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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 (≥120 pmol/l) proved noninferior to BNP (≥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.

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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.

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

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 ethylenediaminetetraacetic acid, and plasma was stored at −70°C in plastic freezer vials. MR-proANP and MR-proADM were mea-

Zealand; §§Athens University Hospital Attikon, Athens, Greece; ‖‖Sant'Andrea Hospital, University La Sapienza, Rome, Italy; ¶¶VA Minneapolis, Minnesota; ##University of Leicester, 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; §§§BRAHMS Aktiengesellschaft Biotechnology Centre Hennigsdorf, Berlin, Germany; and the ‖‖‖Centre for Clinical and Basic Research IRCCS San Raffaele, Rome, Italy. For full author disclosures, please see the end of this article.

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