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ORIGINAL INVESTIGATIONS

B-Type Natriuretic Peptide Levels and Mortality in Patients With and Without Heart Failure

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ABSTRACT

BACKGROUND Circulating B-type natriuretic peptide (BNP) concentrations strongly predict mortality in patients with heart failure (HF). Both cardiac and extracardiac stimuli influence BNP levels, suggesting that BNP might have similar prognostic value in patients without HF.

OBJECTIVES The aim of this study was to compare the prognostic value of BNP between patients with and those without HF.

METHODS Using the Vanderbilt University Medical Center electronic health record, 30,487 patients (median age 63 years, 50% men, 17% black, 38% with HF) who had a first plasma BNP measurement between 2002 and 2013, with follow-up through 2015, were studied. The risk for death according to BNP level was quantified using multivariate Cox proportional hazards models.

RESULTS BNP levels were lower in patients without HF (median 89 pg/ml; interquartile range: 34 to 238 pg/ml) compared with those with HF (median 388 pg/ml; interquartile range: 150 to 940 pg/ml) ($p < 0.0001$). Over 90,898 person-years of follow-up, 5,903 patients without HF (31%) and 6,181 patients with HF (53%) died. In multivariate models including demographic and clinical characteristics, BNP and age were the strongest predictors of death in both patients with and those without HF. In acute care settings and even among outpatients with modestly elevated BNP, the risk for death according to BNP was similar between patients with and those without HF. For instance, a BNP level of 400 pg/ml was associated with a 3-year risk for death of 21% (95% confidence interval: 20% to 23%) and 19% (95% confidence interval: 17% to 20%) in patients with and those without HF, respectively.

CONCLUSIONS Among patients without HF, plasma BNP level is a stronger predictor of death than traditional risk factors. The risk for death associated with any given BNP level is similar between patients with and those without HF, particularly in the acute care setting. (J Am Coll Cardiol 2018;71:2079–88) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

CI = confidence interval

HF = heart failure

HR = hazard ratio

ICD-9 = International Classification of Diseases-9th Revision

LV = left ventricular

LVEF = left ventricular ejection fraction

Natriuretic peptides are cardiac-derived hormones with natriuretic, diuretic, and vasodilatory effects (1). B-type natriuretic peptide (BNP), which is secreted into the circulation in response to increased cardiac wall stress, is a clinically robust diagnostic biomarker for differentiating cardiac and noncardiac causes of dyspnea (2–7). Circulating natriuretic peptide levels are also of prognostic significance, particularly among patients with heart failure (HF), with higher levels associating with greater risk for recurrent HF hospitalizations and death (4,8–11). In clinical settings, however, not all patients in whom BNP is measured have HF. Relatively little is known regarding the prognostic significance of BNP levels among clinically referred patients without HF. Because circulating BNP levels are influenced by cardiac and extracardiac stimuli beyond volume status, we hypothesized that BNP might have similar prognostic value in patients with and those without HF.

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Using 13 years of Vanderbilt University Medical Center electronic health record data, we identified adult patients in whom plasma BNP concentrations were measured. We quantified associations between clinical factors and BNP levels according to HF status. We then tested the hypothesis that the risk for death according to circulating BNP level is similar between patients with and those without HF.

METHODS

STUDY POPULATION. The Vanderbilt University Medical Center Synthetic Derivative is a deidentified copy of the electronic health record (12). It contains approximately 2.5 million patient records spanning more than 20 years, which are searchable for structured (e.g., International Classification of Diseases-9th Revision [ICD-9] codes, laboratory values) and unstructured (e.g., narrative text) data. We queried the Synthetic Derivative to identify black or white adult patients (18 years or older) who had BNP measurements recorded. The Vanderbilt University Institutional Review Board approved this study.

BNP, HF, AND OTHER COVARIATES. Plasma BNP has been clinically measured at Vanderbilt University Medical Center since 2002. For patients with multiple BNP measurements, the first value was used. The Biosite Triage BNP Test (Biosite Diagnostics, San Diego, California) was the first clinical BNP assay used until February 2007. From March 2007 to September 2013, the Beckman Coulter DXI platform (Beckman Coulter, Brea, California) was used to run the Biosite BNP assay. Both platforms have coefficients of variation <12% and lower detection limits of 10 pg/ml.

A patient was categorized as having HF if either of the following criteria was met: 1) 2 or more mentions of a HF ICD-9 code 428.x, where at least 1 code was recorded on the day of or before the date of first BNP measurement; and/or 2) 1 or more mentions of code 428.x and treatment with an intravenous diuretic agent on the same day or within 90 days after the BNP measurement. These criteria were designed to capture chronic and new HF diagnoses, respectively. Patients of mixed phenotype (i.e., both HF and other comorbidities that may contribute to dyspnea, such as asthma or chronic obstructive pulmonary disease, pneumonia, and sepsis) were categorized as having HF.

Age was determined at the BNP measurement date. Coronary artery disease, hypertension, renal disease, and diabetes mellitus status; vital signs; anthropometric data; and laboratory values were extracted using combinations of ICD-9 and Current Procedural Terminology codes and text strings (see the Online Appendix) (13). Estimated glomerular filtration rate was calculated using the MDRD (Modification of Diet in Renal Disease) equation (14). Left ventricular ejection fraction (LVEF) was extracted from transthoracic echocardiography reports closest in time and within 90 days before or after the BNP measurement (15). Left ventricular (LV) diastolic dimensions for septal, posterior, and internal diameter were taken from the same echocardiography reports as LVEF. LV mass (grams) was calculated using the formula: $0.8 \times \{1.04 \times [(\mathrm{LVEDD} + \mathrm{IVSd} + \mathrm{PWTd})^3 - \mathrm{LVEDD}^3]\} + 0.6$, where LVEDD is LV end-diastolic diameter, IVSd is interventricular septal thickness in diastole, and PWTd is posterior wall thickness in diastole, according to American Society of Echocardiography recommendations (16).

OUTCOME: ALL-CAUSE MORTALITY. Death was ascertained through the Social Security Administration's Death Master File linkage, which has similar coverage to the National Death Index (17). The follow-up period was the time elapsed from the date of BNP measurement to the date of death, with censoring at the date of the last clinical encounter for patients who were alive on December 31, 2015.

STATISTICAL ANALYSIS. Patients were categorized according to the presence or absence of HF. Multivariate-adjusted ordinal regression was used to examine factors associated with circulating BNP levels, thereby avoiding assumption of linear