Prognostic Value of Midregional Pro-Adrenomedullin in Patients With Acute Myocardial Infarction

The LAMP (Leicester Acute Myocardial Infarction Peptide) Study

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Objectives
This study sought to assess the prognostic impact of midregional pro-adrenomedullin (MR-proADM) after an acute myocardial infarction (AMI).

Background
Adrenomedullin (ADM) is elevated in heart failure (HF) and after AMI. Another part of its precursor, MR-proADM, is more stable in circulation and ex vivo. We investigated the cardiovascular prognostic value after AMI of MR-proADM and compared it with N-terminal pro-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±12.2 years), 3 to 5 days after chest pain onset.

Results
There were 101 deaths and 49 readmissions with HF during follow-up (median 342, range 0 to 764 days). The MR-proADM was increased in patients with death or HF compared with survivors (median 1.19 nmol/l, range 0.09 to 5.39 nmol/l, vs. 0.71 nmol/l, range 0.25 to 6.66 nmol/l, p<0.0001). Using a multivariate binary logistic model, log MR-proADM (odds ratio 4.22) and log NTproBNP (odds ratio 3.20) were significant independent predictors of death or HF (with creatinine, age, gender, and history of AMI). The areas under the receiver-operating characteristic curve 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 showed the same variables (including log MR-proADM, hazard ratio 3.63; log NTproBNP, hazard ratio 2.67). The MR-proADM provided further risk stratification in those patients who had NTproBNP levels above the median (p<0.0001). Findings were similar for death and HF as individual end points.

Conclusions
The ADM system is activated after AMI. The MR-proADM is a powerful predictor of adverse outcome, especially in those with an elevated NTproBNP. The MR-proADM may represent a clinically useful marker of prognosis after AMI. (J Am Coll Cardiol 2007;49:1525–32) © 2007 by the American College of Cardiology Foundation

The identification of patients at high risk of adverse outcome after acute myocardial infarction (AMI) 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 after AMI (1). The prognostic superiority of these biomarkers compared with consideration of clinical features has been borne out in a range of acute coronary syndromes (2). Newer peptides are emerging that may give complementary and additional information, particularly in a multimarker strategy with NTproBNP. Adrenomedullin (ADM) is a 52-amino-acid peptide that has homology with calcitonin gene-related peptide (3). This peptide was originally isolated from human pheochromocytoma cells by a group of Japanese scientists who were screening these cells by looking for peptides that increased cyclic adenosine monophosphate (cAMP) levels in platelets. Adrenomedullin has subsequently been detected in other tissues, including adrenal medulla, heart, brain, lung, kidney, and gastrointestinal organs (3,4), and its mRNA is highly expressed in endothelial cells (5). The downstream actions of ADM are...
is rapidly cleared from the circulation (10). Recently, the more stable midregional fragment of pro-ADM (MR-proADM), comprising amino acids 45 to 92 of preproADM, has been identified, and is more stable than the active molecule being secreted in equimolar amounts to ADM (11).

The biological activity of ADM in the cardiovascular system is similar to that of B-type natriuretic peptide (BNP) causing vasodilatation (12) via production of nitric oxide (13), increasing cardiac output (14), and inducing diuresis and natriuresis (15). Plasma ADM is increased in heart failure in proportion to the severity of disease (16,17) and is inversely related to left ventricular ejection fraction.

Plasma ADM has been investigated previously in 2 small studies as a prognostic marker comparing it with NT-proBNP and BNP (1,18). One study identified plasma ADM as an independent predictor of cardiogenic shock and short-term mortality (18), whereas ADM had no independent additional prognostic value to NTproBNP in another (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 after AMI, particularly for predicting death and heart failure. We compared this with NTproBNP, a peptide of established prognostic value in this group of patients (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. Acute myocardial infarction was defined at presentation with at least 2 of 3 standard criteria (i.e., appropriate symptoms, acute electrocardiographic changes of infarction [ST-segment elevation or depression, new left bundle branch block], and an increase in troponin I above the 99th percentile for our population). Acute myocardial infarction was subcategorized into ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation 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 min of bed rest, 20 ml of 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.

NTproBNP assay. Our NTproBNP assay was based on a noncompetitive assay as previously published (2). Sheep antibodies were raised to the N-terminal of human NTproBNP, and monoclonal mouse antibodies were raised to the C-terminal. The N-terminal immunoglobulin G was affinity-purified and biotinylated. Samples or NTproBNP 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–labeled streptavidin on an 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 atrial natriuretic peptide, BNP, or C-type natriuretic peptide.

MR-proADM assay. The MR-proADM was detected using a novel commercial assay in the chemiluminescence/coated tube format (BRAHMS AG, Hennigsdorf, Germany) as previously described (21). Briefly, tubes were coated with a purified sheep polyclonal antibody raised against a peptide representing amino acids 83 to 94 of preproADM (Fig. 1). A purified sheep polyclonal antibody raised against a peptide representing amino acids 68 to 86 of preproADM was labeled with methylacridinium N-hydroxysuccinimide ester (InVent GmbH, Hennigsdorf, Germany) and used as a tracer. Dilutions of a peptide representing amino acids 45 to 92 of preproADM in normal horse serum served as standards. The immunoassay was performed by incubating 10–µl samples/standards and 200–µl tracer in coated tubes for 2 h at room temperature. Tubes were washed 4 times with 1-ml immunoassay wash solution (BRAHMS AG), and bound chemiluminescence was measured using an LB952T luminometer (Berthold, Bad Wildbad, Germany). The MR-proADM assay has been characterized in detail previously (21). The lower detection limit of the assay is 0.08 nmol/l; the functional assay sensitivity (defined as the lowest concentration detectable with an interassay coefficient of variation [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 interassay 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 end point of death and heart failure and for death
or heart failure as individual secondary end points. Hospitalization for heart failure was defined as a hospital admission for which heart failure was the primary reason. End points 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 using SPSS version 12 (SPSS Inc., Chicago, Illinois). The continuous variables in the 2 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, gender, serum creatinine, Killip class, and territory of AMI) and peptide markers (including troponin I). Levels of NTproBNP and MR-proADM were normalized by log transformation. Thus, odds ratios and hazard ratios refer to a 10-fold increase in the levels of these markers. Spearman 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 curves were generated and the area under the curve (AUC) was calculated. To identify the independent predictors of death or heart failure, Cox proportional hazard analyses were used. Kaplan-Meier survival curves were generated to visualize the relationship between the peptides NTproBNP and MR-proADM, and the primary and secondary end points and Mantel-Cox log rank tests (22) were 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), dichotomized according to NTproBNP median levels. A 2-sided p value of <0.05 was deemed to be statistically significant. All investigators had full access to the data and take responsibility for its integrity and accuracy of the analysis. All investigators have read and agreed to the article 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 to 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 to 6.66 nmol/l with a median of 0.73 nmol/l, being elevated compared with the established normal range (mean 0.33 nmol/l, range 0.10 to 0.64 nmol/l) (21). The MR-proADM was higher in patients who died (p < 0.0001) or were readmitted with heart failure (p < 0.0001) compared with event-free survivors. Levels were higher in women compared with men (p < 0.0001), in patients with a history of AMI (p < 0.0001) or hypertension (p < 0.0001), and in patients with a history of heart failure (p = 0.001). The MR-proADM levels were not significantly different between STEMI and NSTEMI patients. The MR-proADM was lower in patients who received thrombolytic therapy (p = 0.043) (Table 2).

The MR-proADM correlated with age (r = 0.552, p < 0.0001), log creatinine (r = 0.404, p < 0.0001), Killip class (r = 0.314, p < 0.0001), and NTproBNP (r = 0.519, p < 0.0001).

NTproBNP levels in patients. The 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 men and women...
(p < 0.0001), and those with a Killip class >1 (p < 0.0001) and in patients with a history of heart failure (p = 0.001) or AMI (p = 0.03) (Table 2).

**Primary end points: MR-proADM and NTproBNP as predictors of death and heart failure.** The MR-proADM was increased in patients with death or heart failure compared with survivors (median 1.19 nmol/l, range 0.09 to 5.39 nmol/l, vs. median 0.71 nmol/l, range 0.25 to 6.66 nmol/l; p < 0.0001).

When clinical and demographic characteristics (age, gender, history of AMI, Killip class, log creatinine, NT-proBNP, and MR-proADM) were entered into a multivariate binary logistic model, MR-proADM (odds ratio [OR] 4.22, 95% confidence interval [CI] 1.25 to 14.26, p = 0.001) independently predicted the primary end point along with age (OR 1.04), gender (OR for men vs. women 0.65), history of AMI (OR 2.51), and log creatinine (OR 8.25). The Nagelkerke r² 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 AUC of 0.79 (95% CI 0.75 to 0.84, p < 0.001); for NTproBNP the AUC was 0.79 (95% CI 0.75 to 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 to 0.88, p < 0.001), which exceeded that of either peptide alone (Fig. 2). Cox proportional hazards modeling confirmed that the same variables (namely MR-proADM, NTproBNP, age, gender, history of AMI, and log creatininenuleotide peptide.

### Table 1

**Characteristics of the 983 Patients in the Study Separated by MRproADM Quartiles**

<table>
<thead>
<tr>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.5 ± 10.7</td>
<td>63.5 ± 10.1</td>
<td>67.4 ± 10.3</td>
<td>73.6 ± 10.1</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>25 (10.2)</td>
<td>37 (15.0)</td>
<td>43 (17.5)</td>
<td>59 (24.1)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>52 (21.1)</td>
<td>57 (23.2)</td>
<td>68 (27.6)</td>
<td>72 (29.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (32.5)</td>
<td>105 (42.7)</td>
<td>108 (43.9)</td>
<td>126 (51.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (12.6)</td>
<td>53 (21.5)</td>
<td>43 (17.5)</td>
<td>88 (35.9)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>51 (20.7)</td>
<td>56 (22.8)</td>
<td>59 (24.0)</td>
<td>58 (23.7)</td>
</tr>
<tr>
<td>Current/ex-smokers</td>
<td>166 (67.5)</td>
<td>153 (62.2)</td>
<td>146 (59.3)</td>
<td>140 (57.1)</td>
</tr>
<tr>
<td>ST-segment elevation AMI</td>
<td>187 (76.0)</td>
<td>200 (81.3)</td>
<td>205 (83.3)</td>
<td>201 (82.0)</td>
</tr>
<tr>
<td>Thrombolytic</td>
<td>136 (55.3)</td>
<td>131 (53.3)</td>
<td>146 (59.3)</td>
<td>111 (45.3)</td>
</tr>
</tbody>
</table>

**Table 2**

**Comparison of MR-proADM and NTproBNP Levels in Different Patient Subgroups**

<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>&lt;0.0001</td>
<td>5.929.3 vs. 839.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission with HF vs. no HF</td>
<td>1.10 vs. 0.71</td>
<td>&lt;0.0001</td>
<td>3.932.9 vs. 839.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men vs. women</td>
<td>0.88 vs. 0.70</td>
<td>&lt;0.0001</td>
<td>788.7 vs. 1632.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous AMI vs. no AMI</td>
<td>0.88 vs. 0.71</td>
<td>&lt;0.0001</td>
<td>844.4 vs. 1332.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension vs. normotensive</td>
<td>0.79 vs. 0.70</td>
<td>&lt;0.0001</td>
<td>1,108.8 vs. 812.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous HF vs. no HF</td>
<td>1.10 vs. 0.72</td>
<td>0.001</td>
<td>668.6 vs. 2415.9</td>
<td>0.001</td>
</tr>
<tr>
<td>STEMI vs. NSTEMI</td>
<td>0.73 vs. 0.71</td>
<td>NS</td>
<td>1,021.6 vs. 616.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Killip class above I vs. Killip class I</td>
<td>0.84 vs. 0.68</td>
<td>&lt;0.0001</td>
<td>1,583.4 vs. 631.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HF = heart failure; NSTEMI = non-ST-segment myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.
nine) were independent predictors of death or heart failure (Table 3).

The Kaplan-Meier survival curve showed 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 chi-square test 61.27, p < 0.0001) (Fig. 3). This was also true for NTproBNP (log rank chi-square test 68.27, p < 0.0001) (Fig. 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 NT-proBNP levels above the median (log rank chi-square test for linear trend of factor levels, pooled over NTproBNP strata, 49.07, p < 0.0001) (Fig. 5), and even for patients below the NTproBNP median value, MR-proADM had some predictive value (log rank chi-square test 5.12, p = 0.024) (Fig. 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 quartile 2 (p = 0.018) (Fig. 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 shown in Figure 6, in which the top quartile of MR-proADM (1.04 nmol/l) predicted those at highest risk.

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</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>Gender</td>
<td>0.69</td>
<td>0.46–0.96</td>
<td>0.031</td>
</tr>
<tr>
<td>History 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>

**Secondary end points: MR-proADM and NTproBNP as predictors of death or heart failure as individual end points.** On Cox proportional hazards modeling, the strongest independent predictors of death were MR-proADM (hazard ratio [HR] 4.86, p = 0.001) and NTproBNP (HR 3.64, p < 0.0001), the other independent predictors were age (HR 1.03, p < 0.0001) and history of AMI (HR 1.64, p = 0.019). Such modeling 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 >1 (HR 2.04, p = 0.014), and history of AMI (HR 1.93, p = 0.011). Kaplan-Meier analysis on death or heart failure as individual end points showed a significantly better clinical outcome in patients with MR-proADM below the median compared with those with MR-proADM above the median (log rank chi-square test 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 chi-square test 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 after AMI of MR-proADM in a large cohort of patients from a single center. 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 after AMI. Despite this, outcome remains poor for some patients (23). A multi-marker strategy for outcome after AMI using independent biomarkers may provide complementary information through integrating the different mechanistic pathways involved (24). Our data indicate that although MR-proADM and NTproBNP individually have similar prognostic utility, the 2 markers considered together provide complementary information.

Multivariate analyses (binary and the more statistically powerful Cox regression) showed 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 multimarker risk stratification approach generated an increased area under the receiver-operating characteristic curve and greater predictive accuracy. Importantly, Kaplan-Meier analysis showed that 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 that 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 women. The NTproBNP is a more stable byproduct in the production of BNP (25). In a similar fashion, MR-proADM is the more stable byproduct 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 a poor outcome after AMI.

In a previous study, ADM was found to be weakly predictive of death during follow-up after AMI (1). However, its independent predictive power was lost for death and heart failure when NTproBNP was evaluated. Interestingly, ADM was not increased in patients who later died or developed heart failure (1). In another study, ADM was found to be an independent predictor of death and cardiogenic shock after AMI (18). Adrenomedullin has also been shown to be increased in heart failure (17,26), with levels increasing with the severity of New York Heart Association functional class (16). The apparent discrepancy between our study and the previous investigation (1) 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 because of 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 (11). 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.

Adrenomedullin 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 (6). Adrenomedullin may also play a role in maintaining sodium balance, inhibiting the production of aldosterone despite an elevated renin activity, thereby optimizing cardiac filling at a time when the ventricle has taken an insult (27).

Study limitations. This was a single-center study, and the results need to be replicated in larger multicenter studies. There was a preponderance of ST-segment elevation AMI, because cut points for non–ST-segment elevation AMI may need to be independently established. Our study used blood samples in the recovery phase of AMI, and the utility of initial triage blood samples should be investigated.

Conclusions

This report confirms activation of the ADM system after AMI and MR-proADM to be a powerful new prognostic marker of death or heart failure and the combined end point 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.

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REFERENCES


