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ORIGINAL RESEARCH CONTRIBUTION

Midregional Proadrenomedullin Predicts Mortality and Major Adverse Cardiac Events in Patients Presenting With Chest Pain: Results From the CHOPIN Trial

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Abstract

Objectives: Chest pain is a common complaint to emergency departments (EDs) and clinical risk factors are used to predict which patients are at risk for worse outcomes and mortality. The goal was to assess the novel biomarker midregional proadrenomedullin (MR-proADM) in prediction of mortality and major adverse cardiac events (MACE).

Methods: This was a subanalysis of the CHOPIN study, a 16-center prospective trial that enrolled 2,071 patients presenting with chest pain within 6 hours of onset. The primary endpoint was 6-month all-cause mortality and the secondary endpoint was 30-day and 6-month MACE: ED visits or hospitalization for acute myocardial infarction, unstable angina, reinfarction, revascularization, and heart failure.

Results: MR-proADM performed similarly to troponin (cTnI; c-statistic = 0.845 and 0.794, respectively) for mortality prediction in all subjects and had similar results in those with noncardiac diagnoses. MR-proADM concentrations were stratified by decile, and the cohort in the top decile had a 9.8% 6-month mortality risk versus 0.9% risk for those in the bottom nine deciles ($p < 0.0001$). MR-proADM, history of coronary artery disease (CAD), and hypertension were predictors of short-term MACE, while history of CAD, hypertension, cTnI, and MR-proADM were predictors of long-term MACE.

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Conclusions: In patients with chest pain, MR-proADM predicts mortality and MACE in all-comers with chest pain and has similar prediction in those with a noncardiac diagnosis. This exploratory analysis is primarily hypotheses-generating and future prospective studies to identify its utility in risk stratification should be considered.

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Chest pain is a common cause of emergency department (ED) presentation. It is the second most common complaint in the United States, representing approximately 9% of ED visits and 5.5 million subjects per year.[1,2] Chest pain is a nonspecific but concerning symptom for acute coronary syndrome (ACS) and ischemic heart disease, which in 2011 was the most common cause of death worldwide.[3] Currently, the approach to undifferentiated chest pain includes a combination of history, physical examination, electrocardiogram (ECG), imaging, and laboratory testing.

Several risk scores have been developed, including Thrombolysis in Myocardial Infarction (TIMI);[4–6] Global Registry of Acute Coronary Events (GRACE);[7–10] Fast Revascularisation in Instability in Coronary disease (FRISC);[11] and History, ECG, Age, Risk factors, and Troponin (HEART),[12,13] to identify which patients with chest pain of cardiac etiology are at higher risk for worse cardiovascular outcomes and mortality. These scores are derived from overlapping clinical variables recorded at time of evaluation, including age, vital signs, comorbidities, and biomarkers. Troponin has specific prognostic value in patients who present with cardiac chest pain, predicting mortality up to 2 years after discharge.[14] However, most subjects who present to the ED with chest pain are not diagnosed with ACS, and many are deemed low-risk, based on risk scores. However, there is a subset who still suffer death and incur adverse cardiac events. Our ability to identify these patients may be improved with novel biomarkers.

Adrenomedullin (ADM) is a 52-amino-acid peptide originally discovered from human pheochromocytoma and believed to be secreted in response to lipopolysaccharide stimulation.[15–17] It is synthesized in the adrenal medulla and has vasodilator properties. ADM is elevated in response to a variety of stimuli, including sepsis and ventricular pressure/volume overload.[17–21] A double-monoclonal antibody sandwich immunoassay for the measurement of the more stable midregional (MR) fragment of the precursor (pro-ADM) has been identified.[22] Baseline and the change in MR-proADM concentrations after ACS have been shown to be associated with risk of major clinical events, including death.[23] In this study, we assessed the utility of MR-proADM compared with cardiac troponin I (cTnI) for prediction of mortality and major adverse cardiac events (MACE) in an undifferentiated cohort of patients presenting to the ED with chest pain.

METHODS

Study Design

This was a post hoc subanalysis of the CHOPIN study.[24] The CHOPIN study was conducted in compliance with International Conference on Harmonisation/Good Clinical Practice regulations, and all 16 sites received local institutional review board or ethics committee approval; all patients provided written informed consent for participation.

Study Setting and Population

The CHOPIN study was a 16-center prospective trial that enrolled 2,071 patients presenting to the ED with chest pain within 6 hours of onset. The primary results and details of the trial are already published.[24] A 6-hour time window was preselected by the principal investigators given the various sensitivities of local troponin assays being used. Patients $\geq$ 18 years of age were included if the treating emergency physician had suspicion for ACS. Patients with obvious alternative sources of chest pain, such as trauma, were excluded from the study. Patients were not selected based on any preexisting comorbidities or known prognoses.

CHOPIN Study Protocol

Patients were evaluated and treated per local standard of care. Independent from on-site laboratory values, study laboratory values, including cTnI and MR-proADM, were drawn on presentation. For this study, the blood drawn on presentation was used for all analyses. All physicians were blinded to cTnI and MR-proADM values. The study blood samples were centrifuged and stored at –80°C prior to being sent to the core laboratory for analysis.

Criterion Standard Diagnosis. Two board-certified cardiologists independently reviewed all study subjects. All final diagnoses were assigned to one of six categories: 1) ST-elevation myocardial infarction (STEMI), 2) non-STEMI, 3) unstable angina (UA) pectoris, 4) non-ACS cardiovascular disease, 5) noncardiac chest pain, and 6) unclassified cause of chest pain. Local troponin values and cutoffs were used for this categorization and any discrepancies in diagnoses were adjudicated by an endpoints committee. There were no discrepancies in acute MI (AMI) diagnoses between the two cardiologists for patients included in this analysis. The endpoints committee reviewed all final evaluations for consistency.

Biomarker Assays. MR-proADM was collected in EDTA plasma and detected with a sandwich immunoluminometric assay on the Kryptor system (MR-proADM, BRAHMS AG, Hennigsdorf/Berlin, Germany). The 95th percentile of a normal reference population as reported by the manufacturer is 0.52 nmol/L. 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%) was 0.12 nmol/L. The intraassay CVs at 0.5 and

5 nmol/L are 3 and 3.5%, respectively; the interassay CV at 0.5 and 5 nmol/L was 8.5 and 6.5%, respectively.

Cardiac troponin was measured both locally and as part of the core laboratory (cTnI) collection, at the University of Maryland (RC) with a cTnI Ultra assay on an ADVIA Centaur XP system (Siemens Healthcare Diagnostics, Norwood, MA). The assay's detection range according to the manufacturer is 6 to 50,000 ng/L, with a 99th percentile cutoff of 40 ng/L, and a 10% CV at 30 ng/L.

Natriuretic peptides were not included in the analysis, as only a subset of subjects had B-type natriuretic peptide (BNP; $n = 620$) or N-terminus pro-BNP (NT-proBNP; $n = 175$) measured. Creatinine and hemoglobin were local laboratory values.

Study Endpoints. The primary CHOPIN endpoint was all-cause mortality, including inpatient through 6 months after initial presentation. Secondary endpoints were created by a priori analysis specifically for this secondary analysis, which included 30-day and 6-month major adverse cardiac events (MACE). These were defined as ED visits and/or hospitalization for any of the following: AMI, UA, reinfarction, revascularization, and congestive heart failure (CHF). Thirty-day mortality was not utilized as an endpoint due to a limited number of events.

Data Analysis

For this post hoc analysis, normally distributed values are expressed as means with standard deviation (±SD), and nonnormally distributed variables are expressed as medians and interquartile range (IQR) or counts and percentages, as appropriate. To perform decile analysis, all subjects with MR-proADM measured were used to create 10 groups based on MR-proADM by deciles.

Group comparisons of categorical data were performed using Pearson's chi-square tests. Comparisons of continuous variables were performed with Student's t-test and Mann Whitney U-test, as appropriate. Biomarker data were log-transformed. All statistical tests were two-tailed, with a p-value < 0.05 being considered significant. Relationships between MR-proADM and other covariates were analyzed by using Pearson's correlation coefficient methods. Receiver operator characteristic (ROC) curves were plotted; these curves were compared for statistical significance of the difference between area under curve (AUC) using methods set out by Hanley and McNeil.[25]

Logistic regression analysis was used in prediction of secondary endpoints. Odds ratios (ORs) of log-transformed variables were back-transformed for interpretation. Univariate logistic regression was performed to determine association between covariate and mortality. Covariates were standard clinical predictors (e.g., demographic data, coronary artery disease [CAD] risk factors) chosen from the clinical risk scores mentioned earlier. Ischemic ECG findings were defined as ST elevation, ST depression, T-wave inversions, new left bundle branch block, or readings as AMI. Kaplan-Meier analysis used the log-rank (Mantel-Cox) test to compare cohorts. There were 16 centers with enrollment varying from 250 to 21 subjects from individual sites. Weighted analyses to control for center-to-center variation were not performed.

The statistical analyses were performed using SPSS version 16.0. The data management center (VA San Diego Healthcare System) was responsible for data quality control and statistical analysis. The academic principal investigators of the trial hold an independent copy of the trial database and were able to perform independent statistical analyses.

RESULTS

Patient Characteristics

The baseline demographics of the population that died versus survived are shown in Table 1. These entities include age, sex, ethnicity, past medical history, vital signs, laboratory values, and home medications. On average, patients presented to the ED in 115.9 (±180) minutes within when symptoms began, with 75% of patients presenting within 3 hours of symptom onset.

Patients who ultimately died were older, with more comorbidities, including CAD, CHF, peripheral vascular disease, and chronic kidney disease. They also presented with higher heart rates (HR), lower systolic/diastolic blood pressures (sBP/dBP), lower hemoglobin, and higher creatinine. They were on more medications including clopidogrel and warfarin and had significantly higher (local) troponin and BNP. Causes of death included cardiac/ACS/CHF ($n = 22$), sepsis ($n = 5$), respiratory failure ($n = 3$), and unknown ($n = 6$).

MR-proADM and Outcomes

Of the original cohort, 727 (35.1%) had final diagnoses that were cardiac-related (AMI, UA, stable angina, aortic dissection, CHF, or arrhythmia). In these subjects, MR-proADM was significantly elevated versus those with noncardiac etiologies of chest pain (0.66 nmol/L, IQR = 0.499 to 1.033 nmol/L vs. 0.59 nmol/L, IQR = 0.458 to 0.791 nmol/L; $p < 0.001$). In our cohort, during a mean follow-up of 180 days, 35 patients died, including 12 within 30 days. Patients who ultimately died had higher MR-proADM on presentation compared to those who did not die (1.56 nmol/L, IQR = 0.945 to 2.713 nmol/L vs. 0.609 nmol/L, IQR = 0.468 to 0.842 nmol/L; $p < 0.001$). Figure 1 demonstrates MR-proADM in box-whisker format in all comers, those who ultimately die, and those who ultimately experience MACE. MR-proADM are greater in those who died versus those who did not die and in those who experienced MACE versus those who did not. MR-proADM was stratified by decile (see Data Supplement S1, available as supporting information in the online version of this paper) and those in the top decile had a 9.8% 6-month mortality risk (Figure 2) versus 0.9% risk for those in the bottom nine deciles ($p < 0.0001$). This trend persisted whether final diagnosis for chest pain was cardiac or noncardiac (12 of 18 deaths in the top decile vs. eight of 18 deaths in top the decile, respectively).

Baseline Biochemical and Clinical Correlates of MR-proADM

Table 2 demonstrates correlations between log-transformed MR-proADM and various clinical and biochemi-

Table 1
Demographics

Characteristic	*n*	Death Within 180 Days (*n* = 35)	No Death (*n* = 2,010)	p-value
Age (yr), mean (±SD)	2,045	64.9 (±15.4)	56.3 (±12.8)	<0.001
Male	2,045	25 (71.4)	1,134 (56.4)	0.086
Race				
White		15 (42.9)	1,053 (52.3)	0.307
Black		18 (51.4)	769 (38.3)	0.224
Past medical history				
Coronary artery disease	2,045	22 (62.9)	747 (37.2)	0.003
Hypertension	2,045	27 (77.1)	1,395 (69.4)	0.361
Congestive heart failure	2,045	13 (37.1)	327 (16.3)	0.003
Hyperlipidemia	2,045	21 (60)	1,084 (53.9)	0.499
Cerebrovascular accident	2,045	6 (17.1)	196 (9.8)	0.083
Peripheral vascular disease	2,045	6 (17.1)	112 (5.6)	0.011
Chronic kidney disease	2,045	12 (34.2)	138 (6.9)	<0.001
Diabetes mellitus	2,045	17 (48.6)	566 (28.2)	0.013
Atrial fibrillation	2,045	7 (20.0)	194 (9.6)	0.075
Ventricular tachycardia	2,045	1 (2.9)	61 (3.0)	0.418
Cardiac arrest	2,045	0 (0)	58 (2.9)	0.624
Vitals and local laboratory values*				
Heart rate (beats/min)	2,040	88.2 (±25.0)	81.3 (±19.1)	0.036
Systolic blood pressure (mm Hg)	2,038	128 (±34.1)	142 (±26.5)	0.003
Diastolic blood pressure (mm Hg)	2,038	67.0 (±19.5)	80.6 (±15.9)	<0.001
Respiratory rate (breaths/min)	2,033	19.4 (±4.2)	18.5 (±3.5)	0.127
Creatinine (mg/dL)	2,006	1.5 (1.0–2.6)	0.9 (0.8–1.2)	<0.001
Hemoglobin (g/dL)	1,998	10.9 (9.3–12.7)	13.5 (12.2–14.7)	<0.001
Troponin [local] (mg/dL)	2,026	0.050 (0.03–0.11)	0.01 (0.01–0.04)	<0.001
B-type natriuretic peptide (pg/mL)	615	691 (54–974)	55 (18–215.5)	<0.001
Home medications				
Aspirin	2,045	18 (51.4)	912 (45.3)	0.316
Clopidogrel	2,045	11 (31.4)	302 (15.0)	0.004
Warfarin	2,045	7 (22.0)	154 (7.6)	0.004
Statin	2,045	17 (51.4)	834 (41.5)	0.266
Beta blocker	2,045	16 (45.7)	807 (40.1)	0.266
ACE inhibitor	2,045	14 (40.0)	828 (41.2)	0.887
Calcium channel blocker	2,045	4 (11.4)	392 (19.5)	0.231
Diuretics	2,045	12 (34.3)	568 (28.3)	0.433
Digoxin	2,045	2 (5.7)	50 (2.5)	0.229
Aldosterone antagonist	2,045	0 (0)	24 (1.2)	0.516
Antiarrhythmic	2,045	4 (11.4)	47 (2.3)	<0.001
Nitroglycerin	2,045	10 (28.6)	434 (21.6)	0.321

Data are reported as *n* (%) unless otherwise noted.
*Reported as mean (±SD) or median (IQR)

cal correlates from Table 1. MR-proADM had a moderately positive association with BNP ($r = 0.439$, $p < 0.0001$), cTnI ($r = 0.302$, $p < 0.001$), and age ($r = 0.349$, $p < 0.001$). Additionally, MR-proADM had a moderately negative association with hemoglobin ($r = -0.360$, $p < 0.001$).

Comparison of MR-proADM with cTnI for Discrimination of Mortality

A ROC curve was constructed to predict 6-month mortality based upon MR-proADM on presentation; the AUC was 0.845. Optimal threshold cutoff was 0.944 nmol/L. Sensivity, specificity, negative and positive predictive values, and positive and negative likelihood ratios for MR-proADM at this cutoff are shown in Table 3. For comparison, initial cTnI has an AUC of 0.794 (Figure 3). The AUC for MR-proADM was not significantly greater than AUC for cTnI ($p = 0.415$). Table 4 demonstrates c-statistics for MR-proADM and cTnI in those with final diagnoses of ACS, non-ACS, and non-cardiac diagnoses.

MACE and MR-proADM

From the entire cohort, 58 subjects experienced postdischarge MACE within 30 days of presentation, and 158 subjects experienced postdischarge MACE within 180 days. In patients who had postdischarge MACE within 6 months, MR-proADM was higher than those without an event (0.867 nmol/L, IQR = 0.581 to 1.53 nmol/L vs. 0.603 nmol/L, IQR = 0.466 to 0.823 nmol/L; $p < 0.001$). Similar differences between MR-proADM in those with versus without 30-day MACE were found (0.805 nmol/L, IQR = 0.562 to 1.441 nmol/L vs. 0.610 nmol/L, IQR = 0.468 to 848 nmol/L; $p = 0.002$).

When splitting the cohort by MR-proADM in the top decile versus the bottom nine deciles, there was an 8.3% 30-day event rate ($n = 17$) in the patients with MR-proADM > 1.38 nmol/L versus a 2.2% event rate ($n = 41$) in the rest of the population ($p = 0.002$). By ROC curve analysis, MR-proADM had a c-statistic for 0.714 and 0.595 for predicting 30-day MACE in those with non-cardiac versus cardiac diagnoses, respectively.

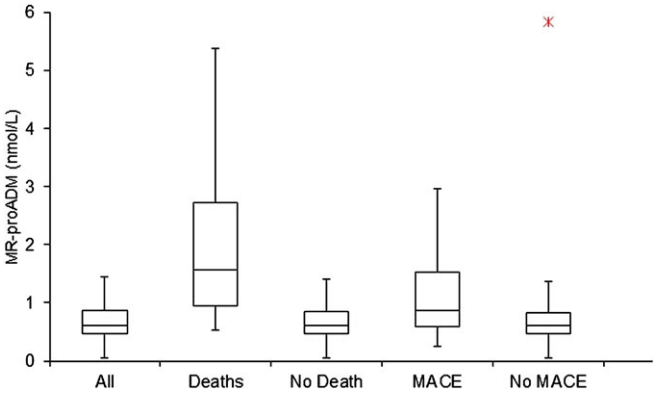

Figure 1. MR-proADM on initial presentation. Box-whisker plots demonstrate median, 25th, 75th, and minimum/maximum of each subgroup of MR-proADM. MACE = major adverse cardiac events; MR-proADM = midregional proadrenomedullin.

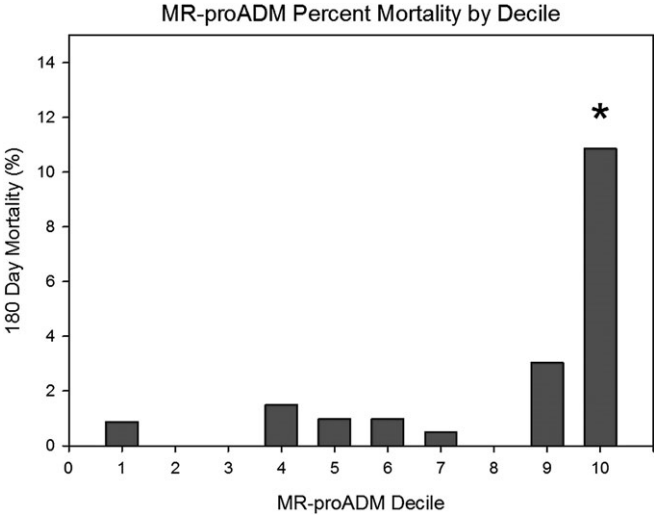

Figure 2. Subjects with MR-proADM levels in the highest decile demonstrate greatest incidence of death over 6 months. MR-proADM = midregional proadrenomedullin. *p < 0.0001.

Association Between Baseline Biomarkers and Outcomes in Logistic Regression Analysis

Univariable logistic regression was performed and the covariates associated with increased mortality were age; history of diabetes mellitus; history of CAD; ischemic ECG findings on presentation; and history concerning for ACS, HR, sBP, cTnI, creatinine, and MR-proADM. The ORs and 95% confidence interval (CI) are shown in Table 5. MR-proADM had a hazard ratio of 4.60 (95% CI = 3.50 to 5.69, p < 0.001). Given only 35 events, the seven clinical covariates with a significant association with mortality (age; diabetes mellitus; CAD; and history concerning for ACS, ECG changes, HR, and sBP) were rerun in multivariable stepwise logistic regression with the final significant predictors being age, history concerning for ACS, HR, and sBP. For comparison, these four predictors were run in multivariable stepwise regression against MR-proADM. Final predictors of mortality were MR-proADM (OR = 4.65, 95% CI = 3.46 to 5.85, p < 0.001), sBP (OR = 0.98, 95% CI = 0.97 to 0.99, p = 0.010), and history concerning for ACS (OR = 1.02, 95% CI = 1.01 to 1.03, p = 0.001). For comparison, the three biomarkers (cTnI, creatinine, and MR-proADM) were rerun in multivariable stepwise regression, and final predictors of mortality were MR-proADM (OR = 4.18, 95% CI = 3.03 to 5.33, p < 0.001) and cTnI (OR = 0.69, 95% CI = 0.28 to 1.12, p = 0.001).

Table 2
Correlations Between MR-proADM and Different Studied Parameters Among the CHOPIN Cohort

Characteristic	MR-proADM (r-value)	p-value
Age	0.349	<0.001
Heart rate	0.066	0.003
Systolic blood pressure	0.015	0.508
Diastolic blood pressure	–0.133	<0.001
Respiratory rate	0.173	<0.001
Hemoglobin	–0.360	<0.001
Creatinine	0.174	<0.001
B-type natriuretic peptide	0.439	<0.001
Cardiac troponin I (core lab)	0.302	<0.001

MR-proADM = midregional proadrenomedullin.

A postdischarge MACE occurred in 58 subjects within 30 days of presentation, and 158 had a MACE within 180 days. Table 6 demonstrates short-term and long-term predictors of adverse cardiac events. The clinical covariates with significant association for 30-day MACE were run in a multivariable stepwise logistic regression with MR-proADM, and final predictors of short-term MACE were as follows: cTnI (OR = 0.61, 95% CI = 0.28 to 0.94, p < 0.001), history of CAD (OR = 2.96, 95% CI = 1.56 to 5.59, p = 0.001), and history of hypertension (OR = 7.06, 95% CI = 1.68 to 29.66, p = 0.008). For long-term outcomes, all variables from Table 5 with significant univariate association were rerun in multivariable stepwise Cox regression, and final predictors of 6-month MACE were as follows: history of CAD (OR = 2.51, 95% CI = 1.71 to 3.67, p < 0.001), history of hypertension (OR = 4.73, 95% CI = 2.23 to 9.89, p < 0.001), cTnI (OR = 0.54, 95% CI = 0.31 to 0.77, p < 0.001), and MR-proADM (OR = 1.40, 95% CI = 0.74 to 2.06, p = 0.001).

Kaplan-Meier Survival Analysis

Kaplan-Meier curve 6-month all-cause mortality for MR-proADM in the top decile versus bottom nine deciles group is shown in Figure 4. The top decile includes subjects with MR-proADM greater than 1.38 nmol/L. Figure 4 demonstrates a significant survival difference between both groups (p < 0.001).

DISCUSSION

In this subanalysis of the CHOPIN trial, we sought to assess the prognostic value of MR-proADM in a cohort of patients presenting to the ED with chest pain. We found that MR-proADM is elevated at the time of presentation in patients who ultimately died or had short-term and long-term adverse cardiac events. Specifically, MR-proADM in the top decile seems to provide the greatest risk in those with a final cardiac or noncardiac

Table 3
MR-proADM Predictive Values for 6-Month Mortality at a Cutoff of 0.944 nmol/L

Characteristic	Value	95% CI
Sensitivity (%)	75.00	57.8–87.9
Specificity (%)	81.47	79.7–83.1
Positive likelihood ratio	4.05	3.3–4.9
Negative likelihood ratio	0.31	0.2–0.5
Positive predictive value	6.68	4.5–9.6
Negative predictive value	99.46	98.9–99.8

MR-proADM = midregional proadrenomedullin.

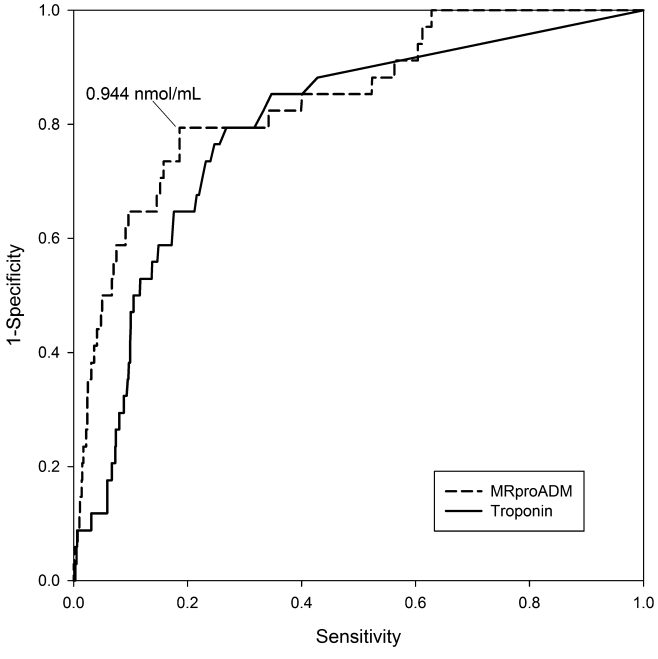

Figure 3. Receiver operating characteristic curve for MR-proADM and troponin to predict mortality. MR-proADM = midregional proadrenomedullin.

diagnosis. MR-proADM performed similarly in prediction of long-term mortality, and short- and long-term MACE, to cTnI in all patients.

MR-proADM and Cardiac Biomarkers

Adrenomedullin has physiologic functions, including vasodilatation, diuresis, and natriuresis,[16–18,26,27] and its expression may be being triggered by cellular stress and ischemia.[28] Given its effect in diuresis and vasodilatation, some experts believe its role to be similar to the natriuretic peptides.[29–31] In patients who present with acute HF, MR-proADM has already been shown to predict short- and long-term mortality, adding value to natriuretic peptides.[32–34] Our analysis demonstrates modest correlation with natriuretic peptides and MR-proADM, serving as a complementary indicator of cardiac hemodynamic stress. The majority of MACE in this study were acute HF admissions, and elevated MR-proADM in patients with chest pain may be an early signal to preclinical HF.

We also show MR-proADM has modest correlation with cTn, a finding previously demonstrated by Maisel et al.[32] Cardiac troponin is incorporated in every algorithm involving the diagnosis of AMI and predicts short-term mortality.[35,36] As high sensitivity assays become more readily available, our understanding of their appropriate use in the evaluation of chest pain will evolve,[37,38] with current studies demonstrating prediction of cardiovascular death 1 year after presentation with chest pain.[39] However, the eligibility study of this trial mandated presentation within 6 hours of symptoms, and the true prognostic value of peak troponin is possibly not captured in our analysis given the time to peak troponin in MI. The role of serial MR-proADM compared to serial troponin in prognostication was not assessed in our analysis, although this would be a worthy investigation in future analyses. As our ability to detect myocardial necrosis improves, markers like MR-proADM may serve a role in providing complementary physiologic information, identifying patients with underlying comorbidities. Our analysis demonstrates that this biomarker is a robust predictor of mortality and MACE. Interestingly, the risk associated with significantly elevated MR-proADM persists in those with a noncardiac etiology for their chest pain presentation. Because MR-proADM shows a strong association with cardiac events, this biomarker may enhance our ability to risk-stratify patients in conjunction with traditional risk factors, a task called for by current biomarker guidelines.[40]

MR-proADM and Noncardiac Disease

Measurement of the stable surrogate MR-proADM has shown prognostic potential in multiple noncardiac settings. In the general population, levels of the biomarker significantly predicted death, MACE, and heart failure

Table 4
ROC Analyses for MR-proADM and cTnI, to Predict 6-Month Mortality in Multiple Cohorts

	All-comers (n = 2,030)		ACS (n = 299)		Non-ACS (n = 1,731)		Noncardiac (n = 1,344)	
Variable	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
MR-proADM	0.845	0.78–0.91	0.697	0.54–0.85	0.892	0.82–0.96	0.883	0.79–0.97
cTnI	0.794	0.72–0.88	0.720	0.56–0.86	0.793	0.70–0.89	0.812	0.70–0.93

ACS = acute coronary syndromes; AUC = area under curve; cTnI = cardiac troponin I; MR-proADM = midregional proadrenomedullin; ROC = receiver operating characteristic.

Table 5
Univariate Logistic Regression for Prediction of 6-Month Mortality (n = 35)

Risk Predictor	OR	95% CI	p-value
Demographics			
Age, yr	1.05	1.03–1.08	<0.001
Male sex	1.76	0.86–3.60	0.121
Risk factors			
Hypertension	1.32	0.62–2.82	0.473
Hyperlipidemia	1.20	0.62–2.35	0.586
Diabetes mellitus	2.27	1.17–4.40	0.015
Coronary artery disease	2.66	1.36–5.24	0.005
Presentation			
History (ACS likelihood 1%–100%)	1.02	1.00–1.03	0.002
ECG changes	2.68	1.24–5.77	0.012
Heart rate	1.02	1.00–1.03	0.048
Systolic blood pressure	0.98	0.96–0.99	0.002
Labs			
cTnI (ng/L)	1.01	0.98–1.04	<0.001
Creatinine (mg/dL)	2.18	1.36–2.99	<0.001
MR-proADM (nmol/L)	4.60	3.50–5.69	<0.001

ACS = acute coronary syndrome; ECG = electrocardiogram; cTnI = cardiac troponin I; MR-proADM = midregional proadrenomedullin.

Table 6
Univariate Logistic Regression for Prediction of Short-term and Long-term MACE

	30-Day MACE (n = 58)			180-Day MACE (n = 158)		
Risk Predictor	OR	95% CI	p-value	OR	95% CI	p-value
Demographics						
Age	1.03	1.01–1.05	0.001	1.03	1.02–1.04	<0.001
Male	1.59	0.92–2.78	0.099	1.53	1.09–2.15	0.015
Risk factors						
Hypertension	8.31	2.60–26.67	<0.001	7.11	3.72–13.59	<0.001
Hyperlipidemia	2.76	1.51–5.08	0.001	2.71	1.87–3.92	<0.001
Diabetes mellitus	2.77	1.64–4.67	<0.001	2.58	1.86–3.58	<0.001
Coronary artery disease	4.19	2.36–7.42	<0.001	4.28	3.01–6.09	<0.001
Presentation						
History*	1.02	1.00–1.02	0.001	1.01	1.00–1.02	<0.001
ECG changes	2.34	1.24–4.41	0.008	1.37	0.86–2.19	0.180
Heart rate	1.01	0.99–1.02	0.358	1.00	0.99–1.01	0.937
Systolic blood pressure	1.01	1.00–1.02	0.049	1.00	0.99–1.00	0.669
Labs						
cTnI	0.688	0.40–0.97	<0.001	0.75	0.60–0.95	<0.001
Creatinine	1.02	0.15–1.29	0.022	1.89	1.34–2.44	<0.001
MR-proADM	2.10	1.20–3.00	<0.001	2.61	2.01–3.20	<0.001

ACS = acute coronary syndrome; cTnI = cardiac troponin I; ECG = electrocardiogram; MACE = major adverse cardiac events; MR-proADM = midregional proadrenomedullin.
*ACS likelihood 1%–100%.

even beyond natriuretic peptides.[41] Additionally, levels are elevated in sepsis, septic shock, and pneumonia.[42,43] MR-proADM in undifferentiated febrile patients in the ED setting may even predict which patients need hospitalization, underlying a relationship with infection.[44] Our analysis demonstrates that MR-proADM (especially >1.38 nmol/L) had a very strong association with mortality, and causes of death were various, including cardiac, sepsis, and respiratory failure. Of note, those in our cohort who died within 6 months of initial presentation had more comorbidities, higher baseline creatinine, and more vital sign abnormalities on presentation. That being said, MR-proADM has multisystemic involvement, providing possible nonspecific prognostic value, reflecting overall body stress, and signaling underlying disease. Notably, those with a noncardiac diagnosis still had an increased incidence of short- and long-term cardiac events when MR-proADM was elevated; this finding may demonstrate detection of underlying cardiac disease in patients who may not otherwise be identified for such risk.

Clinical Implications

MR-proADM has potential to impact clinical practice in three distinct ways. One is to provide insight in to which patients who present with chest pain are at

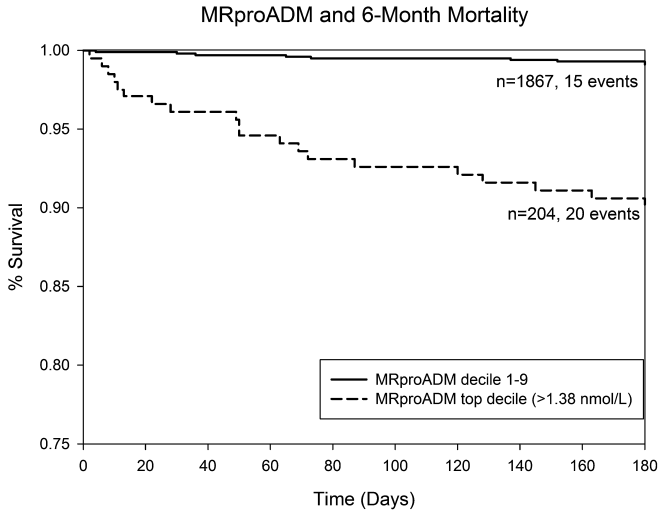

Figure 4. Kaplan-Meier survival curve demonstrating MR-proADM levels greater than 1.38 nmol/L (top decile) portend poor prognosis. MR-proADM = midregional proadrenomedullin.

highest risk for future events, specifically those with significantly elevated MR-proADM. Those who ultimately have a cardiac etiology may merit further investigation with stress testing for significant CAD, while those with a noncardiac diagnosis may merit closer outpatient follow-up. A second way MR-proADM may be used is as a biomarker to guide targeted therapy in chronic conditions such as CHF[45] and infections. It may represent which patients have greater underlying hemodynamic stress and potentially respond most effectively to therapy.[46] Third, it is possible that in the future, MR-proADM measurement may identify individuals who could benefit from targeted therapy, as small studies have demonstrated an anti-ADM antibody reduces mortality in mice.[47] With the multiple potential roles for this marker, MR-proADM may truly represent a death marker whose clinical role will continue to evolve.

LIMITATIONS

This was a post hoc subanalysis of the CHOPIN trial, exploring the role of MR-proADM and its association with mortality and adverse cardiac events. The results and discussion should be viewed primarily as hypothesis-generating. Although we had a priori identified the primary outcome, secondary outcomes were created by post hoc analysis. This was a multicenter (all in the United States) trial with a range of patient risk factors and physician practice styles. Given the site locations, our cohort has an overall lower risk compared to Europe, which likely explains the low mortality rate in this patient population, limiting our ability to construct multivariate regression for death.

The low number of deaths limits our ability to adjust for confounders in multivariate analysis. Ideally, clinical scores such as GRACE or FRISC would have been recreated, but all data were not available. Additionally, all analysis using cTnI were based on core laboratory values of troponin (a contemporary sensitive assay), while study participants used local laboratory troponin, which had a range of sensitivities. The highest sensitivity assays that are now available are improved, and therefore the comparison of MR-proADM to troponin is limited in this manner. Additionally, the difference between local and contemporary troponin assays may have affected the number of patients diagnosed with AMI. However, the current practice in the United States still primarily utilizes similar troponin assays in the management of chest pain, and comparing an investigational assay with this generation of troponin assay for risk prediction can still be viewed as hypothesis-generating.

CONCLUSIONS

In patients presenting with chest pain, midregional proadrenomedullin was significantly elevated in patients who died within 6 months of presentation and those who experienced a postdischarge major adverse cardiac event. Significantly elevated MR-proADM is a signal for future adverse events in those with cardiac and noncardiac diagnoses for their chest pain. When compared with other common clinical covariates, MR-proADM remained a significant predictor of death and major adverse cardiac events. Use of MR-proADM in a panel of biomarkers may improve risk stratification of patients who present with chest pain. Future prospective studies incorporating this novel biomarker in chest pain and other clinical presentations should be considered.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. MR-proADM by decile.