JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 12, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.06.047

Association of B-Type Natriuretic Peptide With Survival in Patients With Degenerative Mitral Regurgitation

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ABSTRACT

BACKGROUND Studies suggesting that B-type natriuretic peptide (BNP) may predict outcomes of mitral regurgitation (MR) are plagued by small size, inconsistent etiologies, and lack of accounting for shifting normal BNP ranges with age and sex.

OBJECTIVES This study assessed the effect of BNP activation on mortality in a large, multicenter cohort of patients with degenerative MR.

METHODS In 1,331 patients with degenerative MR, BNP was prospectively measured at diagnosis and expressed as BNPratio (ratio to upper limit of normal for age, sex, and assay). Initial surgical management was performed within 3 months of diagnosis in 561 patents.

RESULTS The cohort had a mean age of 64 ± 15 years, was 66% male, and had a mean ejection fraction 64 ± 9%, mean regurgitant volume 67 ± 31 ml, and low mean Charlson comorbidity index of 1.09 ± 1.76. Median BNPratio was 1.01 (25th and 75th percentiles: 0.42 to 2.36). Overall, BNPratio was a powerful, independent predictor of mortality (hazard ratio: 1.33 [95% confidence interval: 1.15 to 1.54]; $p < 0.0001$), whereas absolute BNP was not ($p = 0.43$). In patients who were initially treated medically ($n = 770$; 58%), BNPratio was a powerful, independent, and incremental predictor of mortality after diagnosis (hazard ratio: 1.61 [95% confidence interval: 1.34 to 1.93]; $p < 0.0001$). Higher BNP activation was associated with higher mortality ($p < 0.0001$). All subgroups, particularly severe MR, incurred similar excess mortality with BNP activation. After initial surgical treatment ($n = 561$, 42%) BNP activation did not impose excess long-term mortality ($p = 0.23$).

CONCLUSIONS In patients with degenerative MR, BNPratio is a powerful, independent, and incremental predictor of long-term mortality under medical management. BNPratio should be incorporated into the routine clinical assessment of patients with degenerative MR. (J Am Coll Cardiol 2016;68:1297–307) © 2016 by the American College of Cardiology Foundation.

Degenerative mitral valve regurgitation (DMR) is common and highly surgically treatable, with clinical guidelines evolving toward more liberal indications for surgical treatment (1,2). However, triggers for surgical referral are limited and often have deleterious outcome implications. We recently demonstrated that classical triggers (occurrence of heart failure symptoms, decreased ejection fraction below 60%, increased end-systolic diameter over 40 mm, and presence of atrial fibrillation and/or pulmonary hypertension) were associated with profound negative consequences for long-term post-operative mortality and heart failure, despite low operative risk and highly

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Manuscript received April 17, 2016; revised manuscript received June 16, 2016, accepted June 21, 2016.

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

DMR = degenerative mitral valve regurgitation

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

successful repair rates (2). Identifying objective markers to guide surgical intervention prior to development of these complications would be an important step forward in treating DMR.

Pilot studies of B-type natriuretic peptide (BNP) in patients with mitral regurgitation (MR) suggest that plasma level increase with MR severity, left ventricular (LV) remodeling, and symptoms (3–6) and may predict outcomes under conservative management (4,7–9). However the association of survival or event-free survival with BNP has been analyzed in quite small patient samples, and thus the relationship remains uncertain. Moreover, different thresholds have been proposed in the pilot studies to stratify risk (4,8), because differences in population characteristics and use of different non-normalized assays did not allow for standardization. Most importantly, normal values of BNP for age and sex were not taken into account to affirm clinical activation of BNP in excess of the normal range. Thus, although BNP measurement could play an essential role for MR risk stratification as a potential indicator of early myocardial damage, its use as marker of DMR outcome has not been adequately validated for clinical practice and is not yet recommended in clinical guidelines (1).

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To validate BNP as a clinically useful prognostic tool in DMR, mortality should be studied in a large cohort of patients diagnosed with DMR with long-term follow-up, and the shifting normal BNP range with aging and specific to sex has to be taken into account. The objectives of this study were to assess BNP measured at diagnosis, expressed particularly as BNPratio (accounting for the normal BNP range specific to each patient), and its link to mortality following the diagnosis of DMR, thus examining the hypothesis that BNPratio predicts excess mortality independently of baseline characteristics in patients treated conservatively and surgically.

METHODS

We analyzed 1,331 consecutive patients with MR due to flail or prolapse of the mitral valve leaflet(s) with concomitant measurement of BNP in 4 tertiary centers: between January 2001and December 2013, 907 (68%) patients at Mayo Clinic, Rochester, Minnesota; and between January 2006 and December 2013, 182 (14%) patients at University Hospital, Amiens, France; 121 (9%) patients at Université Catholique de Louvain, Brussels, Belgium; and 121 (9%) patients at Hospital Italiano, Buenos Aires, Argentina (Online Appendix).

Patients were enrolled in the present study if they had DMR characterized by prolapsed or flail leaflets, as detected by 2-dimensional transthoracic echocardiography, and had BNP measured at the time of echocardiography. Patients were excluded if they presented with: 1) ischemic MR; 2) significant concomitant aortic valve disease, congenital heart disease, mitral stenosis, and previous valve surgery; 3) contraindication to surgery due to comorbidity; 4) atrial fibrillation with rapid ventricular response; 5) history of or current endocarditis, pericarditis with or without tamponade or sepsis; 6) severe liver, kidney, or brain disease except old stroke; and 7) hyperparathyroidism or Cushing syndrome. These exclusions allowed us to select a group of patients with pure DMR and without extracardiac reasons for elevated BNP (Online Appendix).

CLINICAL DATA. Clinical data were collected by the patients' personal physicians as the Doppler echocardiographic and hormonal assessment during the same episode of care before any surgery or intervention (Online Appendix). The Charlson comorbidity index was calculated as previously published (10). Dyspnea and atrial fibrillation were ascertained by each patient's personal cardiologist. Not all patients with shortness of breath or atrial fibrillation were referred to surgery, given that both dyspnea and atrial fibrillation could also be associated with comorbidities, body habitus, and so on. The link between each of these triggers and DMR was reported by the treating physician who was also responsible for clinical decisions regarding medical management and referral for surgery.

DOPPLER ECHOCARDIOGRAPHY. All patients underwent comprehensive Doppler echocardiography using standard ultrasound systems within routine clinical practice. All measurements and calculations were performed as recommended by echocardiographic societies' recommendations (11). The severity of MR was assessed semiquantitatively on a scale from 1 to 4 by Doppler echocardiography according to the American Society of Echocardiography (ASE) criteria (12).

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 either analyses were immediately performed or plasma samples were frozen at −70°C until assay and analysis was performed within 3 days. Plasma BNP levels were determined by