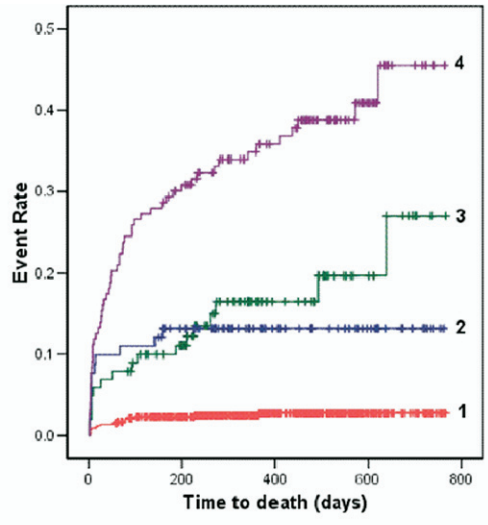
Secondary end points: MR-proANP and NT-proBNP as predictors of HF or recurrent myocardial infarction as individual end points. Midregional proatrial natriuretic peptide and NT-proBNP levels were significantly higher in patients who were readmitted with HF compared with levels in event-free survivors. Cox modeling revealed the following independent significant predictors: MR-proANP, past history of diabetes, and Killip class. Kaplan-Meier analysis revealed a lower readmission rate for HF in those in the lower 3 quartiles of MR-proANP ($p < 0.0001$) and the highest HF readmission rates in those with both biomarkers elevated in the highest quartile ($p < 0.0005$).

Compared with survivors with no end points, patients who had recurrent AMI had similar NT-proBNP and MR-proANP levels.

Discussion

Our data indicated that NT-proBNP and MR-proANP are powerful predictors of death after myocardial infarction. The combination of markers from the A- and B-type natriuretic peptide systems gives added prognostic information above existing clinical characteristics, thus enabling patients to be stratified into low-, intermediate-, or high-risk groups.

Risk stratification at an early stage after AMI remains important and may be useful in helping to select treatment



1 Lower 3 quartiles NT-proBNP, Lower 3 quartiles MR-proANP
2 Lower 3 quartiles NT-proBNP, Highest quartile MR-proANP
3 Highest quartile NT-proBNP, Lower 3 quartiles MR-proANP
4 Highest quartile NT-proBNP, Highest quartile MR-proANP

Figure 4 Combined Kaplan-Meier Survival Curve

Midregional proatrial natriuretic peptide levels (highest quartile vs. lower 3 quartiles) predicting the primary end point of death, in patients stratified by NT-proBNP (highest quartile vs. lower 3 quartiles). Abbreviations as in Figure 1.

regimes in the future. Receiver-operator characteristic curve analysis indicated that NT-proBNP and MR-proANP were of similar accuracy in prediction of death, more so than markers of structural myocardial damage such as troponin or peak creatine kinase. Even though both markers are targeting the natriuretic hormone pathway, they are clearly giving additive and complementary information. Kaplan-Meier analysis revealed MR-proANP was useful irrespective of whether NT-proBNP was high or low. A raised MR-proANP and NT-proBNP in the highest quartile was particularly useful in defining a high-risk group of patients. Multimarker strategies for outcome after AMI using biomarkers that integrate different pathways have been utilized before (17). However, here we show that complementary information can be gained by targeting different biomarkers of the 2 natriuretic peptide neurohormonal systems.

The complementary information provided by MR-proANP and NT-proBNP may partly be due to the different secretion patterns of both markers. There is a clear difference in secretion profile post-AMI of both markers, with MR-proANP peaking on Day 1 as compared with the NT-proBNP peak by Day 2. Also, NT-proBNP levels appear to be more dependent on renal function than MR-proBNP levels. Patients with markedly raised MR-proBNP but low NT-proBNP levels had significantly greater eGFR values and vice versa; this, however, did not have an impact on outcomes. These are the only identifiable differences between the 2 markers, similarities between the 2 being elevated levels in female patients compared with levels in male patients and a strong correlation with eGFR (a surrogate marker of renal function) and left ventricular systolic dysfunction. In the subset with echocardiography data, both biomarkers remained independent predictors of poor outcome. Our data are consistent with previous analyses (e.g., with ejection fraction and a single marker NT-proBNP) (6), which have retained imaging parameters in predicting similar outcomes. Midregional proatrial natriuretic peptide has been investigated in patients after an AMI where it has also been shown to be comparable to NT-proBNP for the detection of impaired left ventricular function (18). This study, unlike ours, is a small investigation in post-AMI patients at a remote time point after the acute event (mean follow-up 687 days).

The benefits of measuring both prohormones over their bioactive peptides include the lack of receptor binding or protein interactions and the longer half-lives resulting in higher plasma levels. The prohormones are also more stable in blood ex vivo, and this makes them generally more applicable in clinical practice (11). Previous studies with ANP or NT-proANP have not revealed independent predictive value of the A-type over the B-type natriuretic peptide systems (5,9). This is in contrast to what we have found, and this could be attributed to performance of different assays. In particular, assays directed to the N- and C-terminals of proANP may be more susceptible to endogenous proteases, providing the rationale for measuring midregional epitopes in the current MR-proANP assay (11). There is evidence of much heterogeneity in molecular forms of both NT-proBNP and NT-proANP, with evidence that midregional epitopes may be relatively preserved in plasma samples (19).

Natriuretic peptides in the post-AMI period probably have a beneficial effect, causing vasodilatation and increasing diuresis at a time when the ventricle has sustained a significant insult. The current findings confirm previous studies about the benefits of measuring the natriuretic peptides after an AMI and suggest that a combination marker approach may be more specific at identifying a higher risk group of patients associated with poor outcome after AMI.

Study limitations. There are some limitations that should be mentioned. This was a single-center study with a preponderance of relatively higher risk ST-segment elevation AMI patients, so that cut-points for non–ST-segment elevation AMI may need to be independently established. Although we used very minimal exclusion criteria, there was a disproportionately higher number of STEMI than NSTEMI. This may, in part, be due to the admission policies that naturally exist where patients with STEMI are more likely to be admitted to a coronary care unit than patients with NSTEMI. Our study employed blood samples in the recovery phase of AMI, and the utility of initial triage blood samples should be investigated. Finally, although both markers predicted 95 of the 101 events, 6 remaining events eluded prediction.

Conclusions

This is the first report showing MR-proANP to be a new prognostic marker of death in patients with AMI, independent of established conventional risk factors. A multimarker approach with MR-proANP and NT-proBNP targeting both the A- and B-type natriuretic neurohormonal pathways is more informative than either marker alone and may be useful for risk stratification in AMI patients.

Reprint requests and correspondence: Dr. Sohail Q. Khan, Department of Cardiovascular Sciences, Clinical Sciences Building, Leicester Royal Infirmary, Leicester, LE2 7LX, United Kingdom. E-mail:sqk1@le.ac.uk.

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