FOCUS ISSUE: BIOMARKERS IN CARDIOVASCULAR DISEASE   **Clinical Research**

Biomarkers and Acute Dyspnea

Mid-Region Pro-Hormone Markers for Diagnosis and Prognosis in Acute Dyspnea

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

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Objectives	Our purpose was to assess the diagnostic utility of mid-regional pro–atrial natriuretic peptide (MR-proANP) for the diagnosis of acute heart failure (AHF) and the prognostic value of mid-regional pro-adrenomedullin (MR-proADM) in patients with AHF.
Background	There are some caveats and limitations to natriuretic peptide testing in the acute dyspneic patient.
Methods	The BACH (Biomarkers in Acute Heart Failure) trial was a prospective, 15-center, international study of 1,641 patients presenting to the emergency department with dyspnea. A noninferiority test of MR-proANP versus B-type natriuretic peptide (BNP) for diagnosis of AHF and a superiority test of MR-proADM versus BNP for 90-day survival were conducted. Other end points were exploratory.
Results	MR-proANP ($\geq$120 pmol/l) proved noninferior to BNP ($\geq$100 pg/ml) for the diagnosis of AHF (accuracy difference 0.9%). In tests of secondary diagnostic objectives, MR-proANP levels added to the utility of BNP levels in patients with intermediate BNP values and with obesity but not in renal insufficiency, the elderly, or patients with edema. Using cut-off values from receiver-operating characteristic analysis, the accuracy to predict 90-day survival of heart failure patients was 73% (95% confidence interval: 70% to 77%) for MR-proADM and 62% (95% confidence interval: 58% to 66%) for BNP (difference $p < 0.001$). In adjusted multivariable Cox regression, MR-proADM, but not BNP, carried independent prognostic value ($p < 0.001$). Results were consistent using NT-proBNP instead of BNP ($p < 0.001$). None of the biomarkers was able to predict rehospitalization or visits to the emergency department with clinical relevance.
Conclusions	MR-proANP is as useful as BNP for AHF diagnosis in dyspneic patients and may provide additional clinical utility when BNP is difficult to interpret. MR-proADM identifies patients with high 90-day mortality risk and adds prognostic value to BNP. (Biomarkers in Acute Heart Failure [BACH]; NCT00537628) (J Am Coll Cardiol 2010;55: 2062–76) © 2010 by the American College of Cardiology Foundation

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In patients presenting with shortness of breath, an accurate and rapid diagnosis is critical. Misdiagnoses result in delayed or erroneous treatment that may lead to adverse outcomes, including increased mortality, and greater costs (1,2). Making a late diagnosis of acute heart failure (AHF) also has significant adverse prognostic ramifications (3). Because natriuretic peptide (NP) testing with either B-type natriuretic peptide (BNP) or N-terminal pro–B-type natriuretic peptide (NT-proBNP) improves diagnostic accuracy, their use in the evaluation of dyspnea is recommended as a standard adjunct to history, physical examination, and other laboratory tests (4). Unfortunately, NP testing is limited by caveats that may make their interpretation challenging. These include intermediate "gray zone" values, and nuances in interpreting levels in the settings of renal dysfunction, obesity, and advanced age.

Adrenomedullin (ADM), a vasodilatory peptide with potent hypotensive effects, is expressed in many different tissues (5). Its plasma levels are elevated in patients with chronic heart failure (6) and increase with disease severity (7,8). However, its clinical application has been impeded due to biologic instability of plasma measurements.

Recently, several novel immunoassays for analytes relevant to cardiovascular regulation have been developed for the detection of the stable prohormone fragment as a "mirror" of mature hormone release (9–12). New immunoassays can be directed at stable mid-region prohormones that are stoichometrically related to synthesis of the biologically active unstable fragment. Thus, the measurement of mid-region pro-atrial natriuretic peptide (MR-proANP) and mid-region pro-adrenomedullin (MR-proADM) can be performed and may provide clinically relevant diagnostic and outcome information in addition to standard NP testing.

Methods

The BACH (Biomarkers in Acute Heart Failure) trial was a prospective, 15-center international study of 1,641 patients presenting to the emergency department (ED) with dyspnea. There were 2 primary end points. The primary diagnostic end point was the diagnosis of AHF, where the noninferiority of MR-proANP compared with BNP was evaluated. The primary prognostic end point tested was 90-day survival, where the superiority of the utility of

MR-proADM versus BNP for predicting survival over a period of 90 days was evaluated in patients with a diagnosis of AHF. Outcomes investigated were all-cause and cardiovascular death, all-cause and cardiovascular rehospitalization, and all-cause and cardiovascular revisit.

Study population. This study was approved by the institutional review boards of all 15 participating centers, and included 8 U.S. centers (831 patients enrolled); 6 European centers in Germany, Switzerland, Italy, Greece, United Kingdom, and Poland (726 patients enrolled); and 1 New Zealand hospital (84 patients enrolled). A total of 1,641 patients were enrolled from March 2007 to February 2008. To be eligible, patients had to report shortness of breath as their primary complaint upon presentation to the ED. Patients were excluded if they were <18 years of age, unable to provide consent, had an acute ST-segment elevation myocardial infarction, were receiving hemodialysis, or had renal failure.

For each patient enrolled in the study, ED physicians, blinded to the investigational marker results, assessed the probability that the patient had AHF or pneumonia by 2 separate visual analog scales, assigning a value of 0% to 100% clinical diagnostic certainty.

Confirmation of diagnosis. To determine the gold standard diagnosis, 2 cardiologists independently reviewed all medical records pertaining to the patient and independently classified the diagnosis as dyspnea due to heart failure or due to another cause. Both cardiologists were blinded to the other's assessments, investigational markers, and the ED physician's diagnosis. They had access to the ED case report forms, which included medical history plus data on chest radiography, radionuclide angiography, echocardiography, and cardiac catheterization as available, as well as the hospital course for patients who were admitted. In the event of diagnostic disagreement between the cardiology reviewers, they were asked to meet to come to a common conclusion. If they were unable to come to a common conclusion, a third cardiology adjudicator was assigned by the end points committee to determine a final diagnosis. In cases of pneumonia, its diagnosis was defined by the criteria modified from Leroy et al. (13) and Fine et al. (14).

Measurement of biomarkers. All blood samples were collected in plastic tubes containing ethylenediaminetetra-acetic acid, and plasma was stored at −70°C in plastic freezer vials. MR-proANP and MR-proADM were mea-

Abbreviations and Acronyms

AHF = acute heart failure

AUC = area under the curve

BNP = B-type natriuretic peptide

CI = confidence interval

CV = coefficient of variation

ED = emergency department

HR = hazard ratio

IQR = interquartile range

MR-proADM = mid-regional pro-adrenomedullin

MR-proANP = mid-regional pro-atrial natriuretic peptide

NP = natriuretic peptide

NT-proBNP = N-terminal pro–B-type natriuretic peptide

ROC = receiver-operating characteristic

Table 1	Patient Characteristics by Diagnosis			
Variables	n	Non-AHF (n = 1,073)	AHF (n = 568)	p Value
Demographics				
Age, yrs	1,641	59.8 ± 17.0	71.2 ± 13.8	<0.001
Male	1,641	504 (47.0)	355 (62.5)	<0.001
Race	1,626			<0.001
White		659 (62.1)	431 (76.3)	
Black		356 (33.6)	120 (21.2)	
Other		46 (4.3)	14 (2.5)	
Recent history				
Smoking	1,593	344 (33.0)	125 (22.7)	<0.001
Wheezing	1,543	359 (35.4)	109 (20.6)	<0.001
Weight gain	1,438	112 (11.8)	137 (28.0)	<0.001
Night sweats	1,495	230 (23.4)	94 (18.3)	0.025
Orthopnea	1,536	349 (35.0)	340 (63.0)	<0.001
Dyspnea at rest	1,605	518 (49.3)	277 (49.9)	0.834
Examination variables				
Heart rate, beats/min	1,632	92.6 ± 21.6	89.2 ± 24.8	0.005
Systolic BP, mm Hg	1,631	139.7 ± 26.8	143.0 ± 31.8	0.027
Diastolic BP, mm Hg	1,630	79.6 ± 16.4	83.0 ± 18.7	<0.001
BMI, kg/m^2	1,399	29.6 ± 9.1	28.5 ± 8.1	0.035
Rales	1,624	216 (20.3)	308 (54.8)	<0.001
S$_3$	1,580	6 (0.6)	38 (7.0)	<0.001
Murmur	1,604	98 (9.3)	156 (28.3)	<0.001
Elevated JVP	1,539	71 (7.0)	200 (38.2)	<0.001
Edema	1,615	244 (23.1)	344 (61.5)	<0.001
Ascites	1,579	15 (1.5)	26 (4.8)	<0.001
Wheezing	1,619	350 (33.0)	102 (18.2)	<0.001
History variables				
Arrhythmia	1,555	168 (16.6)	237 (43.6)	<0.001
Asthma	1,594	288 (27.7)	30 (5.4)	<0.001
CRI	1,584	75 (7.2)	171 (31.3)	<0.001
HF	1,597	203 (19.6)	366 (65.2)	<0.001
CAD	1,587	232 (22.3)	271 (49.5)	<0.001
COPD	1,594	341 (32.7)	130 (23.6)	<0.001
DM	1,621	244 (23.1)	218 (38.6)	<0.001
Hyperlipidemia	1,549	330 (32.4)	240 (45.3)	<0.001
Hypertension	1,614	642 (60.9)	438 (78.2)	<0.001
MI	1,584	128 (12.3)	172 (31.5)	<0.001
Pulmonary embolism	1,604	49 (4.7)	36 (6.5)	0.127
CABG	1,615	66 (6.2)	92 (16.5)	<0.001
Angioplasty/stent	1,602	96 (9.1)	108 (19.6)	<0.001
Stroke/CVA	1,608	89 (8.5)	76 (13.7)	0.001
Pacemaker/ICD	1,616	55 (5.2)	107 (19.1)	<0.001
Prosthetic valve	1,612	13 (1.2)	30 (5.4)	<0.001

sured with an automated sandwich chemiluminescence immunoassay on the KRYPTOR System (BRAHMS AG, Hennigsdorf/Berlin, Germany) in the core laboratory at the University of Maryland School of Medicine. Both automated assays are based on the sandwich chemiluminescence assays, which are described in detail elsewhere (5,6) and which have been used in other studies (15–19).

Performance of MR-proANP in this laboratory included a limit of quantitation of 4.5 pmol/l, within-run imprecision coefficient of variation (CV) of 1.2% and total imprecision (CV) of 5.4%. For MR-proADM, the limit of quantification was 0.23 nmol/l; the within-run imprecision (CV) was 1.9%, and the between-run (CV) was 9.8%. The BNP was measured with Triage 2-site immunoassay reagents (Biosite, San Diego, California) formatted for Beckman-Coulter instrumentation (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%. NT-proBNP was measured by electrochemiluminescence on the ElecSys 2010 analyzer (Roche Diag-

Variables	n	Non-AHF (n = 1,073)	AHF (n = 568)	p Value
Table 1 Continued				
Outpatient medications (known)				
Aspirin	1,616	322 (30.0)	252 (44.4)	<0.001
Clopidogrel	1,617	65 (6.1)	66 (11.6)	0.001
Warfarin	1,615	94 (8.8)	163 (28.7)	<0.001
Beta-blockers	1,613	292 (27.2)	335 (59.0)	<0.001
ACE inhibitors or ARB	1,616	359 (33.5)	321 (56.5)	<0.001
CCB	1,614	221 (20.6)	148 (26.1)	0.047
Statins	1,617	284 (26.5)	233 (41.0)	<0.001
Diuretics	1,618	373 (34.8)	401 (70.6)	<0.001
Digoxin	1,617	32 (3.0)	88 (15.5)	<0.001
Aldosterone inhibitor	1,615	48 (4.5)	101 (17.8)	<0.001
Antiarrhythmics	1,616	33 (3.1)	59 (10.4)	<0.001
Nebulizer/inhaler	1,613	449 (41.8)	112 (19.7)	<0.001
Steroids	1,582	314 (29.3)	77 (13.6)	<0.001
Antibiotics	1,614	161 (15.0)	42 (7.4)	<0.001
Smoking cessation therapy	1,577	24 (2.2)	4 (0.7)	0.049
Other	1,593	668 (62.3)	362 (63.7)	0.785

Values are mean $\pm$ SD or n (%) and compared with independent samples *t* test or Fisher exact test, respectively.

ACE = angiotensin-converting enzyme; AHF = acute heart failure; ARB = angiotensin-receptor blocker; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; CVA = cerebrovascular accident; DM = diabetes mellitus; HF = heart failure; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; MI = myocardial infarction.

nostics, Indianapolis, Indiana). Performance in the laboratory included a limit of quantitation of 10.0 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.

Statistical analysis. Values are expressed as means and standard deviations, medians and interquartile ranges (IQRs), or counts and percentages as appropriate. Diagnostic groups were compared with independent-samples *t* tests and chi-square tests as appropriate. Four primary objectives (MR-proANP as noninferior to BNP and MR-proANP as additive to BNP for diagnosis, and MR-proADM as superior to BNP and MR-proADM as additive to BNP for survival) were evaluated using a p value of 0.0125 as the significance criterion for each to protect the global error level in this trial evaluating multiple biomarkers. All other analyses are exploratory and utilized a p value of 0.05 for significance. The secondary analyses utilized logistic and Cox regressions, McNemar tests, and survival curves plotted by the Kaplan-Meier method. Additional methods included receiver-operating characteristic (ROC) curves and the comparison of correlated ROC curves (20) and Spearman rank-order correlation.

Primary MR-proANP diagnostic utility. The first diagnostic question was whether MR-proANP could be considered noninferior to BNP for diagnosis of AHF. McNemar's test with exact computation was employed as the hypothesis test with a noninferiority margin of 10%. Cut points were pre-specified as 100 pg/ml for BNP and 120 pmol/l for MR-proANP. Using these same cut points, the second primary diagnostic objective was evaluated in a logistic

regression model using elevated BNP and elevated MR-proANP as predictors.

Primary MR-proADM prognostic utility. The first prognostic objective was to test whether MR-proADM was superior to BNP for prognosis in patients admitted for heart failure. Three different outcomes were considered: death, rehospitalization, and revisit to the ED, with all-cause mortality at 90 days considered as the primary end point. Analysis was conducted for all-cause events, as well as for events classified as cardiovascular only. The first step was to conduct ROC analysis separately for MR-proADM and BNP to identify the cut points that maximized the product of sensitivity times specificity. Subjects were categorized as above or below these cut points for both MR-proADM and for BNP. Categories were then compared to outcomes and classified as correct or incorrect in predicting the end point. Correctness of prediction from the BNP cut point was compared with that of the MR-proADM cut point using a 2-sided McNemar's test. Log-transformed values of MR-proADM and BNP were also evaluated in a Cox regression model to evaluate the contribution of MR-proADM over and above that of BNP as the second primary prognostic question.

Finally, to test for differences in the predictive value of MR-proADM and NT-proBNP, we used the likelihood ratio chi-square test for nested models to assess whether MR-proADM adds predictive value to a clinical model with BNP or NT-proBNP and vice versa. For continuous variables, hazard ratios (HRs) were standardized to describe the HR for a biomarker change of 1 IQR; and 95% confidence intervals (CIs) for risk factors and significance levels for

chi-square (Wald test) are given. The predictive value of each model was assessed by the model likelihood ratio chi-square statistic. Survival curves plotted by the Kaplan-Meier method were used for illustrative purposes. The multivariate logistic regression models, adjusted Cox regression models, time-dependent area under the curve (AUC) analysis, as well as Kaplan-Meier plots using quartiles were added to provide a more in-depth picture of predictive performance of the biomarkers under evaluation. They were not part of the statistical analysis plan and are considered to be exploratory.

All statistical analyses were performed using R version 2.5.1 (The R Project for Statistical Computing, Wien, Austria), SAS version 9.1 (SAS Institute, Cary, North Carolina), and Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, Illinois).

The data management center and research department of the VA San Diego Healthcare System, San Diego, California, were 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 analysis.

Results

A total of 1,641 patients were evaluated. Of these, the adjudicated diagnosis was AHF in 568 patients (34.6%). In determining the presence or absence of AHF, the 2 adjudicating cardiologists agreed in all but 25 (1.5%) of 1,641 cases (kappa = 0.966, p < 0.001). In these instances, a third cardiologist made the final determination. The patient characteristics among the AHF and non-AHF groups are presented in Table 1. The AHF cases were older, more likely to be male, and evidenced classic signs and symptoms of heart failure more frequently than non-AHF patients.

Valid measurements for MR-proANP and MR-proADM were obtained for 99.6% of all patient samples (6 failures of 1,641). For BNP and NT-proBNP, the rate was 99.8% (3 failures) and 98.9% (18 failures), respectively. The MR-proANP ranged from 3.9 to 2510.0 pmol/l, with a median of 174.5 pmol/l and IQR from 66.5 to 369.4 pmol/l. The MR-proADM ranged from 0.1 to 12.6 nmol/l, with a median of 0.88 nmol/l and IQR from 0.57 to 1.44 nmol/l. The BNP ranged from 0.5 to 10,746 pg/ml, with a median of 164 pg/ml and IQR from 36 to 574 pg/ml. The NT-proBNP ranged from 3 to 120,083 pg/ml, with a median of 833 pg/ml and IQR from 112 to 4115 pg/ml.

Spearman correlation between MR-proANP and both BNP and NT-proBNP was 0.92, and between BNP and NT-proBNP, it was 0.96. Spearman correlations between MR-proADM and MR-proANP, BNP, and NT-proBNP were 0.78, 0.72, and 0.76, respectively.

Of the 1,641 patients, 568 (34.6%) were diagnosed with AHF, 201 (12.2%) with chronic obstructive pulmonary disease, 130 (7.0%) with asthma, 112 (6.8%) with pneumonia, 106 (6.5%) with chest pain, 61 (3.7%) with bronchitis, 55 (3.4%) with arrhythmia, 39 (2.4%) with acute coronary syndrome, 38 (2.3%) with pulmonary embolism, 27 (1.6%) with influenza, and 304 (18.5%) with other diseases.

Diagnosis of AHF. The primary diagnostic objective of the BACH study was to demonstrate that the MR-proANP cut point of 120 pmol/l would be noninferior to a BNP cut point of 100 pg/ml for the diagnosis of AHF. This level of MR-proANP was defined prospectively and confirmed in pilot data. Table 2 shows the sensitivity, specificity, and overall accuracy (% correct) for both measurements. The absolute difference in accuracy was 0.9%. The upper 95% confidence limit for the difference was 2.1%. That was less than the noninferiority margin of 10% (p < 0.001), supporting the primary diagnostic objective of the study. Differences for sensitivity and specificity were also within the noninferiority margin. These cut points yielded greater sensitivity than specificity for both markers in this patient sample.

Another diagnostic objective was to determine whether elevated MR-proANP could add to the diagnostic utility of elevated BNP. Using the same cut points as above, MR-proANP added significantly to the diagnostic performance of BNP in logistic regression (chi-square increase 89.3, df = 1, p < 0.001). This corresponds to an increase in the C-statistic or AUC from 0.787 to 0.816 (p < 0.001). Requiring both variables to be elevated for the diagnosis of AHF increases the overall accuracy from 73.6% for BNP alone to 76.6% for the combined diagnosis. Both variables contributed to the identification of AHF (BNP odds ratio [OR]: 7.6, 95% CI: 4.6 to 2.4, p < 0.001; and MR-proANP OR: 11.5, 95% CI: 6.5 to 20.6, p < 0.001).

The diagnostic performance was also evaluated by ROC analysis. The curves for MR-proANP, BNP, and NT-proBNP appear in Figure 1A. The AUC was compared between correlated ROC curves. The area for BNP exceeded that of MR-proANP by 0.01 (p < 0.003) whereas the AUCs for MR-proANP and NT-proBNP

Table 2	Acute Heart Failure Diagnostic Performance of MR-proANP Cut at 120 pmol/l and BNP Cut at 100 pg/ml				
Measure	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Accuracy (95% CI)**	**NPV**	**PPV**
BNP 100 pg/ml	95.6% (93.6–97.0)	61.9% (59.0–64.8)	73.6% (71.4–75.6)	96.4%	57.0%
MR-proANP 120 pmol/l	97.0% (95.2–98.2)	59.9% (56.4–62.8)	72.7% (70.5–74.8)	97.4%	56.0%
Difference	−1.4%	2.1%	0.9%	−1.0%	1.0%
Upper 95% limit	−0.2%	3.8%	2.1%		
Noninferiority p value	<0.001	<0.001	<0.001		

BNP = B-type natriuretic peptide; CI = confidence interval; MR-proANP = mid-regional pro-atrial natriuretic peptide; NPV = negative predictive value; PPV = positive predictive value.
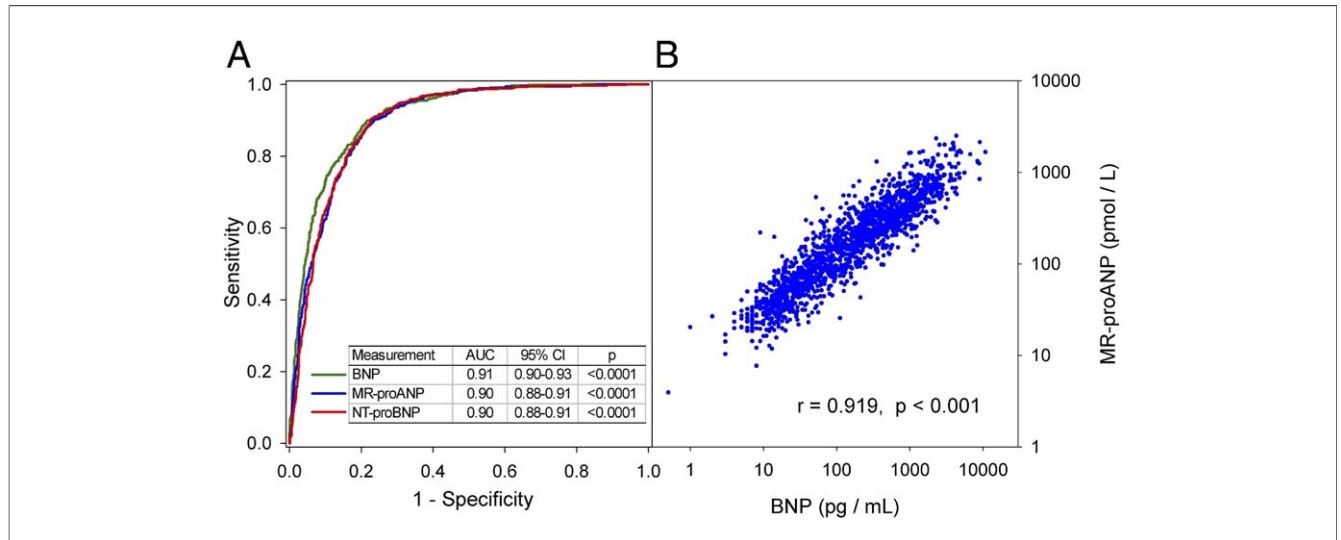
Figure 1 **Comparison of Diagnostic Biomarkers**

(A) Receiver-operating characteristic curves for B-type natriuretic peptide (BNP) **(green line)**, N-terminal pro–B-type natriuretic peptide (NT-proBNP) **(red line)**, and mid-regional pro-atrial natriuretic peptide (MR-proANP) **(blue line)** for detecting acute heart failure. **(B)** Spearman's correlation between BNP and MR-proANP. AUC = area under the curve; CI = confidence interval.

did not significantly differ (p = 0.110). The strong association between BNP and MR-proANP is illustrated in Figure 1B. Overall, 57.9% of the cases had BNP levels >100 pg/ml. The equal-percentile cut point for MR-proANP was 130.3 pmol/l. Likewise, 28% of cases had BNP >500 pg/ml and 28% had MR-proANP >338 pmol/l.

Local clinical laboratory values of BNP (n = 865) or NT-proBNP (n = 157) were available to ED physicians and adjudicating cardiologists in 60% (n = 983) of all patients. The ROC analysis omitting these 893 patients was performed for the remaining 658 patients, of whom 97 (14.7%) had gold standard AHF diagnoses. In this subset of patients, the AUC was 0.90 for both BNP and MR-proANP, and MR-proANP was better than NT-proBNP (0.890, p = 0.009).

The distributions of BNP and MR-proANP across various diagnostic groupings are shown in Figure 2. The patterns and ranges follow closely across groups, with AHF highest and asthma lowest for both markers.

In patients with intermediate BNP or NT-proBNP levels, renal insufficiency (creatinine ≥1.6 mg/dl), obesity (body mass index ≥30 kg/m²), advanced age (age ≥70 years), or with edema present, log-transformed MR-proANP added to a logistic regression model with log-transformed BNP or NT-proBNP to predict adjudicated AHF diagnosis demonstrated incremental value in the case of intermediate (100 to 500 pg/ml) BNP levels (chi-square = 10.53, p = 0.001) and obesity (chi-square = 6.85, p = 0.009). Results were not significant for renal insufficiency, the elderly, or with edema (chi-square = 2.23, 3.14, and 0.77, respectively; p = 0.135, 0.076, and 0.379, respectively). The incremental value of log-transformed MR-
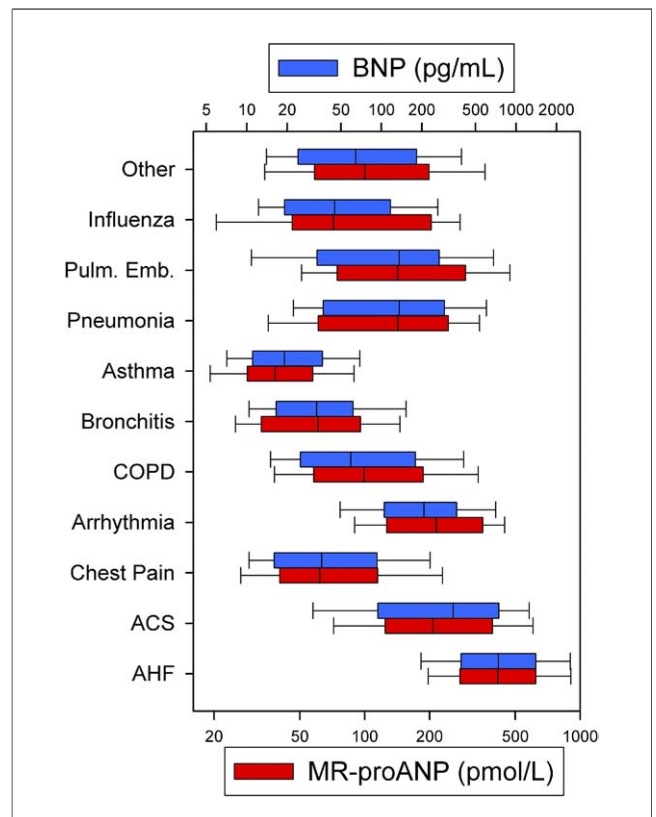

Figure 2 **Box Plots of BNP and MR-proANP**

Box plots of BNP **(blue boxes)** and MR-proANP **(red boxes)** in various diagnostic groups. **Boxes** represent medians and interquartile ranges, **whiskers** represent 10th and 90th percentiles. ACS = acute coronary syndrome; AHF = acute heart failure; COPD = chronic obstructive pulmonary disease; other abbreviations as in Figure 1.

Table 3	Additive Value of MR-proANP in "Gray Zone" Areas for Logistic Regression Models to Predict Acute Heart Failure					
			MR-proANP Adds to BNP		MR-proANP Adds to NT-proBNP	
Subgroup Measure	Subgroup Criterion	n	OR per Log$_{10}$	p Value	OR per Log$_{10}$	p Value
BNP	>100 pg/ml and <500 pg/ml	490	5.7	0.001		
NT-proBNP	>300 pg/ml and <900 pg/ml	228			16.1	0.004
NT-proBNP	>300 pg/ml and <450 pg/ml, if age <50 yrs >300 pg/ml and <900 pg/ml, if age 50–75 yrs >300 pg/ml and <1,800 pg/ml, if age >75 yrs	288			9.5	0.008
Renal	Creatinine >1.6 μmol/l	563	2.5	0.135	9.5	<0.001
Obese	BMI >30 kg/m^2	518	6.8	0.009	17.4	<0.001
Elderly	Age >70 yrs	658	2.6	0.076	6.7	<0.001
Edema	Present	588	1.7	0.379	7.4	0.001

NT-proBNP = N-terminal pro–B-type natriuretic peptide; OR = odds ratio; other abbreviations as in Tables 1 and 2.

proANP was significantly superior in all categories versus NT-proBNP levels (Table 3).

To further illustrate the properties of MR-proANP compared with BNP, Spearman correlation coefficients for both NPs were computed for each variable listed in Table 1. Then, to compare the MR-proANP correlations with the BNP correlations, these were plotted as x-y pairs in Figure 3. The Spearman correlation between sets of correlations for the 2 markers was r = 0.997, illustrating the significant overlap between these variables.

The diagnostic utility of BNP and MR-proANP in a multivariable context is summarized in Table 4. Selected demographic, history, and examination variables were included in logistic regression models with log-transformed

Figure 3   **Spearman Correlations**

Spearman correlations of each variable in Table 1 with BNP as related to the correlation of that variable with MR-proANP. Each **dot** represents a different clinical variable. The proximity of the dot to the **diagonal** shows the similarity of the BNP and MR-proANP relationships to that clinical variable. Abbreviations as in Figure 1.

BNP or MR-proANP to illustrate their utility in models with clinical covariates. Both biomarkers show significance, but the ORs per log cannot be directly compared, since the ranges of BNP and MR-proANP are not the same. Standardizing these predictors yields an OR per standard deviation unit of 7.66 (95% CI: 5.71 to 10.28) for BNP and 6.24 (95% CI: 4.66 to 8.35) for MR-proANP.

Classifying the physician's initial assessment of the probability that the patient had AHF by a visual analog scale into high (>80%, n = 227), low (≤20%, n = 822), and indecisive (>20% but ≤80%, n = 556), the addition of MR-proANP was capable of reducing the subgroup of indecisive by 29%.

Prognosis of MR-proADM in patients with AHF. There were 130 deaths within 90 days (survival rate 92.1%, 95% CI: 90.7% to 93.3%). Survivors had a median MR-proADM of 0.84 nmol/l (IQR 0.55 to 1.35 nmol/l) and nonsurvivors, 1.57 nmol/l (IQR 1.02 to 3.21 nmol/l, p < 0.0001). In the subgroup of 568 patients diagnosed with AHF, there were 65 deaths within 90 days (90-day survival rate 88.6%, 95% CI: 85.6% to 90.9%). Survivors had a median MR-proADM of 1.34 nmol/l (IQR 0.96 to 3.76 nmol/l) and nonsurvivors, 2.07 nmol/l (IQR 1.19 to 3.64 nmol/l, p < 0.0001).

Prognostic end points of death, rehospitalization, and revisit. We evaluated the biomarkers MR-proADM, BNP, and NT-proBNP for their ability to predict both all-cause or cardiovascular death, all-cause or cardiovascular rehospitalization, all-cause or cardiovascular revisit or any of the mentioned events, and all-cause or cardiovascular death in patients diagnosed with AHF, with all-cause mortality at 90 days considered the primary end point. Result are summarized in terms of AUC values in Table 5 for 7, 30, and 90 days after initial presentation at the ED. Prediction of 90-day all-cause and cardiovascular death, rehospitalization, and revisit is illustrated in Figure 4. Prediction was strongest for cardiovascular death for all markers and at all time points, followed by death for any cause. For all other end points, prediction is either nonsignificant or significant but clinically not relevant (AUC <0.65), except for short-term
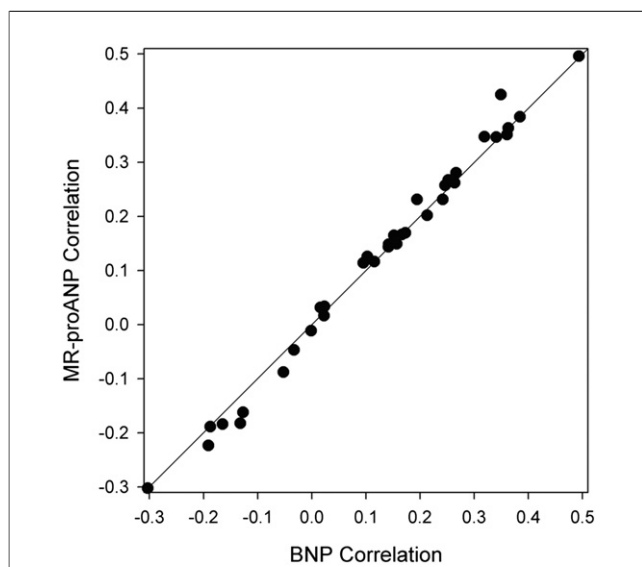
Table 4	Multivariable Diagnosis Models With BNP and MR-proANP					
	Model With BNP			**Model With MR-proANP**		
Variables	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Log_{10} BNP, pg/ml	15.40	10.37–22.86	<0.001			
Log_{10} MR-proANP, pmol/l				47.85	25.82–88.66	<0.001
Age, yrs	1.01	1.00–1.03	0.078	1.00	0.99–1.01	0.968
Male	1.57	1.10–2.24	0.013	1.58	1.12–2.22	0.009
History of						
AHF	2.45	1.70–3.53	<0.001	2.41	1.69–3.44	<0.001
MI	1.00	0.66–1.53	0.991	1.14	0.76–1.72	0.518
COPD	0.42	0.28–0.63	<0.001	0.44	0.30–0.65	<0.001
DM	1.80	1.23–2.64	0.003	1.77	1.22–2.55	0.002
Examination						
Rales	2.26	1.57–3.25	<0.001	2.28	1.61–3.24	<0.001
Wheezing	1.03	0.67–1.59	0.890	0.97	0.64–1.48	0.901
S_3	2.54	0.76–8.52	0.130	2.73	0.77–9.67	0.120
Murmur	1.57	0.99–2.49	0.053	1.42	0.91–2.21	0.119
Edema	1.59	1.11–2.28	0.012	1.67	1.18–2.35	0.004
JVP	2.47	1.57–3.89	<0.001	2.89	1.87–4.46	<0.001

Abbreviations as in Tables 1 to 3.

prediction of revisits. The latter is, however, based on very few events, and must be interpreted carefully.

For prediction of rehospitalization and revisit, BNP performs best, and substantially better than NT-proBNP. This advantage of BNP is lost for cardiovascular events if the ROC analysis is limited to patients whose BNP was not measured by the hospital at the initial ED presentation (n = 166) (Fig. 5), suggesting that BNP knowledge influenced the classification of cardiovascular events.

All-cause mortality. All-cause mortality was the best predictable end point for all biomarkers. Cut points for MR-proADM, BNP, and NT-proBNP were determined from ROC analysis for 90-day survival. The optimal cut points were 1.985 nmol/l (n = 153, or 27% higher) for MR-proADM, 1,021 pg/ml (n = 218, or 38% higher) for BNP, and 6,310 pg/ml (n = 228, or 40% higher) for NT-proBNP. Using these cut points, accuracy was 74% (70% to 77%) for MR-proADM, 62% (58% to 66%) for BNP, and 64% (60% to 68%) for NT-proBNP (p < 0.001 compared with MR-proADM for both). The specificity was 76% (95% CI: 72% to 80%) for MR-proADM, and 63% (59% to 67%) for both BNP and NT-proBNP (p < 0.001 for each vs. MR-proADM). The sensitivity was 53% (95% CI: 41% to 65%) for MR-proADM and BNP (not significantly different), and 69% (95% CI: 57% to 79%) for NT-proBNP (p = 0.094 compared with MR-proADM and BNP).

Using logistic regression models to derive the probability of death from the logs of both BNP and MR-proADM versus BNP alone, net reclassification improvement was calculated following Pencina et al. (21) for probability groups <6%, between 6% and 20%, and >20%. The resulting net reclassification improvement was 38.8%. As Pencina et al. (21) note, the net reclassification improve-

ment is influenced by the probability cut points selected. Therefore, the integrated discrimination improvement was also calculated, and an integrated discrimination improvement of 5.24% was achieved.

Cox and ROC analyses. In univariate Cox proportional hazard analyses, all 3 biomarkers were prognostic of survival at 90 days (Table 6). The HRs per log_{10} unit increase were 14.4 (95% CI: 5.8 to 35.7, p < 0.001) for MR-proADM and 2.2 (95% CI: 1.2 to 3.8, p = 0.008) for BNP. The HRs standardized for an increase by 1 IQR were 2.4 (95% CI: 1.8 to 3.3) for MR-proADM and 1.5 (95% CI: 1.1 to 2.1) for BNP. In multivariable models including both markers, as well as age, sex, and creatinine, only MR-proADM carried independent prognostic utility from BNP and NT-proBNP (Table 6). MR-proADM added to a model using BNP (additional chi-square = 23.90, df = 1, p < 0.001); however, BNP did not add to a model using MR-proADM (additional chi-square = 0.01, df = 1, p = 0.906). Similar results were obtained when NT-proBNP was used instead of BNP (data not shown).

Local laboratory troponin values were available in 511 (90%) of 568 heart failure patients. In 107 (20.9%) patients, they were elevated as per clinical laboratory protocols. In Cox regression models using MR-proADM, BNP, NTproBNP, and troponin status (elevated vs. not elevated with respect to the manufacturer's guidelines of the applied troponin assay), MR-proADM remained an independent prognostic marker. As Table 6 demonstrates, troponin and MR-proADM both provided independent prognostic utility, but BNP and NT-proBNP did not. Among patients with AHF, MR-proADM was an independent predictor of survival after adjusting for left ventricular (LV) ejection fraction (%), LV end-diastolic dimension (cm), normal LV function,

Table 5	Summary of Predictive Performance for BNP, NT-proBNP, and MR-proADM for Predicting All-Cause or Cardiovascular Death, Rehospitalization, Revisit, or Any of the Previous Events at 90, 30, and 7 Days After Initial Presentation to ED				
			AUC		
End Point	**Follow-Up, Days**	**Events, n**	**MR-proADM**	**BNP**	**NT-proBNP**
Mortality					
All-cause	90	65	**0.674**	0.606	**0.664**
All-cause	30	35	**0.739**	0.555	0.641
All-cause	7	13	**0.727**	0.512	0.620
Cardiovascular	90	40	**0.740**	**0.682**	**0.724**
Cardiovascular	30	23	**0.790**	0.584	0.651
Cardiovascular	7	12	**0.728**	0.525	0.613
Rehospitalization					
All-cause	90	205	0.510	0.593	0.536
All-cause	30	105	0.510	0.569	0.501
All-cause	7	21	0.544	0.560	0.541
Cardiovascular	90	129	0.504	0.620	0.540
Cardiovascular	30	71	0.509	0.600	0.512
Cardiovascular	7	15	0.533	0.554	0.545
ED visit					
All-cause	90	144	0.519	0.560	0.508
All-cause	30	79	0.501	0.608	0.516
All-cause	7	16	0.686	0.600	**0.667**
Cardiovascular	90	84	0.519	0.601	0.515
Cardiovascular	30	52	0.507	0.606	0.507
Cardiovascular	7	10	**0.694**	**0.673**	**0.745**
Any event					
All-cause	90	294	0.551	0.588	0.565
All-cause	30	158	0.550	0.561	0.535
All-cause	7	41	0.501	0.546	0.515
Cardiovascular	90	185	0.551	0.620	0.570
Cardiovascular	30	104	0.565	0.583	0.538
Cardiovascular	7	30	0.530	0.542	0.512

Area under the curve (AUC) values above 0.65 are marked in **bold**.

ED = emergency department; MR-proADM = mid-regional pro-adrenomedullin; other abbreviations as in Tables 2 and 3.

and presence of either systolic or diastolic dysfunction as determined by echocardiography (standardized HR: 2.3, 95% CI: 1.5 to 3.6, p < 0.001; 318 [56%] AHF patients with echocardiography done, 295 [52%] AHF patients with valid ejection fraction). MR-proADM was further evaluated in combination with each available baseline covariate. In all bivariable models, MR-proADM remained the strongest predictor (data not shown).

Figure 6 shows the comparison of areas under the ROC curve for 90-day survival using the 3 peptides. The AUCs for 90-day outcome for MR-proADM, BNP, and NT-proBNP are 0.674, 0.606, and 0.664, respectively. For 30-day outcome, used as an exploratory end point, the prognostic performance for MR-proADM increases to 0.739, whereas those for BNP and NT-proBNP decrease to 0.555 and 0.641, respectively. Compared with BNP and NTproBNP, MR-proADM demonstrated a unique prognostic profile in the first 30 days after hospitalization. Survival by quartiles of MR-proADM, BNP, and NT-proBNP in AHF patients is illustrated in Kaplan-Meier curves shown in Figure 7. For MR-proADM, the cutoffs are

0.97, 1.40, and 2.07 nmol/l for the 25th, 50th, and 75th percentiles, respectively. For BNP, cutoffs are 391, 740, and 1,399 pg/ml, respectively; and for NT-proBNP, cutoffs are 2,248, 5,017, and 10,455 pg/ml, respectively. Comparing AHF patients in the highest quartile of MR-proADM to patients in quartiles 1 through 3 resulted in an HR for death of 3.3 (95% CI: 2.0 to 5.4, p < 0.001).

Discussion

This multinational trial, the largest of its kind to date, demonstrated that mid-region prohormone markers have significant diagnostic and prognostic utility in patients presenting in the ED with acute dyspnea. Our findings validate and extend the observations made in previous pilot studies using MR-proANP for the diagnosis of heart failure (18) and MR-proADM for the assessment of prognosis (15–17,19).

MR-proANP is equivalent to BNP or NTproBNP in the diagnosis of AHF in patients presenting with shortness of breath to the ED. The cut-off point for MR-
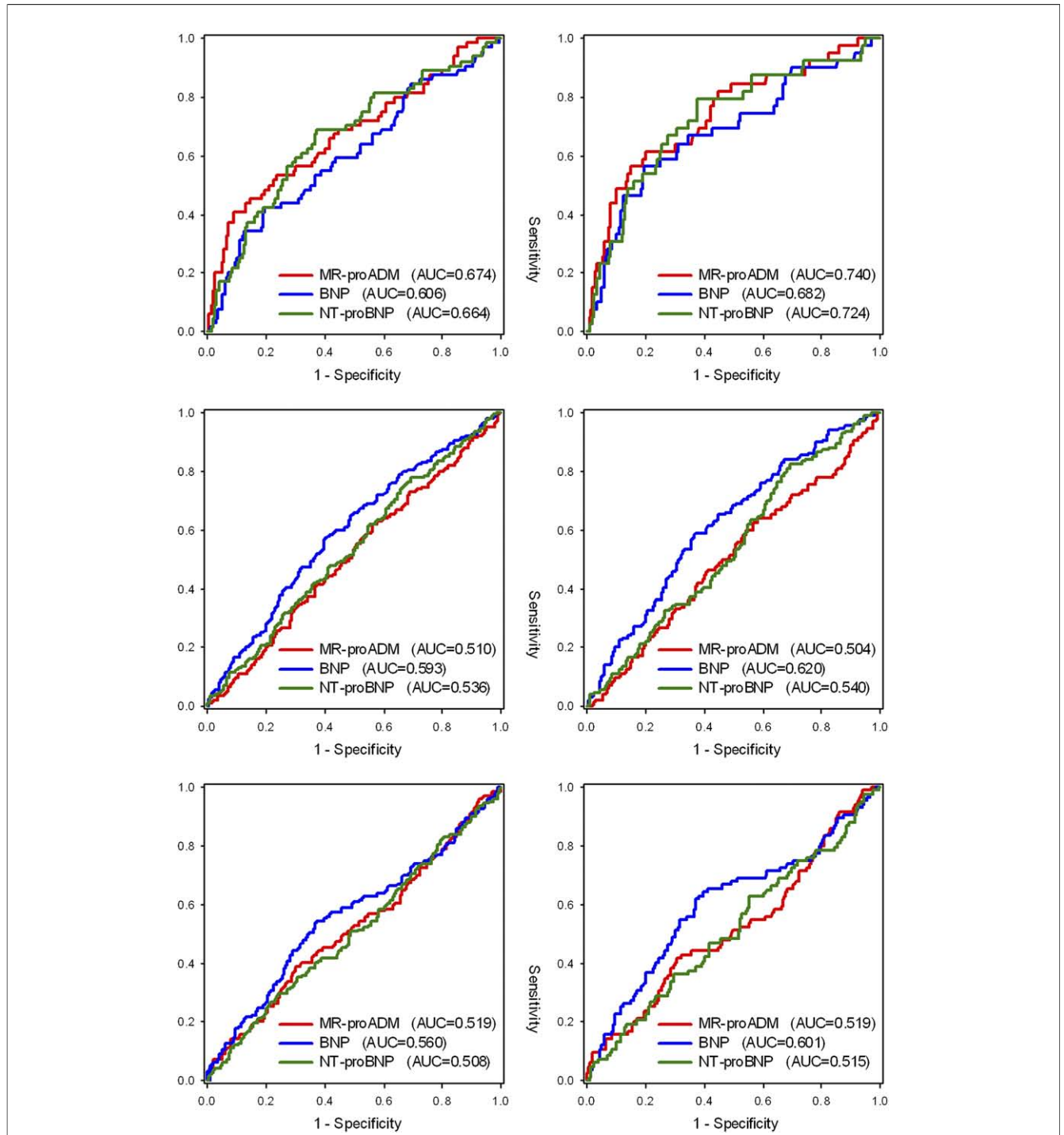
Figure 4   Comparison of Prognostic Biomarkers

Area under the receiver-operating characteristic curve (AUC) for BNP **(blue lines)**, NT-proBNP **(green lines)**, and mid-regional pro-adrenomedullin (MR-proADM) **(red lines)** for prediction of **(left)** all-cause and **(right)** cardiovascular death **(top)**, rehospitalization **(middle)**, and revisit **(bottom)** within 90 days after initial presentation. Abbreviations as in Figure 1.

proANP for making the diagnosis of AHF was based on prior studies (17,18), and was specified a priori in the study protocol as 120 pmol/l. The present findings suggest that a cut point of 130 pmol/l more closely matches a BNP cut point of 100 pg/ml. The calculated AUCs for MR-proANP, NTproBNP, and BNP were 0.90, 0.90, and 0.91, respectively. In the subgroup of 655 patients whose values for BNP or
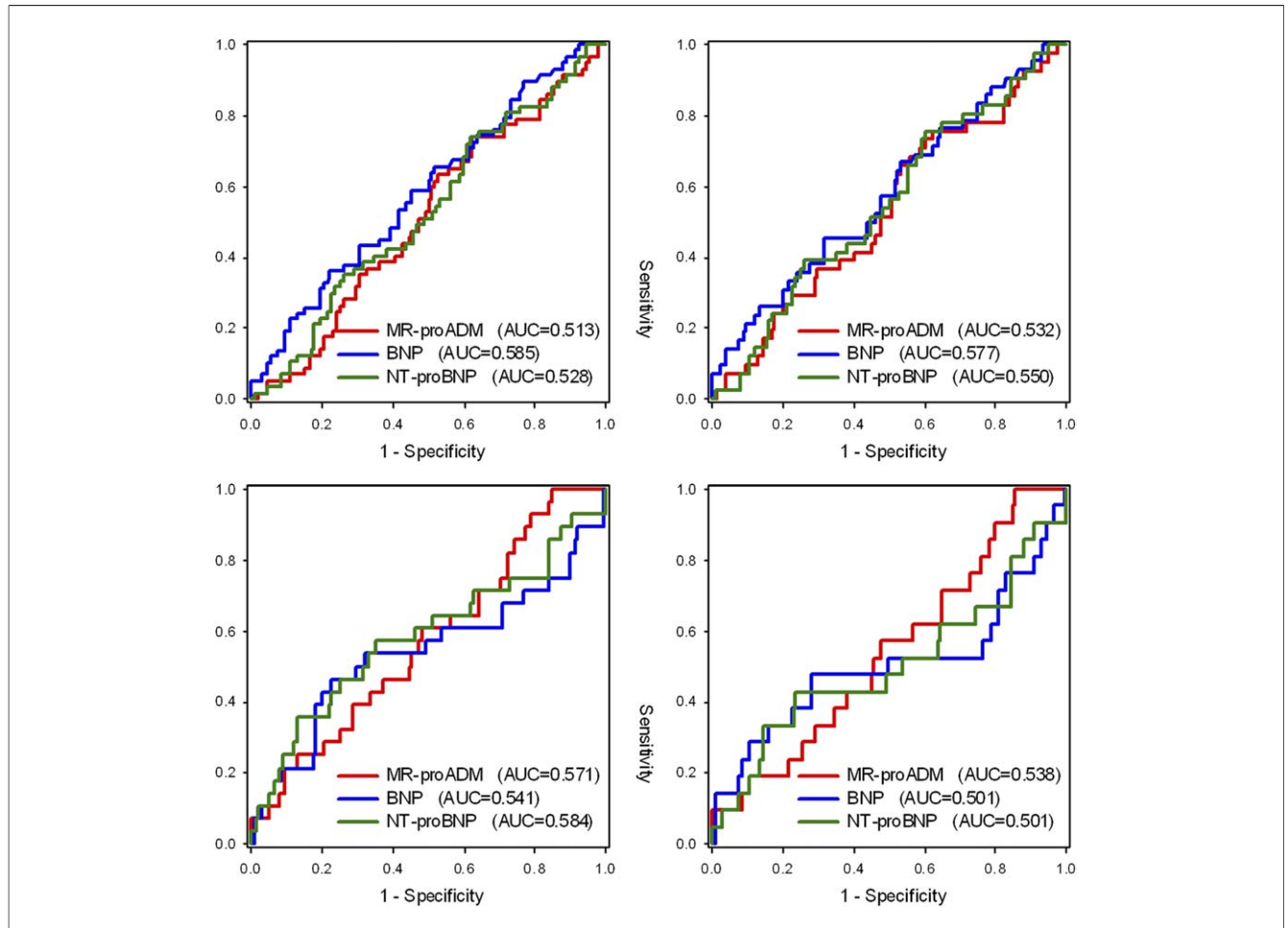
Figure 5   **Comparison of Prognostic Biomarkers for Patients Without BNP Measurement at Time of Evaluation (n = 166)**

Area under the receiver-operating characteristic curve (AUC) for BNP **(blue lines)**, NT-proBNP **(green lines)**, and MR-proADM **(red lines)** for prediction of **(left)** all-cause and **(right)** cardiovascular rehospitalization **(top)** and revisit **(bottom)** within 90 days after initial presentation. Abbreviations as in Figures 1 and 4.

NT-proBNP were not available to the clinicians at the time of diagnosis, the calculated AUCs for MR-proANP and BNP were 0.904 in both cases, but significantly lower for NT proBNP. MR-proANP levels may provide additional diagnostic information for the diagnosis of AHF in addition to BNP or NT-proBNP levels in subgroups for which a correct diagnosis is considered difficult but clinically highly desirable (22–24).

In the prognostic portion of the study, we determined that MR-proADM was superior to BNP and NT-proBNP for predicting 90-day mortality in patients with dyspnea due to AHF. This finding was especially true in an exploratory analysis of the important first 30 days after baseline evaluation, for which MR-proADM clearly outperformed BNP and NT-proBNP. Troponin, which was recently shown to carry prognostic value in patients with heart failure (25), was also added to a multivariable model with the other 3 markers. In this model, MR-proADM still remained an independent prognostic factor. In the 568 BACH patients with a confirmed diagnosis of AHF

(65 deaths within 90 days), the prognostic accuracy of MR-proADM levels assessed in blood samples taken on admission to the ED was 73%. It was found to be lower for BNP and NT-proBNP (62% and 64%, respectively). This was also true when considering all 1,641 enrolled patients, regardless of final diagnosis (data not shown).
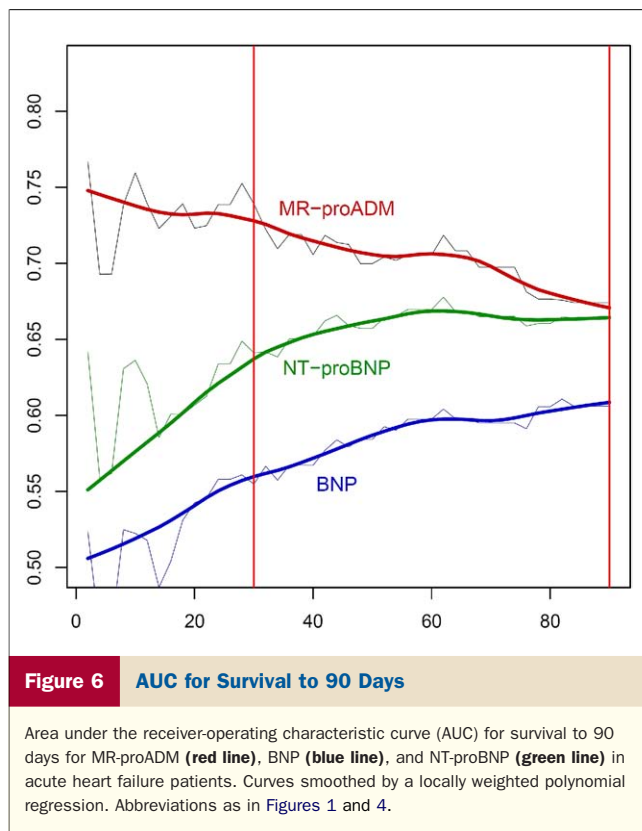
None of the biomarkers was able to predict rehospitalization or revisit to the ED with a clinically relevant performance.

Study limitations. Although we have identified patients at higher risk, as this was a diagnostic study with no randomized intervention above standard care, we cannot comment on the effects of intervention in patients identified as higher risk. As BNP is already part of the standard diagnostic workup in many hospitals, it was therefore regarded as unethical to withhold measurement of BNP at presentation for the diagnosis by the treating physician. Procedurally, it was also not possible to blind the gold standard physicians from biomarker levels taken at the site. Therefore, evaluation of BNP for diagnosis of AHF could lead to positively

Table 6 Single Predictor and Multivariable Cox Proportional Hazard Models for Survival Among Patients With Acute Heart Failure (n = 568)

Predictor	Model 1 Unadjusted					Model 2 Adjusted for Age (yrs) and Sex					Model 3 Adjusted for Age (yrs), Sex, BMI (kg/m^2), and Creatinine (>1.6 mg/dl)				
	HR	95% CI	Chi-Square	p Value	n	HR	95% CI	Chi-Square	p Value	n	HR	95% CI	Chi-Square	p Value	n
Single predictor analysis (using 1 biomarker at a time)															
Log MR-proADM, nmol/l	2.4	1.8–3.3	31	**<0.0001**	564	2.4	1.8–3.2	30.5	**<0.0001**	564	2.3	1.6–3.4	18.8	**<0.0001**	505
Log BNP, pg/ml	1.5	1.1–2.1	7.1	**0.008**	566	1.6	1.1–2.2	8.0	**0.005**	566	1.3	0.9–1.9	2.2	0.137	507
Log NT-proBNP, pg/ml	2.0	1.4–2.9	17.1	**<0.0001**	562	1.9	1.4–2.7	14.2	**0.0002**	562	1.5	1.0–2.3	4.2	**0.041**	504
Troponin, high/low	3.2	1.9–5.4	16.5	**<0.0001**	511	3.2	1.9–5.5	17.8	**<0.0001**	511	3.2	1.8–5.7	15.7	**0.0001**	468
Multivariable analysis 1: MR-proADM and BNP															
Log MR-proADM, nmol/l	2.4	1.7–3.4	24.9	**<0.0001**	563	2.3	1.6–3.3	21.3	**<0.0001**	563	2.4	1.6–3.7	16.2	**<0.0001**	504
Log BNP, pg/ml	1.0	0.7–1.5	0.0	0.91	563	1.1	0.7–1.6	0.2	0.70	563	0.9	0.6–1.4	0.1	0.71	504
Multivariable analysis 2: MR-proADM, BNP, and troponin															
Log MR-proADM, nmol/l	2.0	1.4–2.9	13.6	**0.0002**	508	2.0	1.3–2.9	11.6	**0.0006**	508	2.1	1.4–3.4	10.6	**0.0011**	465
Log BNP, pg/ml	1.0	0.6–1.4	0.1	0.81	508	1.0	0.7–1.5	0.0	0.94	508	0.9	0.6–1.4	0.3	0.57	465
Troponin, high/low	2.6	1.5–4.5	11.0	**0.0009**	508	2.6	1.5–4.6	10.9	**0.0009**	508	2.9	1.6–5.2	11.9	**0.0005**	465
Multivariable analysis 3: MR-proADM and NT-proBNP															
Log MR-proADM, nmol/l	2.2	1.5–3.1	16.0	**<0.0001**	559	2.1	1.5–3.1	15.0	**<0.0001**	559	2.5	1.6–4.0	14.4	**<0.0001**	501
Log NT-proBNP, pg/ml	1.3	0.8–1.9	1.1	0.30	559	1.2	0.8–1.8	0.9	0.35	559	0.9	0.6–1.5	0.1	0.83	501
Multivariable analysis 4: MR-proADM, NT-proBNP, and troponin															
Log MR-proADM, nmol/l	1.9	1.3–2.9	9.9	**0.0016**	503	2.0	1.3–3.0	9.7	**0.0018**	503	2.4	1.4–4.0	11.3	**0.0008**	461
Log NT-proBNP, pg/ml	1.1	0.7–1.6	0.1	0.77	503	1.0	0.7–1.6	0.0	0.96	503	0.8	0.5–1.4	0.5	0.46	461
Troponin, high/low	2.6	1.5–4.4	11.1	**0.0009**	503	2.6	1.5–4.6	11.3	**0.0008**	503	3.0	1.6–5.4	12.9	**0.0003**	461

For each biomarker, and therefore for all reported chi-square, degree of freedom = 1. **Bold** values indicate statistical significance.

Abbreviations as in Tables 2 to 5.

Figure 6   **AUC for Survival to 90 Days**

Area under the receiver-operating characteristic curve (AUC) for survival to 90 days for MR-proADM **(red line)**, BNP **(blue line)**, and NT-proBNP **(green line)** in acute heart failure patients. Curves smoothed by a locally weighted polynomial regression. Abbreviations as in Figures 1 and 4.

biased results to an unknown extent. Therefore, we had to accept this bias in favor of BNP, and selected a noninferiority design with a margin of 10%. Nonetheless, the observed difference in accuracy was <1%. When patients with known clinical laboratory values for BNP or NT-proBNP were excluded, the AUCs for BNP and MR-proANP were identical. In addition, the knowledge of BNP might have also influenced the classification of an outcome event as cardiovascular, which again biases prediction results in favor of BNP. Again, when patients with known clinical laboratory values for BNP were excluded, the observed advantages of BNP for predicting cardiovascular events vanished. However, this finding must be interpreted cautiously as this subset of patients is not representative of the group as a whole. Finally, the number of deaths among patients with AHF was limited by the 90-day follow-up duration, so longer term prognosis cannot be addressed.

Conclusions

Clinical implications. The value of natriuretic peptides in the diagnostic and prognostic assessment of patients with congestive heart failure is reflected in their inclusion in guidelines across the world (26–28) as well as by a recent consensus statements (29). Mid-regional prohormone markers are very stable in blood samples kept at room temperature, and hence may offer some practical analytical advantages (30). The tests for MR-proANP and MR-

proADM are now available in a fast-assessment format, making diagnostic and prognostic information available to the acute care physician within 30 to 60 min. Thus, MR-proANP can now be considered the third valid natriuretic peptide marker for heart failure patients. While it need not replace the other peptides for diagnosis of heart failure, use of MR-proANP levels are acceptable alternatives, depending on the laboratory platform available, pricing, and so forth, and may add to the other natriuretic peptide levels in ambivalent diagnostic cases.

Better prognostic markers help patients in many 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 based on high MR-proADM levels might include specialist consultation by a cardiologist, intensive care unit admission, noninvasive ventilation, and so forth. Additionally, the astute clinician will more closely follow up patients with poor prognostic markers after discharge to prevent relapse and readmission. MR-proADM may also help to identify patients who are in need of longer courses of inpatient therapy to relieve congestion. MR-proADM levels may also serve as a surrogate marker in therapeutic heart failure trials, although both of these suggestions require validation.
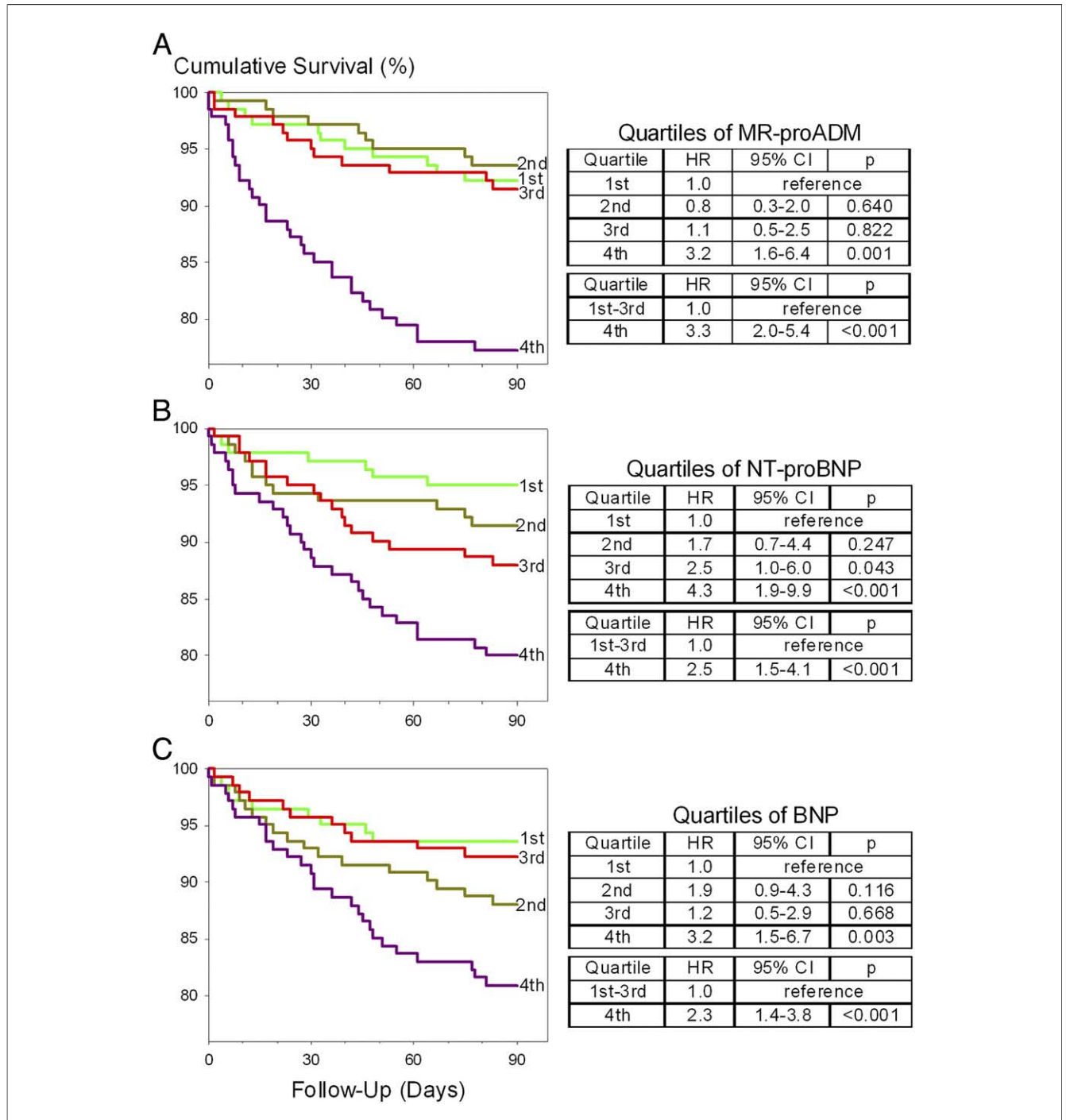
Figure 7 **Kaplan-Meier Survival Curves**

Kaplan-Meier survival curves by quartiles of MR-proADM, NT-proBNP, and BNP for 568 patients with acute heart failure. **(A)** Results for quartiles of MR-proADM. **(B)** Results for quartiles of NT-proBNP. **(C)** Results for quartiles of BNP. CI = confidence interval; HR = heart failure; other abbreviations as in Figures 1 and 4.

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Key Words: pro-hormone ■ markers ■ acute dyspnea ■ BACH.