Prognostic value of Mid-regional pro-Adrenomedullin in Patients With Acute Myocardial Infarction. Leicester Acute Myocardial Infarction Peptide (LAMP) Study

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Conflicts of Interest:

A Bergmann holds ownership in BRAHMS AG, patent rights to the markers of the study and is a member of the board of directors of BRAHMS AG.

J Struck holds patent rights to the markers and is an employee of BRAHMS AG.

N Morgenthaler is an employee of BRAHMS AG.

BRAHMS is a mid-sized company, based in Hennigsdorf, Germany, commercializes immunoassays and has developed the MR-proADM assay, for which it owns patent rights.

This study was not financed by BRAHMS AG.
Abstract

Background

Adrenomedullin (ADM) is elevated in heart failure (HF) and after acute myocardial infarction (AMI). Another part of its precursor, mid-regional proADM (MR-proADM) is more stable in circulation and ex-vivo. We investigated the cardiovascular prognostic value post-AMI of MR-proADM and compared it to N-terminal B-type natriuretic peptide (NTproBNP), a marker of death and HF.

Methods

We measured plasma MR-proADM and NTproBNP in 983 consecutive post-AMI patients (721 men, mean age 65.0±(SD)12.2 years), 3-5 days after chest pain onset.

Results

There were 101 deaths and 49 readmissions with HF during follow up (median 342, range 0-764 days). MR-proADM was raised in patients with death or HF compared to survivors (median [range]nmol/L, 1.19[0.09-5.39] vs. 0.71[0.25-6.66]; p<0.0001). Using a multivariate binary logistic model, log MR-proADM (OR 4.22) and log NTproBNP (OR 3.20) were significant independent predictors of death or HF (with creatinine, age, gender and past history of AMI). The areas under the receiver-operating curve (AUC) for MR-proADM, NTproBNP and the logistic model with both markers were 0.77, 0.79 and 0.84 respectively. Cox models for the predictors of death or HF revealed the same variables (including log MR-proADM (HR 3.63), log NTproBNP (HR 2.67)). MR-proADM provided further risk stratification in those patients who had NTproBNP level above the median (p<0.0001). Findings were similar for death and HF as individual endpoints.

Conclusions

The adrenomedullin system is activated post-AMI. MR-proADM is a powerful predictor of adverse outcome especially in those with an elevated NTproBNP. MR-proADM may represent a clinically useful marker of prognosis after AMI.
**Keywords** Myocardial infarction; heart failure; peptides; Adrenomedullin; N-terminal pro B type natriuretic peptide; prognosis

**Condensed Abstract**

Adrenomedullin (ADM) is elevated in heart failure (HF) and after myocardial infarction (AMI). We investigated the prognostic value of mid-regional pro-Adrenomedullin (MRproADM, a more stable peptide derived from the precursor of ADM) post-AMI. MRproADM independently predicted death or HF post-AMI (whether considered as individual or combined endpoints), together with NTproBNP (N-terminal proB-type natriuretic peptide) and was especially useful in patients with NTproBNP levels above median. The adrenomedullin system is activated post-AMI and MR-proADM may represent a novel clinically useful marker of prognosis after AMI.

**Abbreviations:**

- NTproBNP - N-terminal proB-type natriuretic peptide
- MRproADM - mid-regional pro-Adrenomedullin
- AMI - acute myocardial infarction
- STEMI - ST segment elevation myocardial infarction
- NSTEMI - non-ST segment myocardial infarction
- HF - heart failure
Introduction

The identification of patients at high risk of adverse outcome after acute myocardial infarction remains a challenge. Circulating natriuretic peptide levels such as N-terminal pro B type natriuretic peptide (NTproBNP) provide prognostic information regarding the risk of death and heart failure following (AMI). The prognostic superiority of these biomarkers compared to consideration of clinical features has been borne out in a range of acute coronary syndromes. Newer peptides are emerging which may give complementary and additional information, particularly in a multi-marker strategy with NTproBNP. Adrenomedullin (ADM) is a 52 amino acid peptide which has homology with calcitonin gene related peptide. Originally isolated from human pheochromocytoma cells by a group of Japanese scientists who were screening these cells by looking for peptides which increased cAMP levels in platelets. ADM has subsequently been detected in other tissues including adrenal medulla, heart, brain, lung, kidney, and gastrointestinal organs and its mRNA is highly expressed in endothelial cells. The downstream actions of ADM are mediated by an increase in cAMP levels, causing potent vasodilatation and hypotension and ADM may also have autocrine or paracrine actions. ADM is synthesized as part of a larger precursor molecule, termed preproadrenomedullin. In humans this precursor consists of 185 amino acids. The gene encoding preproadrenomedullin is termed the ADM gene and has been mapped and localized to chromosome 11. ADM is difficult to measure in plasma as it is partially complexed with complement factor H and is rapidly cleared from the circulation. Recently, the more stable midregional fragment of pro-adrenomedullin (MR-proADM), comprising amino acids 45–92 of preproADM, has been identified which is more stable than the active molecule being secreted in equimolar amounts to adrenomedullin. The biological activity of ADM in the cardiovascular system is similar to that of B-type natriuretic peptide (BNP) causing vasodilation via production of NO, increasing cardiac output and inducing diuresis and natriuresis. Plasma ADM is increased in heart failure, in proportion to the severity of disease and is inversely related to LVEF.
Plasma ADM has been investigated previously in two small studies as a prognostic marker comparing it to NTproBNP and BNP.\textsuperscript{1,18} One study identified plasma ADM as an independent predictor of cardiogenic shock and short term mortality\textsuperscript{18}, whereas ADM had no independent additional prognostic value to NTproBNP in another\textsuperscript{1}. The potential role of the more stable prohormone MR-proADM in prognostication after AMI is unknown. In this study we investigated whether MR-proADM would be of benefit in determining the prognosis following AMI, particularly for predicting death and heart failure. We compared this with NTproBNP, a peptide of established prognostic value in this group of patients.\textsuperscript{1,19,20}

**Methods**

**Study population**

We studied 983 consecutive acute myocardial infarction patients admitted to the Coronary Care Unit of Leicester Royal Infirmary. The study complied with the Declaration of Helsinki and was approved by the local ethics committee; written informed consent was obtained from patients. AMI was defined at presentation with at least two of three standard criteria, i.e. appropriate symptoms, acute ECG changes of infarction (ST elevation or depression, new left bundle branch block) and a rise in troponin T above the 99\textsuperscript{th} centile for our population. 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.

**Plasma samples**

Blood samples were drawn at 3 to 5 days after the onset of chest pain for determination of plasma MR-proADM and NTproBNP. 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 blinded fashion in a single batch.

**NTproBNP assay**

Our NTproBNP assay was based on a non-competitive assay as previously published. 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 N-terminal antibody for 24 hours at 4°C. Detection was with methyl-acridinium ester (MAE)–labelled streptavidin on a MLX plate luminometer (Dynex Technologies Ltd., Worthing, UK). 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.

**MR-proADM assay**

MR-proADM was detected using a novel commercial assay in the chemiluminescence/ coated tube-format (BRAHMS AG) as described. Briefly, tubes were coated with a purified sheep polyclonal antibody raised against a peptide representing amino acids 83-94 of preproADM (see figure 1). A purified sheep polyclonal antibody raised against a peptide representing amino acids 68-86 of preproADM was labelled with MACN-Acridinium-NHS-Ester (InVent GmbH, Germany) and used as tracer. Dilutions of a peptide representing amino acids 45-92 of preproADM in normal horse serum served as standards. The immunoassay was performed by incubating 10 µl of samples/standards and 200µl tracer in coated tubes for 2 h at room temperature. Tubes were washed 4 times with 1 ml of immunoassay wash solution (B.R.A.H.M.S AG), and bound chemiluminescence was measured using a LB952T luminometer (Berthold, Germany). The MR-proADM assay has been characterized in detail previously. The lower detection limit of the assay is 0.08 nmol/L; the functional assay sensitivity (defined as the lowest
concentration detectable with an inter-assay CV of 20%) is 0.12 nmol/L. The intra-assay CV at 0.5 and 5 nmol/L is 3% and 3.5%, respectively; the inter-assay CV at 0.5 and 5 nmol/L is 8.5% and 6.5%, respectively.

End points
We assessed the value of both MR-proADM and NTproBNP for the prediction of the combined primary endpoint of death and heart failure and for death or heart failure as individual secondary endpoints. Hospitalization for heart failure was defined as a hospital admission for which heart failure was the primary reason. Endpoints were obtained by reviewing the Office of National Statistics Registry and by contacting each patient. There was a minimum 30-day follow-up of all surviving patients.

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 or heart failure of peptides levels above and below the median, binary logistic regression analyses were conducted. We included as variables baseline patient characteristics (age, sex, serum creatinine, Killip class, and territory of AMI) and peptide markers (including troponin I). Levels of NTproBNP and MR-proADM were normalised by log transformation. Thus, odds ratios and hazard ratios refer to a tenfold rise in the levels of these markers. Spearman’s correlations were performed for peptide values and continuous variables. To compare the predictive value of NTproBNP, MR-proADM or the predicted probability derived from logistic regression analyses, receiver-operating characteristic (ROC) curves were generated and the area under the curves (AUC) was calculated. To identify the independent predictors of death or heart failure, Cox proportional hazard analyses was used. Kaplan Meier survival curves were generated to visualise the relationship between the peptides
NTproBNP and MR-proADM and the primary and secondary endpoints and Mantel-Cox log rank tests\textsuperscript{22} used to assess the significance of the stratification using medians of MR-proADM (and log rank tests for linear trend of factor levels for stratification using ordered quartiles of MR-proADM), dichotomised according to NTproBNP median levels. A 2-sided p value of less than 0.05 was deemed to be statistically significant. All authors had full access to the data and take responsibility for its integrity and accuracy of the analysis. All authors have read and agree to the manuscript as written.

**Results**

**Patient characteristics**

The demographic features of the patient population are shown in Table 1. No patient was lost to follow-up which ranged from 0–764 days with a median of 342 days. During follow-up, 101 (10.3%) patients died and 49 (5.0%) were readmitted with heart failure. In 784 patients, the AMI was a STEMI event.

**MR-proADM levels in patients**

Plasma levels of MR-proADM in patients with AMI ranged from 0.09- 6.66 nmol/L with a median of 0.73 nmol/L, being elevated compared to the established normal range (mean 0.33, range 0.10-0.64 nmol/L).\textsuperscript{21} MR-proADM was higher in patients who died (p<0.0001) or were readmitted with heart failure (p<0.0001) compared to event free survivors. Levels were higher in females compared with males (p<0.0001), in patients with history of prior AMI (p<0.0001) or hypertension (p<0.0001) and in patients with prior history of heart failure (p=0.001). MR-proADM levels were not significantly different between STEMI and NSTEMI patients. MR-proADM was lower in patients who received thrombolytic therapy (p=0.043) (see table 2). MR-proADM correlated with age ($r_s= 0.552$, p< 0.0001), log creatinine ($r_s = 0.404$, p< 0.0001), Killip class ($r_s = 0.314$, p< 0.0001), and NTproBNP ($r_s =0.519$, p< 0.0001).
NTproBNP levels in patients

NTproBNP was higher in patients who died (p<0.0001) or were readmitted with heart failure (p<0.0001). Significant differences in NTproBNP levels were noted between males and females (p<0.0001) and those with Killip class above 1 (p<0.0001) and in patients with a PMH of heart failure (p=0.001) or AMI (p=0.03) (see table 2).

Primary Endpoints: MR-proADM and NTproBNP as predictors of death and heart failure

MR-proADM was raised in patients with death or heart failure compared to survivors (median [range] nmol/L, 1.19; [0.09-5.39] vs. 0.71; [0.25-6.66]; p<0.0001).

When clinical and demographic characteristics (age, sex, PMH of AMI, Killip class, log creatinine, NTproBNP and MR-proADM), were entered into a multivariate binary logistic model MR-proADM (OR 4.22, 95% CI: 1.25-14.26, p=0.02) and NTproBNP (OR 3.20, 95% CI: 2.07-4.94, p<0.0001) independently predicted the primary endpoint along with age (OR 1.04), gender (OR for male vs female 0.65), prior history of AMI (OR 2.51) and log creatinine (OR 8.25). The Nagelkerke $r^2$ was 0.35 suggesting a good fit of the model. Killip class was no longer an independent predictor of death and heart failure. The receiver-operating-characteristic curve for MR-proADM yielded an area under the curve (AUC) of 0.77 (95% CI: 0.72-0.81, p<0.001); for NTproBNP the AUC was 0.79 (95% CI: 0.75-0.84, p<0.001). The predicted probability from the binary logistic model combining the 2 markers yielded an AUC of 0.84 (95% CI: 0.81-0.88, p<0.001), which exceeded that of either peptide alone (figure 2).

Cox proportional hazards modelling confirmed that the same variables (namely MR-proADM, NTproBNP, age, gender, PMH of AMI and log creatinine) were independent predictors of death or heart failure (Table 3).

The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with MR-proADM below the median (0.73 nmol/L) compared with those with MR-proADM above the median (log rank test $\chi^2 61.27$, p<0.0001, figure 3). This was also true for NTproBNP (log
rank test $\chi^2$ 68.27, p<0.0001, figure 4). In patients stratified by NTproBNP (median 914 pmol/L), MR-proADM gave additional information on death and heart failure in those patients who had NTproBNP level above the median (log rank test $\chi^2$ for linear trend of factor levels, pooled over NTproBNP strata, 49.07, p<0.0001, figure 5), and even for patients below the NTproBNP median value, MR-proADM had some predictive value (log rank test $\chi^2$ 5.12, p=0.024, figure 5). Patients in the top quartile for MR-proADM (above 1.04 nmol/L) had a significantly higher mortality than those in quartiles 1 to 3 (p<0.0001 for all). For NTproBNP below the median, those patients in the top quartile of MR-proADM had higher event rates than those in quartile 1 (p=0.006) and 2 (p=0.018), (figure 5).

The event rates at 1 year for both death and heart failure readmission or death alone in patients stratified by median NTproBNP (914 pmol/L) and quartiles of MR-proADM are illustrated in figure 6, in which the top quartile of MR-proADM (1.04 nmol/L) predicted those at highest risk.

**Secondary Endpoints: MR-proADM and NTproBNP as predictors of death or heart failure as individual endpoints.**

On Cox proportional hazards modelling the strongest independent predictors of death were MR-proADM (HR 4.86, p=0.001) and NTproBNP (HR 3.64, p<0.0001), the other independent predictors were age (HR 1.06, p<0.0001), and prior history of AMI (HR 1.64, p=0.019). Such modelling on heart failure readmissions yielded the following independent predictors: MR-proADM (HR 7.29, p<0.0001), NTproBNP (HR 1.71, p=0.034), Killip class above 1 (HR 2.04, p=0.014), and PMH of AMI (HR 1.93, p=0.011). Kaplan-Meier analysis on death or heart failure as individual endpoints revealed a significantly better clinical outcome in patients with MR-proADM below the median compared with those with MR-proADM above the median (log rank test $\chi^2$ 42.4 and 28.65 respectively, p<0.0001). In addition quartiles of MR-proADM predicted those with the highest mortality or readmission with heart failure, stratified by NTproBNP levels
above the median (log rank test $\chi^2$ for linear trend of factor levels, pooled over NTproBNP strata, 34.61 and 21.1 respectively, p<0.0001)

**Discussion**

This is the first report investigating the prognostic potential following AMI of MR-proADM in a large cohort of patients from a single centre. Moreover, we compared this with NTproBNP, a well-established marker of death and heart failure after AMI. Our data indicate by survival analysis using both Kaplan-Meier and Cox proportional hazard models that MR-proADM is a powerful independent predictor of death and heart failure, with combined levels of MR-proADM and NTproBNP giving additive prognostic information.

Reperfusion therapy and the application of secondary prevention therapies have improved survival post AMI. Despite this, outcome remains poor for some patients. A multimarker strategy for outcome post-AMI using independent biomarkers may provide complementary information through integrating the different mechanistic pathways involved. Our data indicate that while MR-proADM and NTproBNP individually have similar prognostic utility, the two markers considered together provide complementary information.

Multivariate analyses (binary and the more statistically powerful Cox regression) demonstrated that both MR-proADM and NTproBNP retained statistically significant power for prediction of death and heart failure independent of other demographic and clinical variables. However the combination of MR-proADM and NTproBNP in a multi-marker risk stratification approach generated an increased area under the ROC curve and greater predictive accuracy. Importantly, Kaplan-Meier analysis revealed MR-proADM was particularly useful in the group of patients in whom NTproBNP was elevated, in particular those with levels above the top quartile (1.04 nmol/L). Our data indicate that patients can be risk-stratified more precisely than is possible using NTproBNP alone.
The complementary prognostic utility of these peptides may suggest there are differences in their pathophysiological roles, or in the stimuli to their release. However there are some common associations, suggesting some similarities in the stimuli leading to the secretion of MR-proADM and NTproBNP; both levels increase with age and both show higher levels in females. NTproBNP is a more stable by-product in the production of BNP. In similar fashion MR-proADM is the more stable by-product of ADM released in a 1:1 ratio. The current findings confirm that the ADM system may be another candidate neurohormonal pathway, in addition to the renin-angiotensin and sympathetic nervous systems that may be associated with poor outcome after AMI.

In a previous study, ADM was found to be weakly predictive of death during follow-up after AMI. However its independent predictive power was lost for death and heart failure when NTproBNP was evaluated. Interestingly, ADM was not raised in patients who later died or developed heart failure. In another study ADM was found to be an independent predictor of death and cardiogenic shock post AMI. ADM has also been shown to be raised in heart failure with levels increasing with the severity of NYHA class. The apparent discrepancy between our study and the previous investigation may relate to the size of populations investigated. However the confirmation of the independent predictive value of MR-proADM together with NTproBNP may have been achieved due to the improved design of the MR-proADM assay which measures prohormone that does not associate with binding proteins or receptors, resulting in a short half life. The benefit of measuring the prohormones over the active peptide is that the lack of receptor binding or protein interactions and the longer half-lives result in higher easily measurable plasma levels.

ADM may have a number of advantageous effects in the post-AMI period causing vasodilation (with reduction of arterial and cardiac filling pressures) at a time when the myocardium has been compromised and may cause increased myocardial contractility via its downstream actions on cAMP. ADM may also play a role in maintaining sodium balance, inhibiting the production of
aldosterone despite an elevated renin activity, and thereby optimizing cardiac filling at a time when the ventricle has taken an insult.\textsuperscript{26}

**Limitations of the study**

This was a single centre study and the results need to be replicated in larger multicentre studies. There was a preponderance of ST elevation AMI, as cut-points for non-ST elevation AMI may need to be independently established. Our study employed blood samples in the recovery phase of AMI, and the utility of initial triage blood samples should be investigated.

**Conclusion**

This report confirms activation of the adrenomedullin system post AMI and MR-proADM to be a powerful new prognostic marker of death or heart failure and the combined endpoint of both outcomes, in patients with AMI, independent of established conventional risk factors and newer plasma biomarkers such as NTproBNP. A multimarker approach with MR-proADM and NTproBNP is more informative than either marker alone and may be useful for risk stratification in AMI patients, with the possibility of changes in the investigation and therapy of such individuals.
References


Acknowledgments

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Legends

Figure 1 Principle of the MR-proADM assay. A sketch of the adrenomedullin precursor is shown, and amino acid positions in prepro-ADM are denoted, at which the precursor is proteolytically processed. Tracer and solid phase-antibodies used in the sandwich immunoassay for the detection of MR-proADM are indicated. Signal: signal peptide; PAMP: pro-adrenomedullin N-terminal 20 peptide; MR-proADM: mid-regional pro-adrenomedullin.

Figure 2 Combined Receiver Operating Characteristic Curve comparing NTproBNP, MR-proADM and the combined predicted probabilities from a binary logistic model for prediction of death or heart failure

Figure 3 Kaplan-Meier Curve: Time to death or heart failure related to plasma MR-proADM

Figure 4 Kaplan-Meier Curve: Time to death or heart failure related to plasma NTproBNP

Figure 5 Kaplan-Meier analysis for quartiles of MR-proADM predicting the primary endpoint of death or heart failure, in patients stratified by NTproBNP< or >median

Figure 6 Annual event rates for death and for death or heart failure, in patients stratified by NTproBNP (< or >median) and MRproADM quartiles.
Table 1 Characteristics of the 983 patients in the study separated by MRproADM quartiles.
Values are means (SD) or numbers (%)

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<th></th>
<th>1st quartile</th>
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<th>3rd quartile</th>
<th>4th quartile</th>
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<td>Age (in years)</td>
<td>55.5 ± 10.7</td>
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<td>59 (24.1)</td>
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<td>53 (21.5)</td>
<td>43 (17.5)</td>
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<td>153 (62.2)</td>
<td>146 (59.3)</td>
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<td>200 (81.3)</td>
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<td>1063.8 ±</td>
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<td>Creatinine (µmol/L)</td>
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<td>91.3 ± 18.2</td>
<td>101.9 ± 26.0</td>
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<td>1923.1 ± 2228.9</td>
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<td>178 (72.3)</td>
<td>177 (72.0)</td>
<td>146 (59.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### Table 2 Table comparing MR-proADM and NTproBNP levels in different patient sub-groups

<table>
<thead>
<tr>
<th></th>
<th>Median MR-proADM (nmol/L)</th>
<th>p value</th>
<th>Median NTproBNP (fmol/ml)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death vs. Survivors</td>
<td>1.31 vs. 0.71</td>
<td>p&lt;0.0001</td>
<td>5929.3 vs. 839.0</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Admission with HF vs. No HF</td>
<td>1.10 vs. 0.71</td>
<td>p&lt;0.0001</td>
<td>3932.9 vs. 839.0</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Males vs. Females</td>
<td>0.88 vs. 0.70</td>
<td>p&lt;0.0001</td>
<td>788.7 vs. 1632.6</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Previous AMI vs. No AMI</td>
<td>0.88 vs. 0.71</td>
<td>p&lt;0.0001</td>
<td>844.4 vs. 1332.3</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Hypertension vs. Normotensives</td>
<td>0.79 vs. 0.70</td>
<td>p&lt;0.0001</td>
<td>1100.8 vs. 812.6</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Previous HF vs. No HF</td>
<td>1.10 vs. 0.72</td>
<td>p=0.001</td>
<td>668.6 vs. 2415.9</td>
<td>p=0.001</td>
</tr>
<tr>
<td>STEMI vs. NSTEMI</td>
<td>0.73 vs. 0.71</td>
<td>p=NS</td>
<td>1021.6 vs. 616.5</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Killip class above 1 vs. Killip class 1</td>
<td>0.84 vs. 0.68</td>
<td>p&lt;0.0001</td>
<td>1583.4 vs. 631.0</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>
**Table 3** Multivariate Cox proportional hazards regression model of significant predictors of death or heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log MR-proADM</td>
<td>3.63</td>
<td>1.48-8.90</td>
<td>0.005</td>
</tr>
<tr>
<td>Log NTproBNP</td>
<td>2.67</td>
<td>1.82-3.90</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.02-1.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.69</td>
<td>0.46-0.96</td>
<td>0.031</td>
</tr>
<tr>
<td>PMH of AMI</td>
<td>1.76</td>
<td>1.24-2.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Log creatinine</td>
<td>4.05</td>
<td>0.99-16.67</td>
<td>0.052</td>
</tr>
</tbody>
</table>
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5
Figure 6