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Midregion Prohormone Adrenomedullin and Prognosis in Patients Presenting With Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,*##||||| Christian Mueller, MD,† Richard M. Nowak, MD,‡ W. Frank Peacock, MD,§ Piotr Ponikowski, MD, PHD,‖ Martin Mockel, MD,¶ Christopher Hogan, MD,# Alan H. B. Wu, PHD,** Mark Richards, MD, PHD,†† Paul Clopton, MS,* Gerasimos S. Filippatos, MD,‡‡ Salvatore Di Somma, MD,§§ Inder Anand, MD, DPHIL (OXON),|||| Leong L. Ng, MD,¶¶ Lori B. Daniels, MD, MAS,## Sean-Xavier Neath, MD, PHD,## Robert Christenson, PHD,*** Mihael Potocki, MD,† James McCord, MD,‡ Oliver Hartmann, MSC,††† Nils G. Morgenthaler, MD, PHD,‡‡‡ Stefan D. Anker, MD, PHD¶§§§

San Diego and San Francisco, California; Basel, Switzerland; Detroit, Michigan; Cleveland, Ohio; Wroclaw, Poland; Berlin, Germany; Richmond, Virginia; Christchurch, New Zealand; Athens, Greece; Rome, Italy; Minneapolis, Minnesota; Leicester, United Kingdom; and Baltimore, Maryland

Objectives The aim of this study was to determine the prognostic utility of midregion proadrenomedullin (MR-proADM) in all patients, cardiac and noncardiac, presenting with acute shortness of breath.

Background The recently published BACH (Biomarkers in Acute Heart Failure) study demonstrated that MR-proADM had superior accuracy for predicting 90-day mortality compared with B-type natriuretic peptide (area under the curve: 0.674 vs. 0.606, respectively, $p < 0.001$) in acute heart failure.

Methods The BACH trial was a prospective, 15-center, international study of 1,641 patients presenting to the emergency department with dyspnea. Using this dataset, the prognostic accuracy of MR-proADM was evaluated in all patients enrolled for predicting 90-day mortality with respect to other biomarkers, the added value in addition to clinical variables, as well as the added value of additional measurements during hospital admission.

Results Compared with B-type natriuretic peptide or troponin, MR-proADM was superior for predicting 90-day all-cause mortality in patients presenting with acute dyspnea (c index = 0.755, $p < 0.0001$). Furthermore, MR-proADM added significantly to all clinical variables (all adjusted hazard ratios: >3.28), and it was also superior to all other biomarkers. MR-proADM added significantly to the best clinical model (bootstrap-corrected c index increase: 0.775 to 0.807; adjusted standardized hazard ratio: 2.59; 95% confidence interval: 1.91 to 3.50; $p < 0.0001$). Within the model, MR-proADM was the biggest contributor to the predictive performance, with a net reclassification improvement of 8.9%. Serial evaluation of MR-proADM performed in patients admitted provided a significant added value compared with a model with admission values only ($p = 0.0005$). More than one-third of patients originally at high risk could be identified by the biomarker evaluation at discharge as low-risk patients.

Conclusions MR-proADM identifies patients with high 90-day mortality and adds prognostic value to natriuretic peptides in patients presenting with acute shortness of breath. Serial measurement of this biomarker may also prove useful for monitoring, although further studies will be required. (Biomarkers in Acute Heart Failure [BACH]; NCT00537628) (J Am Coll Cardiol 2011;58:1057–67) © 2011 by the American College of Cardiology Foundation

Adrenomedullin (ADM), a vasodilatory peptide with potent hypotensive effects, is expressed in many different tissues (1). Its plasma levels are elevated in chronic heart failure (2) and increase proportionally to disease severity (3–8). However, its clinical application has been impeded because of biologic instability of plasma measurements.

From the *VA San Diego Healthcare System, San Diego, California; †University Hospital Basel, Basel, Switzerland; ‡Henry Ford Health System, Detroit, Michigan; §The Cleveland Clinic, Cleveland, Ohio; ‖Medical University, Faculty of Public Health, Wroclaw, Poland; ¶Charité, Campus Virchow-Klinikum, Berlin, Germany; #Virginia Commonwealth University, Richmond, Virginia; **University of California, San Francisco, San Francisco, California; ††University of Otago, Christchurch, New Zealand; ‡‡Athens University Hospital Attikon, Athens, Greece; §§Sant'Andrea Hospital, University La Sapienza, Rome, Italy; ||||Minneapolis VA

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Abbreviations and Acronyms

ADM = adrenomedullin
AHF = acute heart failure
BNP = B-type natriuretic peptide
CI = confidence interval
CV = coefficient of variation
ED = emergency department
HR = hazard ratio
IQR = interquartile range
MR-proADM = midregion proadrenomedullin
MR-proANP = midregion pro–atrial natriuretic peptide
NRI = net reclassification improvement
NT-proBNP = N-terminal pro–B-type natriuretic peptide
PCT = procalcitonin

Recently, several immunoassays of stable analytes stoichiometrically related to ADM synthesis have been developed (9–11). Directed at stable midregion prohormones of the biologically active unstable fragment, measurement of midregion proADM (MR-proADM) may provide clinically relevant prognostic information. In the recently published BACH (Biomarkers in Acute Heart Failure) study, the primary prognostic endpoint was the utility of MR-proADM compared with that of B-type natriuretic peptide (BNP) for 90-day mortality in patients diagnosed with acute heart failure (AHF) (12). Using optimal cutoff values from receiver-operating characteristic curve analysis, the accuracy to predict survival at 90 days for MR-proADM was 73% (95% confidence interval [CI]: 70% to 77%), while it was 62% (95% CI: 58% to 66%) for BNP ($p < 0.001$). In multivariate Cox proportional hazards analysis, MR-proADM, but not BNP, carried independent prognostic value after adjusting for age, sex, creatinine, and troponin elevation ($p < 0.001$). The purpose of this secondary analysis was to further explore the prognostic utility of MR-proADM in all patients, cardiac and noncardiac, presenting with acute shortness of breath, as well as evaluating the added value on top of clinical variables and the added value of additional measurements during hospital admission.

Methods

The BACH trial was a prospective, 15-center international study of 1,641 patients presenting to the emergency department (ED) with dyspnea and has been reported in detail elsewhere (12).

Study population. This study was approved by the institutional review boards of all participating centers, and patients were enrolled from March 2007 to February 2008. To be eligible, patients had to report shortness of breath as their primary symptom upon presentation to the ED. Patients were excluded if they were younger than 18 years of age, were unable to provide consent, had acute ST-segment elevation myocardial infarctions, were receiving hemodialysis, or had renal failure. The study ED physicians were blinded to the investigational marker results. Confirmation of diagnoses and outcomes has been described in detail (12).

Measurement of biomarkers. All blood samples were collected in plastic tubes containing ethylenediamine tetraacetic acid, and plasma was stored at −70°C in plastic freezer vials. Characteristics of blood collection and sampling have been described (12). MR-proADM was measured using an automated sandwich chemiluminescence immunoassay on the KRYPTOR system (B·R·A·H·M·S AG, Hennigsdorf/Berlin, Germany), described elsewhere (10,11). For MR-proADM, the limit of quantification was 0.23 nmol/l; the within-run imprecision (coefficient of variation [CV]) was 1.9%, and the between-run imprecision (CV) was 9.8%. BNP was measured with Triage 2-site immunoassay reagents (Biosite, Inc., San Diego, California) formatted for Beckman Coulter instrumentation (Beckman Coulter, Inc., Brea, California). Performance in the laboratory included a limit of quantitation of 5.0 ng/l, within-run imprecision (CV) of 1.5%, and total imprecision (CV) of 3.0%. All blood samples were processed by personnel blinded from any patient data. Copeptin, midregion pro–atrial natriuretic peptide (MR-proANP), procalcitonin (PCT) (all on the KRYPTOR system) and N-terminal proBNP (NT-proBNP) (Elecsys 2010 analyzer, Roche Diagnostics, Indianapolis, Indiana) were also measured in our central lab, while troponin was measured locally using both troponin T and I assays.

Statistical analysis. Values are expressed as mean ± SD or as counts and percentages as appropriate. Because of the log-normal distribution of the biomarkers, medians and interquartile ranges (IQRs) are reported for those. Spearman's rank correlation coefficient was calculated to describe the relationship between 2 biomarkers. A 2-sided p value ≤0.05 was used for statistical significance.

Health Care System, Minneapolis, Minnesota; ¶¶University of Leicester and NIHR Cardiovascular Biomedical Research Unit, Leicester, United Kingdom; ##University of California, San Diego, California; ***University of Maryland, Baltimore, Maryland; †††University of California, San Diego School of Medicine, San Diego, California; ‡‡‡B·R·A·H·M·S Aktiengesellschaft Biotechnology Centre, Hennigsdorf/Berlin, Germany; §§§Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and the ||||San Diego Veterans Affairs Medical Center, San Diego, California.
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All outcome prediction results reported are for all-cause mortality within 90 days after presentation to the ED. For simplicity, we used the previously identified cutoff for MR-proADM of 1.985 nmol/l for illustrations of predictive performance (12).

Log-transformed values of all biomarkers were evaluated in univariate, bivariate, and multivariate Cox regression models to evaluate the contribution of MR-proADM over and above that of other variables. Because differences with respect to outcome prediction between patients diagnosed with AHF and those diagnosed as not having AHF were negligible for all biomarkers and clinical variables, the multivariate analysis is reported for all patients only. To test for differences in the predictive value of MR-proADM and other variables, we used the likelihood ratio chi-square test for nested models to assess whether MR-proADM added predictive value to a clinical model and vice versa. First, we performed bivariate Cox regression models to demonstrate that MR-proADM is independent of each of the reported variables. Second, we determined the best clinical model by selecting the top 9 prognostic variables in univariate analysis among patient characteristics, physical examination, medical history, and routine laboratory variables. To account for outcome differences with respect to the main diagnosis (patients with AHF are more likely to die), this variable was also included. To this multivariate model, limited to include 10 variables to have sufficient events for evaluation, MR-proADM was added and the added value evaluated using both nested Cox regression models and net reclassification improvement (NRI) (13). Risk percentile cutoffs were approximately the 10th and 90th percentiles of predicted risk on the basis of the best clinical model (predicted risk at 2% and 19%, respectively).

For continuous variables, hazard ratios (HRs) were standardized to describe the HR for a biomarker change of 1 IQR. The predictive value of each model was assessed by the model likelihood ratio chi-square statistic. The c index is given as an effect measure. It is equivalent to the concept of area under the curve adopted for binary outcomes. For multivariate models, a bootstrap-corrected version of the c index is given. Kaplan-Meier survival curves were plotted using the MR-proADM cutoff.

To evaluate whether re-evaluation of the biomarker at a later point in time provided additional prognostic information, we applied a time-dependent Cox regression model. Missing values were replaced using the last-observation-carried-forward rule, and missing draw times were replaced using the median draw times (1 day for the second measurement and 7 days for the discharge value).

All statistical analyses were performed using R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.1 (SAS Institute Inc., Cary, North Carolina), or SPSS version 16.0 (SPSS, Inc., Chicago, Illinois).

The data management center and research department of the VA San Diego Healthcare System (San Diego, California) was responsible for data quality control and statistical analysis.

Results

Description of general population. A total of 1,641 patients were evaluated. Of these, the adjudicated diagnosis was AHF in 568 patients (34.6%). Of the 1,073 remaining patients (65.4%), final diagnoses were chronic obstructive pulmonary disease in 201 (12.2%), asthma in 130 (7.0%), pneumonia in 112 (6.8%), chest pain of unknown origin in 106 (6.5%), bronchitis in 61 (3.7%), arrhythmia in 55 (3.4%), acute coronary syndromes in 39 (2.4%), pulmonary embolism in 38 (2.3%), influenza in 27 (1.6%), and "other" diseases as a primary diagnosis in 304 (18.5%). There were 130 deaths within 90 days (survival rate 92.1%; 95% CI: 90.7% to 93.3%). Of the 568 patients with AHF, 65 died within 90 days (90-day survival rate 88.6%; 95% CI: 85.6% to 90.9%). Among the 1,073 patients without AHF, there were 65 deaths within 90 days (90-day survival rate 93.9%; 95% CI: 92.3% to 95.2%).

The patient characteristics of patients alive or dead at 90 days are presented in Table 1. Patients who died were older, more likely to be white, had lower blood pressures, had lower body mass indexes, and were more likely to be overtly volume overloaded, as evidenced by rales, elevated jugular venous pressure, edema, and ascites. They were also more likely to be on warfarin, diuretic agents, digoxin, or aldosterone inhibitors (data not shown). The trend for all differences was identical in patients with AHF and in those without. In the non-AHF group, patients who died were more likely to be male, had higher heart rates, were more likely to have pacemakers or to have undergone percutaneous coronary intervention, and were less likely to be on nebulizers or to use inhalers, while no significant differences were observed for these variables in the AHF group (Online Table 1). Causes of death as recorded were as follows: congestive heart failure in 39 (30%), other cardiac diseases in 10 (7.7%), chronic obstructive pulmonary disease in 12 (9.2%), sepsis in 7 (5.4%), lower respiratory tract infection in 4 (3.1%), and other reasons not further specified in 58 (44.6%).

Descriptive analysis of biomarker measurements. Valid measurements for MR-proADM were obtained for 99.6% of all patient samples (6 failures among 1,641 patients). For BNP and NT-proBNP, the rates were 99.8% (3 failures) and 98.9% (18 failures), respectively. MR-proADM levels ranged from 0.03 to 12.6 nmol/l, with a median of 0.88 nmol/l and an IQR of 0.57 to 1.44 nmol/l. Spearman's correlation coefficients between MR-proADM and BNP, NT-proBNP, and troponin were 0.72, 0.76, and 0.32, respectively. Table 2 shows the biomarker median values by outcome at 90 days. All biomarkers were significantly higher in patients who died during follow-up ($p < 0.002$) (see also Online Fig. 1).

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Table 1 Patient Demographics

Variable	n	Dead (n = 130)	Alive (n = 1,511)	p Value
Demographics				
Age (yrs)	1,641	72.8 ± 13.2	63 ± 17	<0.0001
Male	1,641	79 (60.8%)	780 (51.6%)	0.0543
Race	1,626			0.0005
White		976 (65.2%)	114 (88.4%)	
Black		462 (30.9%)	14 (10.9%)	
Other		59 (3.9%)	1 (0.8%)	
Recent history				
Smoking	1593	32 (26.9%)	437 (29.6%)	0.6013
Wheezing	1,543	26 (22.6%)	442 (31%)	0.0725
Weight gain	1,438	24 (22.9%)	225 (16.9%)	0.1394
Night sweats	1,495	26 (23.2%)	298 (21.5%)	0.7205
Orthopnea	1,536	67 (55.8%)	622 (43.9%)	0.0129
Dyspnea at rest	1,605	76 (59.8%)	719 (48.6%)	0.0162
Examination variables				
Heart rate (beats/min)	1,641	94.4 ± 23.3	91.2 ± 22.8	0.1344
Systolic BP (mm Hg)	1,641	129.2 ± 28.8	141.8 ± 28.4	<0.0001
Diastolic BP (mm Hg)	1,641	76.3 ± 17.8	81.2 ± 17.2	0.0031
BMI (kg/m^2)	1,399	24.9 ± 6.0	29.5 ± 8.9	<0.0001
Rales	1,624	68 (53.1%)	456 (30.5%)	<0.0001
S_3	1,580	5 (4%)	39 (2.7%)	0.3887
Murmur	1,604	33 (26.2%)	221 (15%)	0.0020
Elevated JVP	1,539	40 (33.9%)	231 (16.3%)	<0.0001
Edema	1,615	69 (54.3%)	519 (34.9%)	<0.0001
Ascites	1,579	8 (6.5%)	33 (2.3%)	0.0115
Pulse oximetry (%)	1,609	92.3 ± 8.4	95.4 ± 4.9	<0.0001
Wheezing	1,619	30 (23.8%)	422 (28.3%)	0.3029
History variables				
Arrhythmia	1,555	42 (35.6%)	363 (25.3%)	0.0164
Asthma	1,594	8 (6.4%)	310 (21.1%)	<0.0001
CRI	1,584	41 (33.1%)	205 (14%)	<0.0001
HF	1,597	60 (49.2%)	509 (34.5%)	0.0016
CAD	1,587	49 (40.2%)	454 (31%)	0.0425
COPD	1,594	42 (33.6%)	429 (29.2%)	0.3080
DM	1,621	38 (30.2%)	424 (28.4%)	0.6815
Hyperlipidemia	1,549	40 (34.5%)	530 (37%)	0.6181
Hypertension	1,614	90 (71.4%)	990 (66.5%)	0.2794
MI	1,584	29 (23.6%)	271 (18.5%)	0.1870
Pulmonary embolism	1,604	9 (7.2%)	76 (5.1%)	0.2998
CABG	1,615	13 (10.3%)	145 (9.7%)	0.7570
Angioplasty/stent	1,602	17 (13.7%)	187 (12.7%)	0.6763
Stroke/CVA	1,608	23 (18.1%)	142 (9.6%)	0.0054
Pacemaker/ICD	1,616	14 (11%)	148 (9.9%)	0.6460
Prosthetic valve	1,612	7 (5.6%)	36 (2.4%)	0.0742
Routine laboratory values				
Sodium (mmol/l)	1,512	136.4 ± 4.9	138.6 ± 4.3	<0.0001
Potassium (mmol/l)	1,513	4.3 ± 0.9	4.1 ± 0.7	0.0258
Creatinine (mg/dl)	1,514	1.6 ± 1.1	1.3 ± 1.2	0.0015
WBCs (per nl)	1,519	11.2 ± 8.1	9.6 ± 8.5	0.0364
Hemoglobin (g/dl)	1,520	12.1 ± 2.2	12.9 ± 2.2	<0.0001
Hematocrit (%)	1,517	36.8 ± 7.8	38.7 ± 6.7	0.0084
Platelets (per 10^9 l)	1,508	243.9 ± 114.8	256.8 ± 109.2	0.2232

Values are mean ± SD or n (%).

BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; CVA = cardiovascular accident; DM = diabetes mellitus; HF = heart failure; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; MI = myocardial infarction; S_3 = third heart sound; WBC = white blood cell.

Table 2 Biomarker Values Based on 90-Day Outcomes

Biomarker	n	Alive (n = 1,511)	Dead (n = 130)	p Value
MR-proADM (nmol/l)	1,635	0.8 (0.6–1.4)	1.6 (1.0–3.2)	<0.0001
Copeptin (pmol/l)	1,627	11.6 (5.2–28.8)	45.0 (13.6–98.4)	<0.0001
NT-proBNP (pg/ml)	1,623	704.9 (98.1–3,606.0)	5,037 (812.2–14,776.0)	<0.0001
MR-proANP (pmol/l)	1,635	159.8 (63.2–342.2)	438.9 (174–755.4)	<0.0001
BNP (pg/ml)	1,638	140 (32–526)	525 (174–1436)	<0.0001
PCT (ng/ml)	1,631	0.07 (0.05–0.12)	0.16 (0.08–0.31)	<0.0001
Troponin T or I (quantile transformed)	1,162	0.40 (0.29–0.72)	0.74 (0.39–0.90)	<0.0001
Troponin T (mg/l)	408	0.01 (0.01–0.03)	0.04 (0.01–0.10)	<0.0001
Troponin I (mg/l)	761	0.04 (0.02–0.06)	0.06 (0.03–0.18)	0.0011

Values are median (interquartile range).

BNP = B-type natriuretic peptide; MR-proADM = midregion proadrenomedullin; MR-proANP = midregion pro–atrial natriuretic peptide; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCT = procalcitonin.

Prediction of all-cause mortality within 90 days in patients without AHF. In patients without AHF, all-cause mortality at 90 days was best predicted by MR-proADM (chi-square = 89.8, c index = 0.788, $p < 0.00001$), followed by copeptin (chi-square = 66.5, c index = 0.736, $p < 0.00001$), NT-proBNP (chi-square = 59.8, c index = 0.745, $p < 0.00001$), MR-proANP (chi-square = 51.5, c index = 0.717, $p < 0.00001$), BNP (chi-square = 47.0, c index = 0.724, $p < 0.00001$), PCT (chi-square = 46.9, c index = 0.735, $p < 0.00001$), and troponin T or I (quantile transformed; chi-square = 11.7, c index = 0.646, $p = 0.00064$). In terms of c index, all markers performed slightly better than for patients with AHF (12). However, the ranking of the biomarkers remained unchanged, confirming the trend that outcome prediction is independent of the main diagnosis observed for the clinical variables (Online Tables 2 and 3).

Prediction of all-cause mortality within 90 days in all patients. In all patients with acute dyspnea, all-cause mortality at 90 days was also best predicted by MR-proADM (chi-square = 129.7, c index = 0.755, $p < 0.00001$), followed by copeptin (chi-square = 96.6, c index = 0.727, $p < 0.00001$), NT-proBNP (chi-square = 83.8, c index = 0.721, $p < 0.00001$), MR-proANP (chi-square = 77.7, c index = 0.705, $p < 0.00001$), BNP (chi-square = 60.1, c index = 0.691, $p < 0.00001$), PCT (chi-square = 55.5, c index = 0.704, $p < 0.00001$), and troponin T or I (quantile transformed; chi-square = 28.7, c index = 0.655, $p < 0.00001$).

Compared with clinical variables and routine lab variables, MR-proADM was the strongest predictor (chi-square = 129.7), followed by age (chi-square = 45.5), body mass index (chi-square = 37.0), rales on examination (chi-square = 26.3), history of chronic renal insufficiency (chi-square = 25.6), sodium concentration (chi-square = 25.5), systolic blood pressure (chi-square = 25.4), pulse oximetry (chi-square = 25.3), elevated jugular venous pressure on examination (chi-square = 20.2), and history of asthma (chi-square = 19.7) (the top 9 variables; all p values <0.0001). In bivariate Cox regression models, MR-proADM added significantly to all clinical variables (added chi-square >91.5 for all, $p < 0.00001$), and the adjusted HR ranged from 3.28 to 3.79. MR-proADM was also superior to all other biomarkers; it significantly added to each of the other biomarkers (added chi-square > 41.9 for all, $p < 0.00001$). In contrast, of the new biomarkers, only copeptin (added chi-square = 9.2, $p = 0.0024$) and PCT (added chi-square = 4.8, $p = 0.0292$) provided additional prognostic information beyond MR-proADM.

Multivariate prediction of all-cause mortality within 90 days. From the set of clinical and routine lab variables, we determined the best clinical model for outcome prediction by selecting the top 9 univariate variables (as listed previously) and adding the main diagnosis (AHF). MR-proADM added significantly to this model (added chi-square = 33.7; bootstrap-corrected c index increase: 0.775 to 0.807; adjusted standardized HR: 2.59; 95% CI: 1.91 to 3.50; $p < 0.0001$). Within the model, MR-proADM was the biggest contributor to the predictive performance (chi-square = 38.2, $p < 0.0001$), followed by body mass index (chi-square = 19.1, $p < 0.0001$) and sodium (chi-square = 10.9, $p = 0.0010$), while all other variables did not reach significance (Table 3).

Table 4 illustrates the NRI for adding MR-proADM to the best clinical model. Net reclassification for deaths placed 7 patients (7.9%) in higher risk categories (i.e., 12 were pushed to higher risk, and 5 were pushed to lower risk), while at the same time, 93 of the survivors (9.0%) ended up in lower risk categories (i.e., 140 were pushed to lower risk, and 47 were pushed to higher risk) (Table 4). The overall NRI using risk categories of <2%, 2% to 19%, and >19% is 100 of all patients (8.9%). The overall NRI for BNP was 3.9%, and that for NT-proBNP was 7.4%. Figure 1 illustrates the prognostic performance for MR-proADM in all patients (Kaplan-Meier plot for MR-proADM deciles), as well as performance on the basis of an optimal cut point in patients with AHF and in those without AHF separately. Figure 2 depicts Kaplan-Meier survival curves illustrating the superiority of MR-proADM over BNP and NT-proBNP. Receiver-operating characteristic–optimized cut-offs were used for all markers (optimization on the basis of patients diagnosed with AHF only [12]).

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Table 3 Multivariate Prediction of All-Cause Mortality

	Best Clinical Model			Including MR-proADM			Including BNP and MR-proADM			Including NT-proBNP and MR-proADM		
Variable	Wald Chi-Square	df	p Value	Wald Chi-Square	df	p Value	Wald Chi-Square	df	p Value	Wald Chi-Square	df	p Value
MR-proADM (log10, pmol/l)	—	—	—	38.2	1	<0.0001	24.3	1	<0.0001	18.3	1	<0.0001
BNP (log10, pg/ml)	—	—	—	—	—	—	0.7	1	0.3955	—	—	—
NT-proBNP (pg/ml)	—	—	—	—	—	—	—	—	—	0.5	1	0.4797
BMI (kg/m^2)	14.3	1	0.0002	19.1	1	<0.0001	18.2	1	<0.0001	17.7	1	<0.0001
Sodium (mmol/l)	22.7	1	<0.0001	10.9	1	0.0010	11.1	1	0.0009	10.4	1	0.0013
Systolic BP (mm Hg)	10.4	1	0.0012	2.4	1	0.1229	2.5	1	0.1110	2.5	1	0.1133
Pulse oximetry (%)	8.5	1	0.0035	2.1	1	0.1435	2.3	1	0.1259	2.3	1	0.1319
JVP on examination (yes)	2.4	1	0.1196	1.6	1	0.2118	1.5	1	0.2157	1.5	1	0.2203
Age (yrs)	5.0	1	0.0259	1.3	1	0.2638	1.1	1	0.2988	0.9	1	0.3515
History of asthma (yes)	1.6	1	0.2073	0.6	1	0.4223	0.6	1	0.4281	0.6	1	0.4336
Diagnosis of AHF (yes)	0	1	0.8658	0.6	1	0.4550	1.2	1	0.2751	0.9	1	0.3473
History of CRI (yes)	4.9	1	0.0265	0.2	1	0.6514	0.2	1	0.6256	0.2	1	0.6726
Rales on examination (yes)	0.3	1	0.5751	0	1	0.9992	0	1	0.9814	0	1	0.9965

AHF = acute heart failure; df = degrees of freedom; other abbreviations as in Tables 1 and 2.

The presented results demonstrate that MR-proADM provides superior and independent prognostic information to all other available data in patients with or without heart failure.

Prediction of all-cause mortality by diagnostic group. Figure 3 shows the percent of patients who died during follow-up for each gold-standard diagnostic group on the basis of MR-proADM concentration higher or lower than 1.985 nmol/l. Across the spectrum of diagnoses, (cardiac and noncardiac) patients with MR-proADM values higher than 1.985 nmol/l had a significantly higher mortality rate.

Treatment monitoring using MR-proADM: value of serial measurements. Of the 1,641 patients enrolled, 532 (32.4%) were discharged on the same day. Of the remaining 1,109 patients, 981 had at least 1 additional blood draw within 14 to 48 h after presentation and/or at discharge. The median time to discharge was 7 days (IQR: 3 to 12 days). Of the 981 patients included in our analysis, 120 (12.2%) died within 90 days after admission, and 40 (4.1%) died while in the hospital.

Including all 3 serial measurements into the time-dependent Cox model gave added value compared with the model with the admission values only (added chi-square = 15.2, added degrees of freedom [df] = 2, p = 0.0005). Both bivariate models showed added value (admission plus second measurement 14 to 48 h later: added chi-square = 4.8, added df = 1, p = 0.0285; admission plus discharge measurement: added chi-square = 15.2, added df = 1, p = 0.0001). Once discharge values were combined with admission values, the second measurement no longer added prognostic utility (added chi-square = 0, added df = 1, p = 1.00).

To illustrate these findings, we grouped all patients into 1 of 4 cohorts: MR-proADM high (>1.985 nmol/l) at admission and remaining high at discharge (group A, high/high), MR-proADM high at admission but lower than 1.985 nmol/l at discharge (group B, high/low), MR-proADM low at admission and remaining low at discharge (group C, low/low), and MR-proADM low at admission but higher than 1.985 nmol/l at discharge (group D, low/high). Patients who died before discharge were grouped as if they would have remained in their risk categories at admission (i.e., they were grouped as either high/high if high at admission or low/low if low at admission). Figure 4 illustrates the added value of a second MR-proADM measurement at discharge. At admission, a total of 191 patients (19.5%) had increased MR-proADM concentrations. Of those, 70 (36.6%)

Table 4 Net Reclassification Index for Adding MR-proADM to the Best Clinical Model

Best Clinical Model	Add MR-proADM (log10, nmol/l)			MR-proADM (log10, nmol/l)	Add Best Clinical Model		
Events	(0, 0.02)	(0.02, 0.19)	(0.19, 1.00)	Events	(0, 0.02)	(0.02, 0.19)	(0.19, 1.00)
(0, 0.02)	2	0	0	(0, 0.02)	0	1	0
(0.02, 0.19)	0	42	12	(0.02, 0.19)	2	34	18
(0.19, 1.00)	0	5	28	(0.19, 1.00)	0	2	32
Nonevents	(0, 0.02)	(0.02, 0.19)	(0.19, 1.00)	Nonevents	(0, 0.02)	(0.02, 0.19)	(0.19, 1.00)
(0, 0.02)	231	23	0	(0, 0.02)	102	35	0
(0.02, 0.19)	107	571	24	(0.02, 0.19)	231	535	47
(0.19, 1.00)	0	33	47	(0.19, 1.00)	5	32	49

MR-proADM = midregion proadrenomedullin.

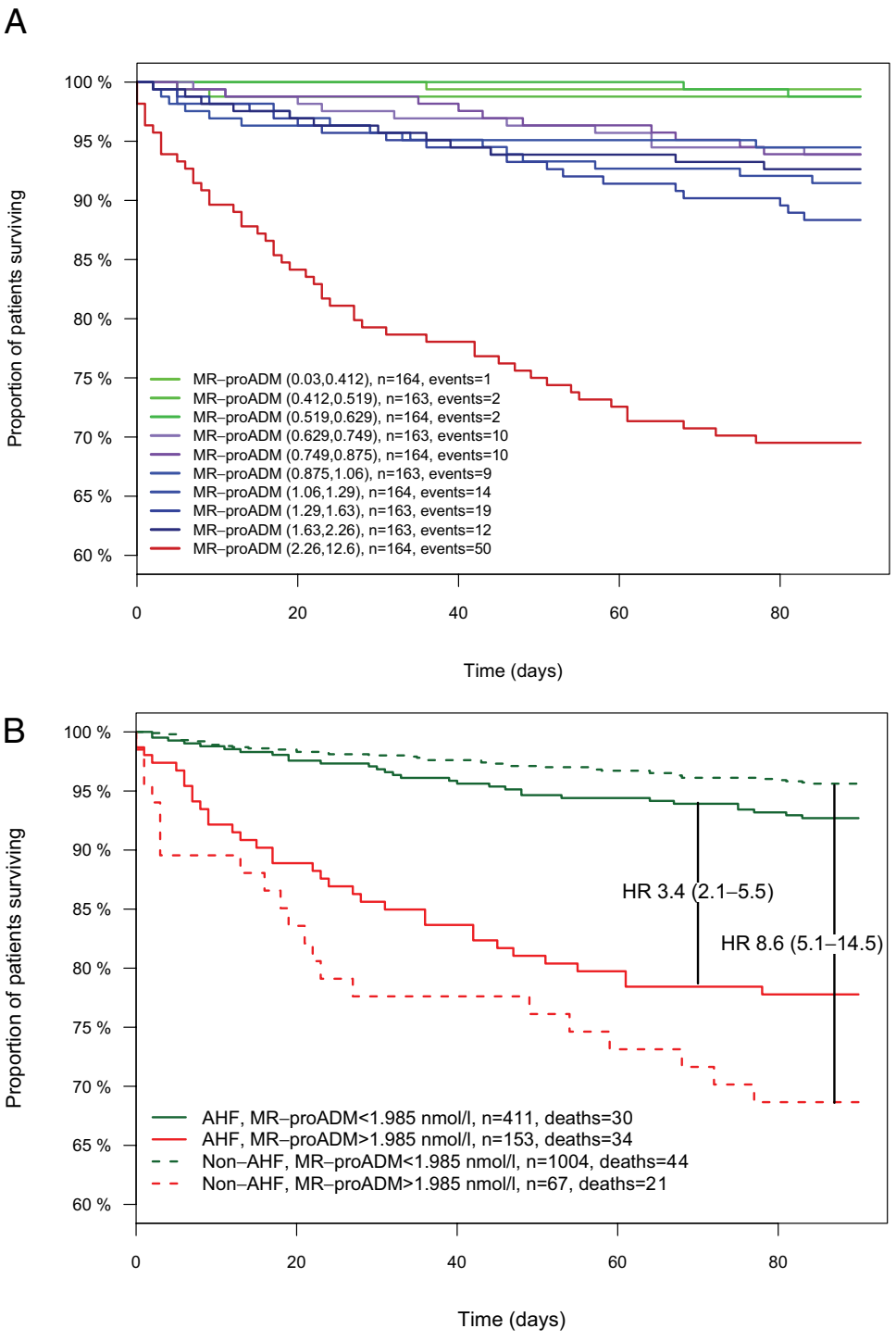

Figure 1 **Kaplan-Meier Survival Curves**

(A) Kaplan-Meier survival curves on the basis of deciles of midregion proadrenomedullin (MR-proADM) for all patients with dyspnea (n = 1,635). Patients with MR-proADM concentrations within the normal range or slightly higher (first 3 deciles) had very good 90-day prognoses (survival rates ranging from 98.8% to 99.4%), whereas those with elevated (deciles 4 to 9; survival rates ranging from 88.3% to 94.5%) or highly elevated (highest decile; survival rate 69.5%; 95% confidence interval: 61.8% to 75.9%) concentrations did considerably worse. Ranges of MR-proADM concentrations for each decile (nanomoles per liter) are shown in **brackets**. **(B)** Kaplan-Meier survival curves on the basis of a receiver-operating characteristic–optimized cutoff of 1.985 nmol/l for MR-proADM (optimization based on patients diagnosed with acute heart failure [AHF] only) for patients with and without AHF diagnoses. HR = hazard ratio.

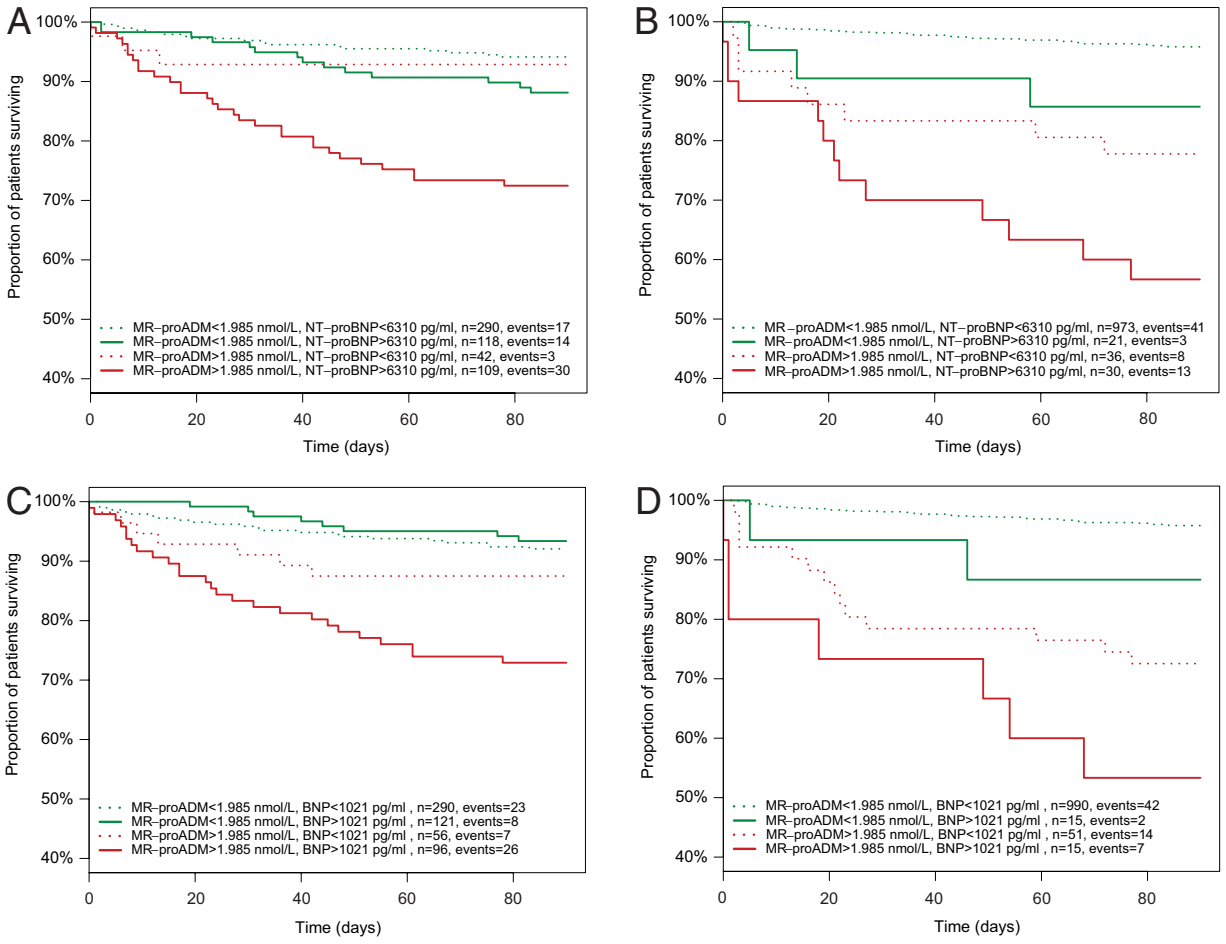

Figure 2 **Kaplan-Meier Survival Curves Illustrating the Superiority of MR-proADM Over BNP or NT-proBNP**

Receiver-operating characteristic–optimized cutoff used for B-type natriuretic peptide (BNP) and midregion proadrenomedullin (MR-proADM) (optimization based on patients diagnosed with acute heart failure [AHF] only) for patients diagnosed with **(A, C)** and without **(B, D)** AHF. Among patients with MR-proADM levels lower than 1.985 nmol/l, patients remain at low risk for dying within 90 days, irrespective of their BNP or N-terminal proBNP (NT-proBNP) concentrations. Among patients with MR-proADM levels higher than 1.985 nmol/l, BNP higher than 1,021 pg/ml or NT-proBNP higher than 6,310 pg/ml further increased their risk for dying.

could be identified by the biomarker evaluation at discharge as low-risk patients.

Note that Figure 4 is based on combined information from admission and discharge, and conclusions regarding the prognostic value of the discharge measurement alone may not be drawn, because a significant portion of deaths (n = 40) occurred in the hospital.

Discussion

This international trial, the largest of its kind to date, demonstrates that MR-proADM has significant prognostic utility in patients presenting with acute shortness of breath to the ED. We determined that MR-proADM was superior to BNP and NT-proBNP for predicting 90-day mortality in patients with dyspnea due to AHF (12). This was especially true during the first 30 days after baseline evaluation, for which MR-proADM clearly outperformed BNP and NT-proBNP (W. F. Peacock, unpublished data). Troponin, recently shown to carry prognostic value in patients with heart failure (14), was also added to a multivariate model with the other 3 markers. In this model, MR-proADM still remained a strong independent prognostic factor. In the 568 BACH patients with confirmed diagnoses of AHF (35 deaths within 30 days, 65 deaths within 90 days), the prognostic accuracy (area under the curve) of MR-proADM levels assessed in blood samples taken on admission to the ED was 0.739 and 0.674 for 30- and 90-day follow-up, respectively. This was greater than for both BNP (0.555 and 0.606, respectively) and NT-proBNP (0.641 and 0.664, respectively).

The present study extends these findings in a number of important ways. First and foremost, this marker appears to be robust across the entire spectrum of patients with dyspnea. MR-proADM added significantly to all clinical models and was better than any biomarker studied, including natriuretic peptides and troponin. The

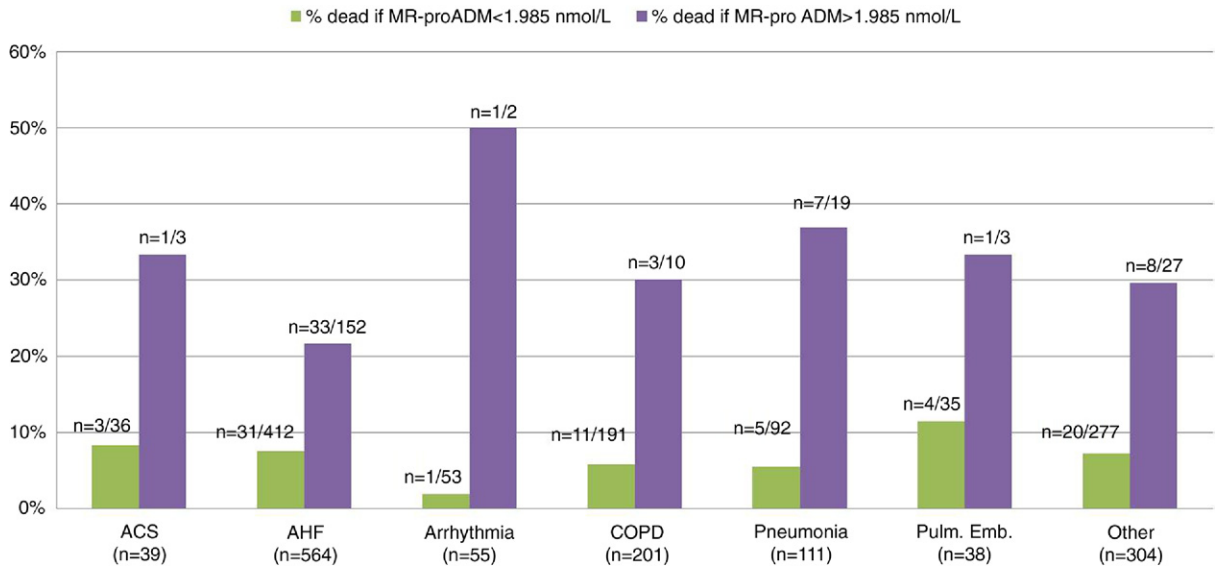

Figure 3 **Percent of Patients Who Died During Follow-Up for Each Gold-Standard Diagnostic Group and Dependent on MR-proADM Concentration Higher or Lower Than 1.985 nmol/l**

For the primary diagnostic subgroups of asthma, bronchitis, chest pain, and influenza, no deaths were observed. **Numbers above each bar** denote number of deaths/number of all patients in the respective subgroup. ACS = acute coronary syndrome; AHF = acute heart failure; MR-proADM = midregion proadrenomedullin; Pulm. Emb. = pulmonary embolism.

overall NRI using MR-proADM was almost 10% when adding MR-proADM to the best clinical model. Therefore, those who use natriuretic peptides to risk stratify patients, either in the ED or the hospital, may gain significant benefit by also measuring MR-proADM. In patients without AHF, especially those with chronic obstructive pulmonary disease, pneumonia, and pulmonary embolism, MR-proADM was a superb predictor of 90-day mortality. These findings complement the prognostic utility of MR-proADM in a number of other settings (e.g., patients with acute myocardial infarction [15] or non–ST-segment elevation myocardial infarction [16], lower respiratory tract infections [17], or community-acquired pneumonia [18]).

Both natriuretic peptides (BNP, NT-proBNP, and MR-proANP) and troponin were mainly introduced and are applied for diagnostic purposes: natriuretic peptides for the diagnosis of AHF and troponin for the diagnosis of acute myocardial infarction. Although MR-proADM proves to add information that neither the natriuretic peptides nor troponin (or anything else we evaluated) provided, it cannot replace the other biomarkers for their diagnostic purposes.

Better prognostic markers may help patients in multiple ways, as they identify those patients who should "move to the front of the line" with respect to immediate therapeutic interventions. In the emergency setting, untreated AHF worsens rapidly and can lead to respiratory compromise, intubation with mechanical ventilation, and even death. Thus, interventions worth exploring based on high MR-proADM levels might include specialist consultation by a cardiologist, intensive care unit admission, noninvasive ventilation, and so on. If acute dyspnea is of unclear etiology, a high MR-proADM level might be a strong enough reason for hospital and possible intensive care unit admission. Additionally, the astute clinician may follow patients with poor prognostic markers more closely after discharge to prevent relapse and readmission. MR-proADM levels may also serve as a surrogate marker in therapeutic heart failure trials, although both of these suggestions require validation. Interventional trials are needed to prove these hypotheses.

Our data also suggest that therapy monitoring using serial measurements of MR-proADM may be possible. About one-third of patients considered at high risk on the basis of MR-proADM concentrations at admission had lower concentrations at discharge. Their survival rate was almost as high as that of patients who were never at risk, on the basis of MR-proADM. This analysis has various caveats: The necessity to replace missing values for this specific analysis (roughly 10% of all measurements) has potential risks to overestimate or underestimate the potential usefulness of serial measurements. However, it is necessary, because missing values in serial measurements do not all occur at random. Although 1 day after admission might be too early for a revision of the original risk stratification, for some patients, the changing pattern is already present in the first 24 h (data not shown).

It appears that MR-proADM, a reliable surrogate of ADM, might be more prognostic in patients with dyspnea than biomarkers currently used in the clinical arena. Future studies should center on MR-proADM as a guide to

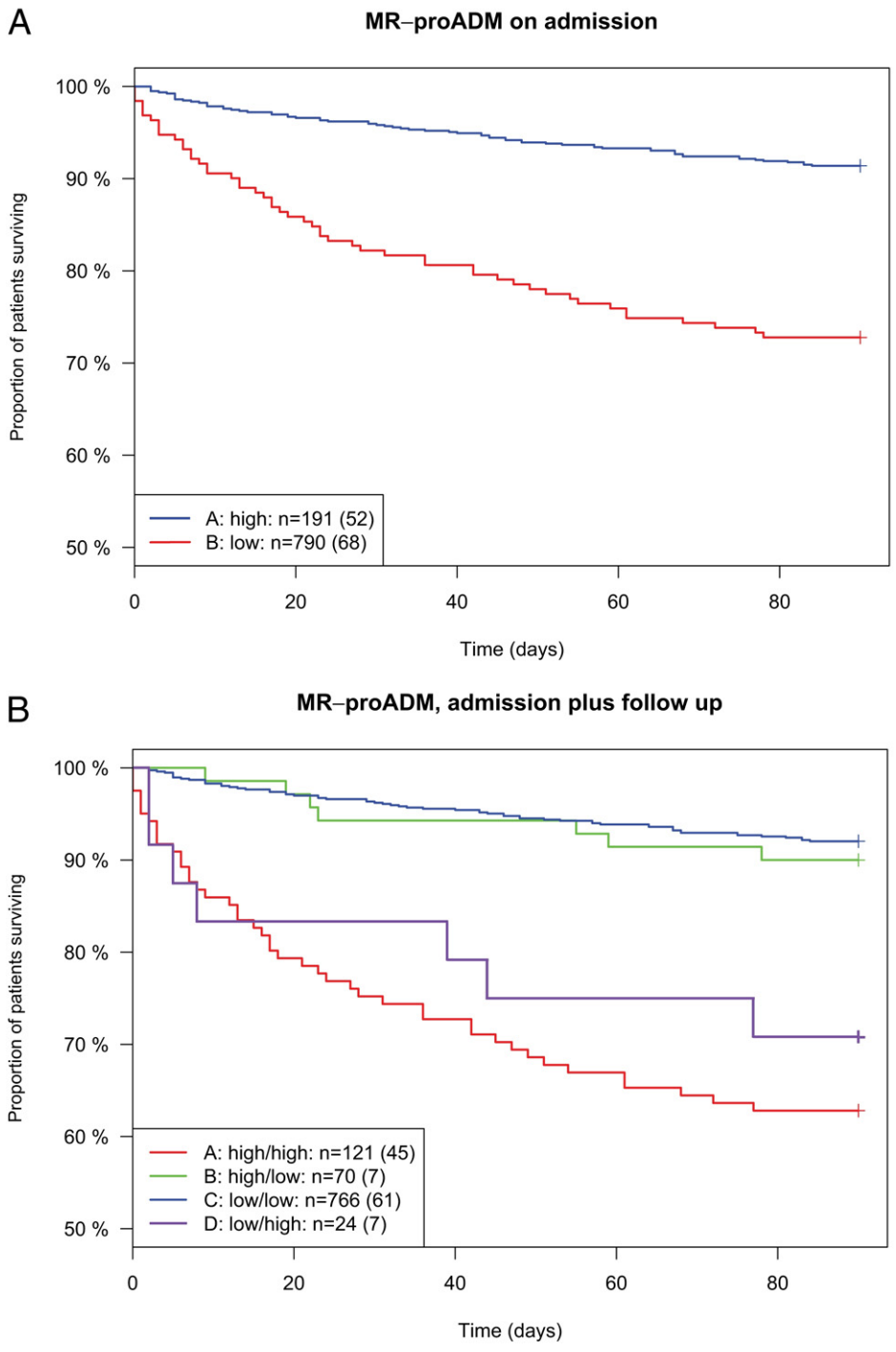

Figure 4 **Kaplan-Meier Survival Curves on the Basis of ROC-Optimized Cutoff for MR-proADM (1.985 nmol/l, Optimized Cutoff for Outcome Prediction in Patients Diagnosed With AHF), for All Patients With Follow-Up Blood Draws**

(A) Midregion proadrenomedullin (MR-proADM) concentration available at admission grouped 191 of all patients (19.5%) as high risk (group A; estimated survival rate 72.8% [95% confidence interval (CI): 66.7% to 79.4%] vs. 91.4% [95% CI: 89.5% to 93.4%] in low-risk group B). **(B)** Combined information from both MR-proADM concentrations on admission and at discharge grouped 70 patients (36.6%) who were originally considered high risk at admission as low risk (group B), with an estimated survival rate of 90.0% (95% CI: 83.2% to 97.3%) (only slightly lower than the survival rate of patients who remained low [group C]: 92.0% [95% CI: 90.1% to 94.0%]), while patients remaining at high risk (group A) were now estimated with a survival probability of 62.8% (95% CI: 54.8% to 72.0%). Patients who showed increasing MR-proADM concentrations (group D, the smallest subgroup; n = 24 [2.4%]) had an estimated survival rate of 70.8% (95% CI: 54.8% to 91.6%). Patients who died before discharge were grouped as if they would have remained in their risk categories at admission (i.e., they were grouped as either high/high if high at admission or low/low if low at admission).

admission, follow-up, and therapeutic interventions. However, it is important to recognize that our analysis must be viewed as a post hoc reanalysis of a previously published study with other primary endpoints. Accordingly, the conclusions will need to be confirmed in a new study with pre-specified endpoints.

Study limitations. First, the number of missing values for the multivariate analysis has potential risks, because this might result in a biased population. Because the replacement of missing values did not change the results, we consider this controlled. With respect to the results reported for troponin, the fact that only measurements in a subset of patients based on locally used assays were available may have reduced its prognostic performance. In future studies, MR-proADM should be compared with contemporary high-sensitive troponins. For interventional trials, multiple cut points may be considered for MR-proADM. Although results from observational trial can identify patients at high risk, for whom additional therapies may prove helpful, they are not suitable to determine a subgroup of patients for whom treatment could be reduced. If this is the goal of an interventional trial, a second, lower cutoff might be introduced. For the evaluation of serial measurements, absolute or relative change to identify a clinically meaningful change may also prove more useful than a single cutoff, which we used for illustration. It should also be noted that biomarkers alone may not identify all patients at risk for death, particularly if all-cause mortality is evaluated. For example, using the cutoff optimized in patients with AHF, 33 of the 65 patients who died within 90 days in the group with heart failure and 44 of the 65 who died in the group without heart failure had MR-proADM levels below this cut point. Thus, the majority of deaths were not identified by this marker alone. And finally, despite the size of the trial (BACH is the largest biomarker trial in AHF to date), the number of observed deaths within 90 days is still limited (n = 130 [<10%]), especially for any subgroup analysis.

Reprint requests and correspondence: Dr. Alan Maisel, VASDHS Cardiology 9111-A, 3350 La Jolla Village Drive, San Diego, California 92161. E-mail: amaisel@ucsd.edu.

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Key Words: adrenomedullin ■ biomarker ■ heart failure.

APPENDIX

For supplementary tables and figures and their legends, please see the online version of this article.