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%) BNPratio 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 highl
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).

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 BNP ratio (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 BNP ratio 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 2001 and 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 ethylene diaminetetraacetic 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
3 different assays: Biosite Triage (Biosite Inc., San Diego, California), Vista LOCI BNP assay (Siemens Healthcare, Erlangen, Germany), and Alere Triage BNP Test (Alere Inc., Waltham, Massachusetts).

**ENDPOINTS.** The primary endpoint of this study was the overall mortality after diagnosis, and secondary endpoints were mortality under medical treatment and after mitral valve surgery. For the secondary endpoints, all patients who underwent mitral valve surgery within 3 months after baseline echocardiographic evaluation were classified as the initial surgical treatment group. In all patients of this group, the decision to refer the patient to surgery was made by the treating physician at the time of echocardiographic/clinical evaluation. Patients who did not undergo mitral valve surgery or who underwent mitral valve surgery >3 months after echocardiographic evaluation were classified as the initial medical treatment group. In patients with delayed surgery (i.e., >3 months), only medical follow-up was taken into account (i.e., follow-up was censored at the time of surgery).

Deaths and surgical reports were reviewed and validated by the investigators within each participating center. Cause of death was adjudicated by review of death certificates, physician and hospital notes, and autopsy certificate, if available. The follow-up was complete up to death, the end of the study, or at least 5 years in 1,328 (99.8%) patients.

**STATISTICAL ANALYSIS.** Results are expressed as mean ± SD, median with interquartile range, or percentage when appropriate. Continuous variables were tested for distribution normality with the Shapiro-Wilk test. Because creatinine, BNP absolute values, and BNPratio were not normally distributed, natural log transformations of creatinine, BNP, and BNPratio were used for continuous variable analyses. BNPratio was also categorically analyzed. Analysis of survival used patients with normal BNP levels as the reference group, and compared them with patients with BNP clinical activation overall or stratified into 2 groups: those with a BNPratio of 1 to 4 or a BNPratio of >4.

We analyzed survival in the whole cohort with the use of univariable and multivariable Cox proportional hazards models. Patients were separated into 2 groups according to treatment—the initial surgical treatment group and initial medical treatment group—to assess the relationship between BNPratio and survival separately after surgery and under medical management. In the initial medical treatment group, patients who underwent surgery after 3 months of medical follow-up (n = 260) were censored at the time of surgery, and only follow-up under medical management was taken into account for this subanalysis.

To analyze the incremental value of BNPratio, we defined background models to predict mortality. Clinically relevant variables and/or variables with a p value <0.05 on univariate analysis were included in background multivariate models. In the whole cohort and in the medical management group, background multivariate models included age-weighted Charlson score index, sex, body surface area, atrial fibrillation, dyspnea, creatinine level, systolic blood pressure, DMR severity, and left ventricular ejection fraction (LVEF). Mitral valve surgery was used as a time-dependent covariate in the multivariable Cox proportional hazards models in the entire cohort analysis. To analyze the incremental value of BNPratio after mitral valve surgery, we defined a second background model to predict mortality, including age-weighted Charlson score index, sex, creatinine level, systolic blood pressure, type of surgery (i.e., repair vs. replacement), and LVEF. All variables in the Cox models verified the proportional hazards assumption on the basis of inspection of trends in the Schoenfeld residuals (all p > 0.31).

BNP’s additional effect on survival after diagnosis was analyzed by adding BNP (expressed as a continuous or categorical variable) to the background survival model and assessing model incremental power using the likelihood ratio test. Survival models for BNP are presented with hazard ratio (HR) and 95% confidence interval (CI). A p value <0.05 was considered to be statistically significant. Statistical analyses were performed with JMP version 12.0.1 (SAS Institute, Cary, North Carolina) and SPSS version 20 software (IBM, Armonk, New York).

**RESULTS**

**BASELINE CHARACTERISTICS.** The baseline clinical, laboratory, and echocardiographic characteristics of the entire cohort (n = 1,331) are presented in Tables 1 and 2, left column. Consistent with typical characteristics of patients diagnosed with moderate to severe DMR, mean age was 64 ± 15 years, and 875 (66%) patients were male. With a mean LVEF of 64 ± 9%, the DMR was severe in the majority of cases, with mean effective regurgitant orifice 0.44 ± 0.23 cm² and mean regurgitant volume 67 ± 31 ml. In terms of comorbidity, the prevalence of atrial fibrillation (18%), diabetes (5%), coronary artery disease (16%), history of heart failure (19%), and moderate chronic kidney disease (7%) were as expected in a population of that age with DMR. These comorbidities led to a Charlson score of 1.09 ± 1.76. Median BNP was 91 (25th and 75th percentiles: 36 to 248) pg/ml and that of BNPratio was 1.01 (25th and 75th percentiles: 0.42 to 2.36), with
TABLE 1  Baseline Clinical and Laboratory Characteristics of the Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Cohort (n = 1,331)</th>
<th>Initial Conservative Management (n = 770; 58%)</th>
<th>Immediate Mitral Surgery (n = 561; 42%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>64.4 ± 14.6</td>
<td>66.3 ± 14.8</td>
<td>61.9 ± 14.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>875 (66)</td>
<td>482 (63)</td>
<td>393 (70)</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.1 ± 4.2</td>
<td>24.7 ± 4.3</td>
<td>25.5 ± 4.1</td>
<td>0.0007</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.87 ± 0.22</td>
<td>1.85 ± 0.22</td>
<td>1.91 ± 0.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114 ± 25</td>
<td>114 ± 25</td>
<td>112 ± 24</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77 ± 22</td>
<td>76 ± 22</td>
<td>78 ± 23</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>70 ± 15</td>
<td>70 ± 14</td>
<td>71 ± 16</td>
<td>0.08</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>238 (18)</td>
<td>142 (19)</td>
<td>96 (18)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypertension</td>
<td>773 (58)</td>
<td>447 (58)</td>
<td>326 (58)</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes</td>
<td>65 (5)</td>
<td>44 (6)</td>
<td>21 (4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>214 (16)</td>
<td>120 (16)</td>
<td>94 (17)</td>
<td>0.60</td>
</tr>
<tr>
<td>Moderate renal disease</td>
<td>92 (7)</td>
<td>62 (8)</td>
<td>30 (5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.09 ± 1.76</td>
<td>1.34 ± 2.06</td>
<td>0.74 ± 1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>761 (57)</td>
<td>396 (51)</td>
<td>365 (65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE or ARBs</td>
<td>583 (44)</td>
<td>351 (46)</td>
<td>231 (41)</td>
<td>0.12</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>523 (39)</td>
<td>307 (40)</td>
<td>216 (38)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diuretic</td>
<td>627 (47)</td>
<td>349 (45)</td>
<td>278 (50)</td>
<td>0.13</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>91 (36-248)</td>
<td>90 (33-286)</td>
<td>92 (38-214)</td>
<td>0.99</td>
</tr>
<tr>
<td>BNPratio</td>
<td>1.01 (0.42-2.36)</td>
<td>0.91 (0.37-2.39)</td>
<td>1.13 (0.56-2.30)</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.0 (0.9-1.2)</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0 (0.9-1.2)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or median (25th to 75th percentile).  
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; BNPratio = B-type natriuretic peptide ratio to upper limit of normal for age, sex, and assay.

BPN clinical activation noted in 50% of patients (36% having BNPratio of 1 to 4 and 14% >4).

Among our 1,331 patients, 561 (42%) underwent a mitral valve surgery within 3 months. These patients were younger (62 years vs. 66 years), more often male (70% vs. 63%), had fewer comorbidities (Charlson score 0.74 ± 1.15 vs. 1.34 ± 2.06) and had more severe DMR (all p < 0.005) (Tables 1 and 2).

Overall survival in the whole cohort. During a mean follow-up of 5.1 ± 2.6 years, there were 818 mitral valve surgeries and 229 deaths among the total cohort of 1,331. Overall survival at 2, 5, and 8 years was 92 ± 1%, 85 ± 1%, and 75 ± 2%, respectively. In univariable analysis, expressed as continuous variables, ln BNP (HR: 2.19; 95% CI: 1.96 to 2.44; p < 0.0001) and ln BNPratio (HR: 1.85; 95% CI: 1.66 to 2.06; p < 0.0001) were associated with increased overall mortality.

However, patients with higher absolute BNP were older (p < 0.0001) and more often women (all p < 0.0001), and patients with higher BNPratio were older (p < 0.0001). Hence, we adjusted for the background model described in the Methods section, which showed that lnBNP did not remain independently predictive of mortality (p = 0.43), whereas initial BNPratio (HR: 1.33; 95% CI: 1.15 to 1.54; p < 0.0001) remained an independent predictor of mortality after diagnosis. When added into the background model with initial BNP, initial BNPratio significantly improved the predictive value of the model (p < 0.0001). Also, a significant interaction (p = 0.04) between initial BNPratio and surgical treatment (as a time-dependent variable) suggested a different effect of the BNPratio on survival under medical management versus post-mitril surgery.

Overall survival in medically treated patients. Among the 770 patients who were under initial medical treatment, 257 subsequently underwent mitral valve surgery >3 months after diagnosis, and their medical follow-up was censored at that time. Hence, under purely medical treatment (3.9 ± 2.7 years), there were 156 deaths. Baseline characteristics of patients who were initially medically treated are presented in Tables 1 and 2, central column.

Under medical treatment, overall survival at 2, 5, and 8 years was 89 ± 1%, 79 ± 2%, and 64 ± 3%, respectively. The BNPratio (HR: 1.98; 95% CI: 1.74 to 2.24; p < 0.0001) was associated with increased mortality in univariable analysis and independently after adjustment for the background model (HR: 1.61; 95% CI: 1.34 to 1.93; p < 0.0001). The addition of initial BNPratio to the background comprehensive model of survival determinants showed that BNPratio considerably increased model predictive power (p < 0.0001), and the net reclassification index to predict death at 1 year under medical management was 16%.

BNP clinical activation (i.e., BNPratio >1) as a categorical variable was independently associated with

TABLE 2 Baseline Echocardiographic Characteristics of the Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Cohort (n = 1,331)</th>
<th>Initial Conservative Management (n = 770; 58%)</th>
<th>Immediate Mitral Surgery (n = 561; 42%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial volume, ml</td>
<td>108 ± 58</td>
<td>99 ± 54</td>
<td>123 ± 64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>56 ± 7</td>
<td>55 ± 7</td>
<td>58 ± 7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end systolic diameter, cm</td>
<td>35 ± 7</td>
<td>34 ± 7</td>
<td>36 ± 6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>64 ± 9</td>
<td>63 ± 9</td>
<td>65 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitral regurgitation severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>856 (64)</td>
<td>396 (52)</td>
<td>460 (82)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>407 (31)</td>
<td>309 (40)</td>
<td>98 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>68 (5)</td>
<td>65 (8)</td>
<td>3 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Effective regurgitant orifice area, cm²</td>
<td>0.44 ± 0.23</td>
<td>0.37 ± 0.20</td>
<td>0.54 ± 0.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant volume, ml</td>
<td>67 ± 31</td>
<td>55 ± 26</td>
<td>84 ± 29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mm Hg</td>
<td>45 ± 18</td>
<td>44 ± 18</td>
<td>47 ± 18</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). 
LV = left ventricular.
excess mortality (HR: 2.51; 95% CI: 1.62 to 3.99; \( p < 0.0001 \)). Survival at 8 years under medical management was 82 ± 4% for the normal BNP group versus 46 ± 5% for the activated BNP group (\( p < 0.0001 \)). Each degree of BNP activation (moderate [BNPratio 1 to 4] or severe [BNPratio >4]) was associated with incremental excess mortality versus the normal BNP reference group. Additionally, the severely elevated BNPratio group demonstrated 60% increased mortality compared with the moderately elevated BNPratio group (Figure 1A).

Including or censoring patients with initial surgical treatment at the time of surgery did not influence the results (Online Appendix). Adjusting the background model by effective regurgitant orifice or regurgitant volume instead of MR severity grade provided similar results (Online Appendix).

The effect of BNP activation was consistent across multiple DMR subgroups without interaction among BNP activation and atrial fibrillation (\( p = 0.59 \)), dyspnea (\( p = 0.60 \)), DMR severity (\( p = 0.94 \)), age (\( p = 0.73 \)), sex (\( p = 0.79 \)), LVEF (\( p = 0.84 \)), body surface area (\( p = 0.87 \)), Charlson score (\( p = 0.67 \)), or creatinine level (\( p = 0.46 \)), with similar risk ratios attached to BNP activation across all subgroups even after adjustment for age and sex (Figure 2). Specifically, in patients with severe DMR treated medically, BNPratio was independently predictive of survival after comprehensive adjustment (\( p = 0.02 \)). The 5-year survival under medical treatment in patients with severe DMR was vastly superior in those with a normal BNPratio (93 ± 2%) compared with those with moderately and severely elevated BNPratio (70 ± 6% and 38 ± 8%, respectively; \( p < 0.0001 \)).

**OVERALL SURVIVAL IN PATIENTS TREATED MEDICALLY AND WITHOUT CLASS I OR IIa TRIGGER.** Among our 770 patients treated medically, 287 were asymptomatic, with no atrial fibrillation, no heart failure, no pulmonary hypertension, LVEF ≥60%, and LV end systolic diameter ≤40 mm. After comprehensive adjustment, lnBNPratio was a strong predictor of mortality under medical treatment (HR: 2.36; 95% CI: 1.45 to 3.95; \( p = 0.0007 \)). Accordingly, BNP activation (i.e., BNPratio >1; HR: 2.68; 95% CI: 1.12 to 6.70; \( p = 0.03 \)) was independently associated with mortality (Figure 3) as well as BNPratio groups (\( p = 0.0001 \)). Moderately elevated BNPratio (i.e., 1 < BNPratio ≤4; HR: 2.48; 95% CI: 1.05 to 6.20; \( p = 0.04 \)) and severely elevated BNPratio (i.e., BNPratio >4; HR: 20.14; 95% CI: 4.23 to 73.15; \( p = 0.0009 \)) compared with patients with normal BNPratio (i.e., BNPratio ≤1). In this particular subgroup, the addition of lnBNPratio to the background comprehensive model of survival determinants, showed that the BNPratio considerably increased model predictive power (\( p = 0.01 \)), and the net reclassification index to predict death at 1 year under medical management was 10%.

**OVERALL SURVIVAL IN PATIENTS WITH INITIAL SURGICAL TREATMENT.** Among the 561 patients who underwent mitral valve surgery within 3 months of diagnosis, a large majority (96%) underwent mitral valve repair. There were 9 deaths within 30 days after surgery leading to an operative mortality of 1%. During mean post-operative follow-up of 5.0 ± 2.7 years, there were 54 deaths. Baseline characteristics of patients who underwent mitral valve surgery within 3 months after diagnosis are presented in Table 1, right column.

After mitral valve surgery, overall survival at 2, 5, and 8 years was 96 ± 1%, 92 ± 1%, and 83 ± 3%, respectively. In univariable analysis, lnBNPratio was associated with increased mortality (HR: 1.62; 95% CI: 1.28 to 2.06; \( p < 0.0001 \)). Similarly to patients who were medically treated, BNP activation and groups of elevated BNPratio were univariate predictors of mortality compared with normal BNP (BNPratio ≤1; all \( p < 0.001 \)) (Figure 1B). However, after adjustment for the background model, BNP and BNPratio as continuous or nominal variable (all \( p > 0.23 \)) did not reach statistical significance as independent predictors of mortality (Figure 1B). When analyses were performed with all patients who underwent mitral valve surgery (i.e., immediate and delayed), the results were similar with no statistically significant relationship between the lnBNPratio (\( p = 0.43 \)), BNP activation (\( p = 0.47 \)), or elevated BNPratio group (\( p = 0.34 \)) and mortality after mitral valve surgery.

**DISCUSSION**

The main finding of this prospective, multicenter, international study was that BNP activation expressed using the BNPratio (i.e., the ratio of measured BNP to be expected maximal BNP value for age and sex of each patient) is a predictor of survival in patients with degenerative MR. Elevated BNPratio is linked to worse survival after diagnosis under medical treatment, independently of classical determinants of survival, with incremental predictive power and notable net reclassification index (Central Illustration). Furthermore, BNP is a quantitative marker of excess mortality, with higher activation levels associated with higher risk of mortality. Similar hazard ratios linked to BNP activation are observed in all subsets of DMR, and most specifically, in patients with severe DMR. Conversely, BNPratio was not an independent predictor of survival after mitral valve surgery. Hence, BNP activation is a powerful marker
of poor outcome in patients with significant DMR who are under medical treatment; this is not yet included in guidelines, but it is important to consider in the management of these patients.

**IMPORTANCE OF BNP IN MR.** Natriuretic peptides are secreted by the myocardium in response to stretch (13). Measurement and clinical use of BNP levels in cardiovascular diseases, such as heart failure or myocardial
infarction, has been largely documented and is well accepted to stratify risk and predict outcome (14–16). In valvular heart diseases and especially in MR, pilot studies have shown that BNP is linked to and integrates many other important characteristics, including symptoms, severity of DMR, atrial fibrillation, left atrial and ventricular volumes, myocardial performance, and pulmonary artery pressure (4,5,17). However, BNP activation in MR is much less prominent in the organic than in the functional subset (5), raising concerns that it may be an insignificant predictor of outcome. Pilot data suggests that elevated BNP levels may be of outcome significance. In dogs developing spontaneous DMR, BNP elevation may be associated with heart failure development (18,19). In humans, data on survival under medical management are minimal, but higher levels of BNP appeared to be associated with worse survival (4), although most patient values still fell within the normal range. Other pilot studies suggest that BNP levels may act as a determinant of the rates of morbid events under medical management (7,8). However, the BNP-linked outcome could not be clearly separated from that attached to LV contractile reserve (20), and in small series, the concept of whether BNP was a surrogate or independent marker remained uncertain (21). A postoperative outcome link to BNP has also only been analyzed in small series and is considered controversial (22,23). Besides small size and soft endpoints, these studies’ BNP thresholds for risk varied considerably (31 to 145 pg/ml) and did not account for normal BNP ranges that change considerably with age, sex, and each specific assay (i.e., by calculating the patient-specific BNPratio). Expressed in that manner, in patients with valve disease activation of BNP (i.e., BNPratio >1) is a powerful independent predictor of mortality in aortic stenosis (26). Hence, our study was designed.
with these essential issues and gaps of knowledge in mind.

**BNPratio as a Predictor of Outcome in DMR.** Timing of mitral valve surgery for DMR remains controversial (27,28). A recent large, multicenter study demonstrated that early surgery (i.e., in asymptomatic patients) was associated with survival benefit (29). This association is probably linked to the fact that all triggers for surgical referral (class I: heart failure symptoms, impaired LVEF, and large LV end-systolic dimension; and class II: atrial fibrillation and pulmonary hypertension) are associated postoperatively with excess mortality (2). Thus, there is a clinical evolution toward early surgery for DMR. However, mitral valve surgery is not a benign procedure: operative mortality varies between 0.5% and 3.1%, and valve replacement (instead of repair) is performed nationwide in 20% to 30% of potentially repairable DMR patients (22-23). Hence, despite much progress achieved in the treatment of MR, it is essential to develop new markers of outcome that are simple and that can help determine which patients are at risk under medical management without implying the considerable risk attached to the major surgical triggers (1).

The BNPratio, as demonstrated in the present study, exhibits a biomarker profile of great interest in DMR. The association of BNPratio with excess mortality is powerful, particularly for patients who are initially managed medically. Conversely, BNPratio’s prognostic value is blunted after mitral surgery, suggesting successful interruption of deleterious myocardial damage after surgical correction of DMR. Thus, a BNPratio <1 is reassuring when no other triggers prompting valve repair are present. With BNP activation (BNP ratio ≥1), survival under medical management is affected independently of other triggers. More importantly, there is a quantitative link between the degree of BNP activation and the degree of excess mortality, so that higher BNPratios should be more alarming. Hence, the promptness with which surgical referral should be considered also may rely on BNPratio levels. Changes in BNPratio over time should not be missed (8), although more long-term studies are needed to evaluate this aspect. However, the data in the present, uniquely large, multicenter, international study demonstrates that a single BNPratio measurement at echocardiographic evaluation of DMR has considerable stand-alone value in determining prognosis, implying that BNP should be measured in routine practice, and its values should be integrated to the clinical decision-making process.

**STUDY LIMITATIONS.** Therapeutic decisions in the present study were left to the discretion of the patient’s treating physician, in accordance with centerspecific standards of clinical practice and following individual interpretation of international heart valve guidelines (1,35,36). Thus, the patients’ personal physicians interpreted the symptoms, the signs, their estimated link to the DMR, and the balance of risk/benefit ascribed to mitral surgical indications. However, the high percentage of valve repair achieved shows that all centers met the requirements to qualify as advanced valve repair centers. Our study is multicenter with a wide range of absolute values of BNP normal range, but BNPratio values that are normalized to each center’s scale of normal provide a standardized approach to BNP utilization. MR assessment was performed in each center without a core laboratory as part of routine practice according to MR assessment guidelines (29,30). Hence, it is important to note that no center effect was found regarding DMR severity, LV geometry/function, symptoms, or mitral valve surgery and their interaction with BNP’s effect on outcome (all p > 0.21). Moreover, no center or assay effect was found with regard to the relationship between BNPratio and survival (Online Appendix). Centers, guideline adherence, period of enrollment, hospitalization versus ambulatory, and geographical origin (Europe vs. America) of patients did not affect the predictive value of BNPratio (p > 0.15) (Online Appendix). Patients who were excluded according to eligibility criteria were not kept in the study database,
so their effect on BNP cannot be analyzed. N-terminal pro-BNP was not measured in the present study, and our data cannot affirm an equivalence between peptides measured, which implies that this issue will have to be addressed in future studies.

**CONCLUSIONS**

This prospective, multicenter, international study showed that BNP activation, expressed as BNPratio, is a powerful predictor of survival in medically-managed patients with degenerative MR. Elevated BNPratio at DMR diagnosis is linked to worse survival under medical treatment, independently of classical determinants of survival, with incremental predictive power and notable net reclassification index. Furthermore, BNP is a quantitative marker of excess mortality with a higher activation level associated with a high risk of mortality. Hazard ratios linked to BNP activation are observed in all subsets of DMR, specifically in patients with severe DMR. BNPratio was not an independent predictor of survival after mitral valve surgery. Hence, BNP activation is a marker of poor survival in patients with significant DMR who are under medical treatment. BNP is not yet included in guidelines, but is essential to consider in the management of patients with DMR.

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COMPETENCY IN MEDICAL KNOWLEDGE: The blood level of BNP, when normalized for age, sex, and assay, is an independent predictor of heart failure and mortality in patients with DMR, but its prognostic effect is ameliorated by mitral valve surgery.

REFERENCES


KEY WORDS brain natriuretic peptide, degenerative mitral regurgitation, Doppler echocardiography, survival, valvular heart disease

APPENDIX For an expanded Methods and Results section, please see the online version of this article.