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Brief Report

Plasma bioactive adrenomedullin as a prognostic biomarker in acute heart failure☆,☆☆

Wesley H. Self, MD, MPH [a,*], Alan B. Storrow, MD [a], Oliver Hartmann, PhD [b], Tyler W. Barrett, MD [a], Gregory J. Fermann, MD [c], Alan S. Maisel, MD [d], Joachim Struck, PhD [b], Andreas Bergmann, PhD [b], Sean P. Collins, MD [a]

[a] Department of Emergency Medicine, Vanderbilt University, Nashville, TN, USA
[b] Sphingotec, GmbH, Hennigsdorf, Germany
[c] Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH, USA
[d] Coronary Care Unit and Heart Failure Program, San Diego Veterans Affairs Medical Center, San Diego, CA, USA

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ABSTRACT

Objective: The objective was to evaluate the prognostic performance of a new biomarker, plasma bioactive adrenomedullin (bio-ADM), for short-term clinical outcomes in acute heart failure.
Methods: A multicenter prospective cohort study of adult emergency department (ED) patients suspected of having acute heart failure was conducted to evaluate the association between plasma bio-ADM concentration and clinical outcomes. The primary outcome was a composite of the following within 30 days: death, cardiac arrest with resuscitation, respiratory failure, emergency dialysis, acute coronary syndrome, hospitalization >5 days, and repeat ED visit or hospitalization. Prognostic accuracy was evaluated with a nonparametric receiver operating characteristic curve. In addition, a multivariable logistic regression model was constructed to assess the additive prognostic performance of bio-ADM while adjusting for other biomarkers routinely used clinically, including B-type natriuretic peptide, cardiac troponin I, creatinine, and sodium concentration.
Results: Two hundred forty-six patients were enrolled, including 85 (34.6%) patients with the primary outcome. Plasma bio-ADM concentrations were higher among patients who experienced the primary outcome (median, 80.5 pg/mL; interquartile range [IQR], 53.7-151.5 pg/mL) compared with those who did not (median, 54.4 pg/mL; IQR, 43.4-78.4 pg/mL) ($P < .01$). Area under the receiver operating characteristic curve was 0.70 (95% confidence interval, 0.63-0.75). After adjusting for the other biomarkers, plasma bio-ADM remained a strong predictor of the primary outcome (adjusted odds ratio per IQR change, 2.68; 95% confidence interval, 1.60-4.51).
Conclusions: Bioactive adrenomedullin concentrations at the time of ED evaluation for acute heart failure were predictive of clinically important 30-day outcomes, suggesting that bio-ADM is a promising prognostic marker for further study.

1. Introduction

Acute heart failure (AHF) is one of the most common illnesses treated in emergency departments (EDs) in the United States [1]. After establishing an AHF diagnosis and initiating treatment, a major clinical decision facing emergency physicians is whether to pursue hospitalization for inpatient management [2]. Approximately 80% of patients diagnosed with AHF in US EDs are hospitalized [1]. Hospitalization allows for close observation and titration of intravenous medications, but is also associated with substantially higher cost than outpatient management and places patients at risk for nosocomial complications, such as infections, delirium, and falls [2–5]. Ideally, hospitalization would be reserved for patients at high risk for short-term severe complications of AHF, such as respiratory and renal failure, and those needing specific inpatient therapies, such as intravenous vasoactive medications [2,3]. However, ensuring clinical stability and estimating the risk of severe short-term outcomes are problematic with existing prognostic tools. This prognostic uncertainty plays a significant role in the high admission rate for AHF patients [1–3,6].

A prognostic biomarker that accurately identified AHF patients at high risk for short-term complications would be invaluable for guiding

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* Corresponding author. Vanderbilt University, 1313 21st Ave S, 703 Oxford House, Nashville, TN 37220. Tel.: +1 615 836 8047; fax: +1 615 936 3754.
E-mail address: wesley.self@vanderbilt.edu (W.H. Self).

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management decisions, particularly decisions regarding hospitalization. Natriuretic peptides, such as B-type natriuretic peptide (BNP), are widely used as diagnostic biomarkers for AHF, but their prognostic performance is suboptimal [7,8]. Although patients with an elevated cardiac troponin, renal dysfunction, and hyponatremia are at increased risk for severe outcomes, a subset of patients without these risk factors also experiences adverse events, suggesting that additional biomarkers are needed [9–12].

Adrenomedullin is a vasodilatory peptide that is elevated in patients with chronic heart failure and may also acutely rise in AHF [13–15]. Elevated levels of midregion proadrenomedullin, a stable fragment derived from the same precursor peptide as adrenomedullin, have previously been shown to predict 90-day mortality among patients presenting with acute shortness of breath, including those with AHF [8,16]. Midregion proadrenomedullin measurement does not distinguish between biologically active amidated adrenomedullin and the nonfunctional adrenomedullin variant containing a glycine-extended C-terminal residue. Recently, a sandwich immunoassay has been developed to specifically measure the biologically active form of adrenomedullin—bioactive adrenomedullin (bio-ADM)—making it feasible to use it as a biomarker in clinical medicine [17–19]. Because of the need for better prognostic markers in AHF and a biologically plausible association between bio-ADM and AHF severity, we evaluated the prognostic accuracy of plasma bio-ADM for predicting severe, short-term clinical outcomes in patients evaluated in the ED for AHF.

2. Methods

2.1. Study design

We conducted a multicenter prospective cohort study to evaluate plasma bio-ADM as a prognostic biomarker in adults presenting to the ED with signs and symptoms consistent with AHF at 2 university-affiliated tertiary care EDs and 2 community EDs in the United States. We studied single measurements of bio-ADM in plasma collected at the time of initial ED presentation. This study used a subset of patients recruited for the STRATIFY and DECIDE studies [20]. Methodological details of patient recruitment and enrollment have been reported previously [20]. The local institutional review boards of the participating sites approved the study. All enrolled patients provided written informed consent for participation.

2.2. Study population

We randomly selected 250 patients enrolled in the STRATIFY/DECIDE cohort between July 20, 2007, and February 4, 2011 [20]. Enrolled patients presented to the ED with acute cardiopulmonary symptoms, met the Modified Framingham Criteria for AHF [20], and were clinically suspected of having AHF. To ascertain if AHF was truly the cause of each patient's acute symptoms, a panel of 3 cardiologists reviewed the medical record of each enrolled patient's ED visit and subsequent hospitalization. Each cardiologist classified the primary cause of symptoms as *AHF* or *not AHF*. Two cardiologists initially reviewed each case. If the classifications by the initial 2 cardiologists were discordant, a third cardiologist reviewed the case, with the final diagnosis based on majority. Interrater agreement between the initial 2 reviewers was calculated with Cohen κ. The prognostic accuracy of bio-ADM was evaluated both in the full study population (*Suspected AHF Population*) and separately in the subset of patients who had AHF confirmed based on the cardiologists' review (*Confirmed AHF Population*).

2.3. Biomarker measurement

Trained research personnel collected and banked plasma from patients in the ED. Samples were frozen within 2 hours and stored at −80°C. Plasma bio-ADM concentrations were measured by investigators blinded to clinical data at Sphingotec GmbH (Hennigsdorf, Germany). The bio-ADM assay has been previously described [19]. In brief, it is a 1-step sandwich chemiluminescence immunoassay based on Acridinium NHS-ester labeling for the detection of human ADM in unprocessed, neat plasma. It uses 2 mouse monoclonal antibodies, one directed against the midregion (solid phase) and the other directed against the amidated C-terminal moiety of ADM (labeled antibody). The assay uses 50 μL of plasma samples/calibrators and 200 μL of labeled detection antibody. The analytical assay sensitivity is 2 pg/mL. In prior work [19], the median bio-ADM concentration of 200 healthy adults was 20.7 pg/mL; the 99th percentile was 43.0 pg/mL.

Patients also had additional, standard-of-care biomarkers measured while in the ED, including BNP, cardiac troponin I, creatinine, and sodium concentration.

2.4. Outcomes

Research personnel ascertained outcomes 30 days (±2 days) after the index ED visit via phone interviews and medical record review. Two categories were evaluated: severe clinical outcomes and health care utilization outcomes. A *severe clinical outcome* was defined as the occurrence of ≥1 of the following events: death, cardiac arrest with return of spontaneous circulation, respiratory failure with intubation, emergency dialysis, and acute coronary syndrome. [21] Health care utilization outcomes included hospital length of stay (LOS) greater than 5 days, return ED visit for AHF within 30 days, and repeat hospitalization for AHF within 30 days. Five days was chosen to denote prolonged LOS because this represents the median hospital LOS for AHF in the United States [1].

The primary study outcome was a composite of all severe clinical and health care utilization outcomes. In secondary analyses, we separately evaluated severe clinical outcomes without the health care utilization outcomes.

2.5. Data analysis

2.5.1. Unadjusted analyses

In the primary analysis, we evaluated the prognostic accuracy of plasma bio-ADM concentration in the Suspected AHF Population (all enrolled patients) for a composite of all 30-day outcomes. Bioactive adrenomedullin concentrations in patients who experienced ≥1 outcome were compared with those who did not experience any outcomes with the Wilcoxon rank sum test. A nonparametric receiver operating characteristic (ROC) curve was constructed to display the performance of bio-ADM to discriminate between patients who did and did not experience a 30-day outcome. We also used the 25th, 50th, and 75th percentile of bio-ADM concentration in the study population as cut points and calculated the proportion of patients with bio-ADM levels greater than and less than these cut points who experienced the primary outcome.

Secondary analyses were also performed after limiting study outcomes to the severe clinical outcomes and limiting the study population to the Confirmed AHF Population. Therefore, 3 secondary analyses were conducted: (1) severe clinical outcomes in the Suspected AHF Population, (2) all 30-day outcomes in the Confirmed AHF Population, and (3) severe clinical outcomes in the Confirmed AHF Population.

2.5.2. Multivariable biomarker model

A multivariable logistic regression model was constructed to assess the additive prognostic performance of bio-ADM while adjusting for other biomarker results, including BNP, cardiac troponin I, creatinine, and sodium concentration. Data for bio-ADM, BNP, cardiac troponin I, and creatinine were logarithmically transformed (log-10) because of highly skewed distributions. The study population for this model included suspected AHF patients who had nonmissing data for all 5 biomarkers. The dependent variable was a composite of all 30-day outcomes. Independent variables included bio-ADM log-10 transformed,