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B-Type Natriuretic Peptide Clinical Activation in Aortic Stenosis

Impact on Long-Term Survival

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Objectives This study was conducted to define the association between serum B-type natriuretic peptide (BNP) activation and survival after the diagnosis of aortic stenosis (AS).

Background In AS, the link between BNP levels and clinical outcome is in dispute. Failure to account for the normal shifting of BNP ranges with aging in men and women, not using hard endpoints (survival), and not enrolling large series of patients have contributed to the uncertainty.

Methods A program of prospective measurement of BNP levels with Doppler echocardiographic AS assessment during the same episode of care was conducted. BNP ratio (measured BNP/maximal normal BNP value specific to age and sex) >1 defined BNP clinical activation.

Results In 1,953 consecutive patients with at least moderate AS (aortic valve area 1.03 ± 0.26 cm^2; mean gradient 36 ± 19 mm Hg), median BNP level was 252 pg/ml (interquartile range: 98 to 592 pg/ml); BNP ratio 2.46 (interquartile range 1.03 to 5.66); ejection fraction (EF) 57% ± 15%, and symptoms present in 60% of patients. After adjustment for all survival determinants, BNP clinical activation (BNP ratio >1) independently predicted mortality after diagnosis ($p < 0.0001$; hazard ratio [HR]: 1.91; 95% CI: 1.55 to 2.35) and provided incremental power to the survival predictive model ($p < 0.0001$). Eight-year survival was 62 ± 3% with normal BNP levels, 44 ± 3% with BNP ratio of 1 to 2 (adjusted HR: 1.49; 95% CI: 1.17 to 1.90), 25 ± 4% with BNP ratio of 2 to 3 (adjusted HR: 2.12; 95% CI: 1.63 to 2.75), and 15 ± 2% with BNP ratio of ≥3 (adjusted HR: 2.43; 95% CI: 1.94 to 3.05). This strong link to survival was confirmed in asymptomatic patients with normal EF (adjusted HR: 2.35 [95% CI: 1.57 to 3.56] for BNP clinical activation and 2.10 [95% CI: 1.32 to 3.36] for BNP ratio of 1 to 2, 2.25 [95% CI: 1.31 to 3.87] for BNP ratio of 2 to 3, 3.93 [95% CI: 2.40 to 6.43] for BNP ratio of ≥3). Aortic valve replacement was associated with survival improved by a similarly high margin ($p = 0.54$) with BNP ratio of <2 (HR: 0.68; 95% CI: 0.52 to 0.89; $p = 0.003$) or BNP ratio of >2 (HR: 0.56; 95% CI: 0.47 to 0.66; $p < 0.0001$).

Conclusions In this large series of patients with AS, BNP clinical activation was associated with excess long-term mortality incrementally and independently of all baseline characteristics. Higher mortality with higher BNP clinical activation, even in asymptomatic patients, emphasizes the importance of appropriate clinical interpretation of BNP levels in managing patients with AS. (J Am Coll Cardiol 2014;63:2016–25) © 2014 by the American College of Cardiology Foundation

Plasma levels of B-type natriuretic peptide (BNP) have been shown to be predictive of outcome and to be clinically useful in diagnosis, management, and risk stratification of cardiovascular diseases such as heart failure and acute coronary syndromes (1–4). In aortic stenosis (AS), pilot studies have suggested that BNP levels may be related to disease severity, symptoms, and mixed measures of outcome (5–10), but a recent prospective analysis raised a concern that these presumptive outcome implications may have been

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overemphasized (11). Survival association with BNP levels was analyzed in very small sets of mostly symptomatic patients (9,12,13) and thus remains undefined. Another source of uncertainty is that these pilot studies used different assays and forms of BNP that are not well harmonized (6–9). Considerably different absolute thresholds proposed in these studies to stratify risk may reflect low power in small, variably selected patient populations with short follow-up or may reflect the instability of soft outcome endpoints (aortic valve replacement, symptom onset, or combined endpoint of variable cardiac events). Furthermore, normal values of BNP for age and sex were not taken into account to affirm BNP clinical activation in excess of the normal range. Thus, the use of BNP as a marker of AS outcome has not been adequately validated for use in clinical practice and is not recommended in guidelines (14,15).

Obtaining objective markers of outcome is crucial in AS. Indeed, AS is frequent (16) and is the most common valvular disease referred for valve replacement (17), which is the only effective AS treatment (14,15), including transcutaneous insertion (15). The role of symptom onset has been emphasized (18,19), but epidemiological changes, with the current predominance of degenerative AS, are characterized by elderly patients being predominantly affected and in whom evaluation and interpretation of symptoms is challenging (20). Therefore, objective markers of risk are crucial in that environment; as such, BNP could play an essential role in risk stratification. For that purpose, it is essential to account for the shifting normal BNP range with aging and specific to each sex and to assess a hard endpoint, particularly mortality, requiring a large cohort of patients diagnosed with AS.

Thus, the objectives of our study were to assess the link between BNP values measured at diagnosis, particularly BNP clinical activation (accounting for the normal BNP range specific to each patient) and mortality following the diagnosis of moderate or severe AS, and to examine the hypothesis that BNP clinical activation independently predicts excess mortality after adjustment for all baseline characteristics, even in asymptomatic patients. A secondary hypothesis examined was that higher levels of activation are associated with more severe outcomes.

Methods

Following a pilot study of natriuretic peptides in valvular heart diseases (21,22), we initiated a program of prospective and systematic measurement of BNP levels with comprehensive Doppler echocardiographic evaluation of valve diseases performed during the same episode of care. For the purpose of the present study, we gathered 1,953 consecutive patients who were diagnosed with moderate or severe AS based on aortic valve area (AVA) of $\leq$1.5 cm^2 by Doppler echocardiography and who underwent this combined clinical, hormonal, and Doppler echocardiographic assessment. Patients with known rheumatic valve disease (clinically and/or echocardiographically); congenital heart disease (except overt or unknown bicuspid valve or patent foramen ovale); previous valvular surgery; acute myocardial infarction within 8 weeks preceding AS diagnosis; atrial fibrillation with rapid ventricular response; history or current endocarditis; pericarditis with or without tamponade; sepsis; severe liver, kidney, or brain disease except old stroke; hyperparathyroidism; or Cushing disease were excluded. Non-U.S. citizens were excluded to ensure homogeneous Social Security death data. The study was approved by our institutional review board.

Abbreviations and Acronyms

AS = aortic stenosis
AVA = aortic valve area
AVR = aortic valve replacement
BNP = B-type natriuretic peptide
LVEF = left ventricular ejection fraction

Clinical data. Clinical data were collected by the patients' personal physicians during the same episode of care as the Doppler echocardiographic and hormonal assessment. The Charlson score index was calculated as previously published (23). Symptomatic patients presented with syncope or near syncope, dyspnea, and/or probable or classic angina.

Doppler echocardiography. All patients underwent comprehensive Doppler echocardiography using standard ultrasound systems, including interrogation from all possible windows (24). All measurements and calculations were performed as recommended by echocardiographic societies' recommendations (25). After measurement in systole of aortic annulus diameter, flow velocity and time velocity integral of left ventricular outflow tract by pulsed-wave Doppler, and AS jet by continuous-wave Doppler, we measured peak jet velocity and mean gradient and calculated AVA by continuity equation as an absolute value and indexed to body surface area. AS severity was graded according to current guidelines (14) and recent community studies (20) as moderate AS with AVA of 1.0 to 1.5 cm^2 or severe AS with AVA of $\leq$1.0 cm^2.

Laboratory data. Venous blood samples were drawn from an antecubital vein into chilled ethylenediaminetetraacetic acid Vacutainer test tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey). Plasma separation was immediately performed at −4°C, and plasma samples were frozen at −70°C until assay. Plasma BNP levels were determined by immunoenzymatic assay (Triage, Biosite Inc., San Diego, California) within 3 days. The ratio between measured serum BNP level and maximal normal BNP level for age and sex (BNP ratio) was calculated for each patient (26). The maximal normal values of BNP specific to age and sex were derived from Mayo Clinic laboratory procedures. Patients with elevated BNP levels (i.e., BNP ratio >1) were considered as displaying BNP clinical activation.

Endpoints. The primary endpoint of this study was the overall mortality after diagnosis, and the secondary endpoint was mortality under medical treatment. This secondary endpoint was assessed in the whole cohort with censoring at the time of aortic valve replacement (AVR) if performed. Due to the large size of our series, we elected to follow up