Plasma B-Type Natriuretic Peptide Levels and Recurrent Arrhythmia After Successful Ablation of Lone Atrial Fibrillation

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Background—Plasma B-type natriuretic peptide (BNP) is abnormally elevated in patients with lone atrial fibrillation (AF). The exact significance and prognostic implications of this elevation have yet to be determined. Little is known about BNP in lone AF patients undergoing arrhythmia ablation. We sought to determine the relationship between BNP levels and the risk of recurrent arrhythmia after ablation of lone AF.

Methods and Results—We followed up 726 patients with lone AF undergoing first-time arrhythmia ablation. All had BNP levels measured on the day of ablation with the point-of-care Triage Meter assay (Biosite Diagnostics, San Diego, CA). At baseline, factors associated with elevated BNP levels in multivariable linear regression analysis (with log BNP being the dependent variable) were older age (β regression coefficient for +1-year change, 0.025; P<0.0001), longer duration of AF (β for +1-year change, 0.031; P<0.01), nonparoxysmal AF (versus paroxysmal; β, 0.52; P<0.0001), and larger left atrial size (β for +1-cm² change, 0.040; P<0.0001). The BNP levels were strongly associated with arrhythmia recurrence in univariate- (hazard ratio for +1-log-BNP change, 2.32; 95% confidence interval, 2.11 to 2.74; P<0.0001) and covariate- (hazard ratio for +1-log-BNP change, 2.13; 95% confidence interval, 2.06 to 2.38; P<0.0001) adjusted Cox proportional hazards analysis. The covariate-adjusted hazard ratios for recurrent arrhythmia were 1.6, 2.7, 4.3, and 5.7 for the second, third, fourth, and fifth quintiles, respectively, compared with patients in the lowest quintile (P for trend across quintiles <0.001).

Conclusions—B-type natriuretic peptide levels correlate with AF burden (chronicity, altered hemodynamics, and anatomic remodeling) in patients with lone AF and are strong predictors of recurrent arrhythmia after ablation. Elevated BNP levels may reflect increased cardiac chamber wall stress and/or intrinsic atrial disease, thus increasing the risk of arrhythmia recurrence. (Circulation. 2011;123:2077-2082.)

Key Words: atrial fibrillation ■ catheter ablation ■ natriuretic peptides
were found to have BNP elevation without significant atrial natriuretic peptide elevation.9 The exact significance and prognostic implications of these observations have yet to be determined. In particular, very few studies in the literature evaluated the natriuretic peptide axis in lone AF patients undergoing radiofrequency ablation of their arrhythmia.14–16 We sought to determine the relationship between BNP levels and arrhythmia recurrence after radiofrequency ablation of lone AF.

Methods

Study Population
All 1871 consecutive patients presenting to our institution for first-time AF ablation between January 2003 and December 2005 were included in our AF ablation data registry and screened for eligibility for the present study during routine clinical encounters scheduled in the 3-month period before to the procedure. Their medical history was reviewed, and all had transthoracic echocardiograms within 3 months before ablation. We aimed to follow a population with lone AF and no comorbid conditions that can predispose to AF recurrences. We excluded patients in a stepwise manner according to the following exclusion criteria (in order): previous catheter ablation, previous cardiac surgery, previously established diagnosis of hypertension or coronary disease, echocardiographic evidence of valvular disease, ventricular systolic or diastolic dysfunction, and established diagnosis of diabetes mellitus or sleep apnea (Figure 1). All included patients gave written informed consent before the mapping and ablation procedures and were enrolled in our prospectively maintained AF data registry. The Cleveland Clinic Foundation Institutional Review Board approved the study.

Pulmonary Vein Isolation Procedure
Our pulmonary vein isolation (PVI) protocol has been described in detail.31 In brief, all antiarrhythmic drugs were stopped 4 to 5 half-lives before ablation, except for amiodarone, which was stopped a minimum of 4 to 5 months before the procedure. A transesophageal echocardiogram was obtained for patients presenting in AF if they had a subtherapeutic international normalized ratio within 3 weeks before ablation. A 10F phased-array intravascular ultrasound catheter (Siemens AG Inc, Malvern, PA) was placed in the right atrium to assist with performing transeptal punctures, to guide catheter location and manipulation within the left atrium, and to monitor for cardiac complications during ablation. All pulmonary vein antra were isolated in all patients under intracardiac echocardiographic guidance. Electric isolation was confirmed by the absence of pulmonary vein potentials along the antrum or inside the veins by use of a circular mapping catheter. In all patients, the superior vena cava was mapped and potentials were ablated when there was no phrenic nerve stimulation.

B-Type Natriuretic Peptide Assays
Plasma BNP levels were obtained in all patients before PVI on the day of ablation with the Triage Meter assay (Biosite Diagnostics, San Diego, CA). Whole-blood specimens were collected from each patient into a tube containing potassium EDTA, kept at room temperature, and analyzed within 4 hours of collection. The assay is a sandwich fluorescence immunoassay that uses a disposable device to which 250 µL whole blood or plasma is added. A murine recombinant polyclonal antibody is bound to the fluorescent label, and a murine monoclonal antibody against BNP is bound to the solid phase. The Triage Meter detects the fluorescent signal that reflects the BNP concentration. The precision, analytic sensitivity, and stability characteristics of the system have previously been described.18 The system correlates reasonably well with N-terminal prohormone BNP,19 and can reliably measure BNP concentrations ranging from 5 to 1300 pg/mL with a within-assay coefficient of variation of 9.5% to 13.9%.

Follow-Up
A 24-month follow-up postablation was considered for the study population. Intensive follow-up is usually considered for all patients undergoing AF ablation at our institution, especially in the first 2 years after the procedure. All success rates were determined in patients off antiarrhythmic medications. Atrial arrhythmias that occurred during the first 2 months after PVI were not counted as recurrences. This is considered a blanking period: arrhythmias occurring very early after PVI may be transient and do not necessarily imply failure of the procedure.20 Antiarrhythmic medications were generally continued during the 2-month period. These drugs included sotalol, propafenone, flecainide, or dofetilide, with the managing electrophysiologists determining the choice. Amiodarone was never used after ablation. Antiarrhythmics were discontinued in all patients during the third month after ablation unless continuing recurrent arrhythmia indicated the need for continued treatment. All patients with documented arrhythmia and those maintained on antiarrhythmics for control of AF beyond the blanking period were counted as recurrences.

All patients wore rhythm transmitters for a minimum of 3 months after PVI, and were asked to record when they experienced symptoms as well as weekly, even when asymptomatic. Additional event recorder monitoring was obtained beyond the 3-month period if patients had atrial tachyarrhythmia within the first 3 months or developed symptoms consistent with arrhythmia. Patients had scheduled clinical visits, 12-lead ECG, and 48-hour Holter monitoring at 3, 6, and 12 months after ablation and then yearly after the first year. Interrogation of implanted devices was also used when available to confirm arrhythmia recurrence. Arrhythmia recurrence was identified by symptoms with ECG documentation of an atrial tachyarrhythmia lasting ≥30 seconds on a 12-lead ECG, event recording, or Holter monitor recording.

Statistical Analysis
All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). A 2-sided value of P<0.05 was considered statistically significant. The Student t test was used for comparison of means as appropriate. Simple linear regression analysis was used to evaluate the relationships between BNP levels and clinical characteristics. Multivariable linear regression analyses were then carried out to determine the variables independently associated with baseline values of BNP with the natural log of BNP as the dependent variable. Only variables found to have a statistically significant association with BNP in univariate analyses were included in the multivariable model. The β regression coefficients from linear regression are reported. Kaplan-Meier curves were used to present cumulative arrhythmia recurrence during follow-up across BNP quintiles, which was compared by the log-rank test. Cox proportional hazards models were then used to assess the value of BNP and covariates for the prediction of AF recurrence. In these models, BNP levels were analyzed as a continuous variable for which the natural log of BNP was used and as categorized into quintiles. Univariate
Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
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<th>Study Population</th>
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<tbody>
<tr>
<td>n</td>
<td>726</td>
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<tr>
<td>Male sex, %</td>
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</tr>
<tr>
<td>Age, y</td>
<td>56.9±10.7</td>
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<tr>
<td>Nonparoxysmal AF, %</td>
<td>22.5</td>
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<tr>
<td>Duration of AF, median (first and third quartiles), y</td>
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<tr>
<td>Weight, kg</td>
<td>89.8±16.5</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>0.90±0.19</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55.3±5.0</td>
</tr>
<tr>
<td>Left atrial size, cm²</td>
<td>23.1±6.7</td>
</tr>
<tr>
<td>BNP, median (first and third quartiles), pg/mL</td>
<td>52 (37–87)</td>
</tr>
</tbody>
</table>

Failed antiarrhythmic, %

Propafenone 63.9
Flecainide 51.1
Sotalol 38.0
Amiodarone 16.1
Dofetilide 9.1

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; and BNP, plasma B-type natriuretic peptide.

Cox models were first used to determine factors associated with arrhythmia recurrence. All factors found to have a statistically significant relationship with arrhythmia recurrence in univariate analyses were included in the multivariable Cox model. Hazard ratios (HRs) and their 95% confidence intervals (CIs) are reported from the proportional hazards models.

Results

Of 1871 patients, 726 consecutive patients with lone AF were identified and included in the study (Table 1). The mean age of our patients was 56.9±10.7 years, and 70.7% were male. They had their arrhythmia for a median duration of 5 years before ablation (first and third quartiles, 4 and 7 years). The arrhythmia ablated was nonparoxysmal in 22.5% of patients. The median value of BNP level on the day of ablation was 52 pg/mL (first and third quartiles, 37 and 87 pg/mL). All patients had failed at least 1 antiarrhythmic medication with a negative dromotropic agent before referral for ablation. On the day of ablation, 284 patients (39.1%) presented in AF and had higher BNP levels than those who presented in sinus rhythm (natural log of BNP, 4.27±1.07 versus 4.09±1.09; P=0.02). Factors independently associated with elevated BNP levels in multivariable linear regression analysis (with log BNP as the dependent variable) were older age (β regression coefficient for 1-year change, 0.025; 95% CI, 0.012 to 0.037; P<0.0001), longer duration of AF (β for 1-year change, 0.031; 95% CI, 0.016 to 0.046; P=0.01), nonparoxysmal AF (versus paroxysmal; β, 0.52; 95% CI, 0.24 to 0.80; P<0.0001), and larger left atrial size (β for +1-cm² change, 0.040; 95% CI, 0.018 to 0.062; P<0.0001), suggesting an association between higher AF burden (chronicity, altered hemodynamics, and anatomic remodeling) and elevated BNP levels. During the blanking period, 276 patients (38%) had documented arrhythmia, with most occurring during the first month (231 patients, 83.7%). B-type natriuretic peptide levels were not found to be associated with arrhythmia documented during the blanking period (HR for +1-log-BNP change, 1.24; 95% CI, 0.96 to 1.53; P=0.12). Over the course of the third month after ablation, attempts were made to stop antiarrhythmics for all patients, but 18 (2.5%) had very early arrhythmia recurrence within days of stopping the antiarrhythmics; thus, the antiarrhythmics were ultimately restarted. By the end of the third month, 708 (97.5%) were off antiarrhythmics, but 24 (3.4%) had recurrence during the fourth month (cumulative arrhythmia recurrence at the end of the fourth month was 5.8%, excluding arrhythmia occurrence during the blanking period). Over a median follow-up of 26 months (range, 14 to 38 months) after ablation, 154 patients (21.2%) had AF recurrence and 572 patients (78.8%) remained arrhythmia free.

In univariate Cox proportional hazards analysis, factors associated with arrhythmia recurrence were found to be male sex (versus female; HR, 1.41; 95% CI, 0.92 to 1.63; P=0.021), older age (HR for +1-year change, 1.02; 95% CI, 1.01 to 1.03; P=0.003), higher body mass index (HR for +1-kg/m² change, 1.11; 95% CI, 1.04 to 1.31; P=0.001), nonparoxysmal AF (versus paroxysmal AF; HR, 1.87; 95% CI, 1.32 to 3.73; P<0.001), longer duration of AF (HR for +1-year change, 1.07; 95% CI, 1.05 to 1.11; P<0.001), lower left ventricular ejection fraction (HR for −1% change, 1.09; 95% CI, 1.03 to 1.31; P=0.02), larger left atrial size (HR for +1-cm² change, 1.08; 95% CI, 1.05 to 1.10; P<0.001), and rhythm on the day of ablation (AF versus sinus; HR, 1.34; 95% CI, 1.16 to 1.45; P=0.02). Importantly, BNP was found to be associated with arrhythmia recurrence (HR for +1-log-BNP change, 2.32; 95% CI, 2.11 to 2.74; P<0.001). In covariate-adjusted analysis, variables found to be independent predictors of arrhythmia recurrence were mass index (HR for +1-kg/m² change, 1.09; 95% CI, 1.02 to 1.28; P=0.02), nonparoxysmal AF (versus paroxysmal AF; HR, 1.98; 95% CI, 1.36 to 3.79; P<0.001), longer duration of AF (HR for +1-year change, 1.06; 95% CI, 1.04 to 1.39; P<0.001), larger left atrial size (HR for +1-cm² change, 1.14; 95% CI, 1.06 to 1.29; P=0.03), and higher plasma BNP (HR for +1-log-BNP change, 2.13; 95% CI, 2.06 to 2.38; P<0.001). The results of Cox proportional hazards analysis are summarized in Table 2.

The cumulative event rate of recurrent arrhythmia during the study follow-up increased with increasing BNP quintiles (P<0.01, log-rank test; Figure 2). The unadjusted HRs for recurrent arrhythmia were 1.9 (95% CI, 1.8 to 2.1), 3.8 (95% CI, 3.6 to 4.1), 6.8 (95% CI, 6.7 to 7.3), and 8.4 (95% CI, 7.8 to 9.4) for the second, third, fourth, and fifth quintiles, respectively, compared with patients in the lowest quintile (P for trend across quintiles <0.001). This strong and graded association persisted in multivariable analysis. The covariate-adjusted HRs for recurrent arrhythmia were 1.6 (95% CI, 1.5 to 1.8), 2.7 (95% CI, 2.5 to 2.9), 4.3 (95% CI, 4.1 to 4.6), and 5.7 (95% CI, 5.4 to 6.1) for the second, third, fourth, and fifth quintiles, respectively, compared with patients in the lowest quintile (P for trend across quintiles <0.001; Table 3).

Discussion

This study is the largest to date to evaluate the relationship between BNP and the risk of recurrent arrhythmia after...
Ablation of lone AF. A main finding in our study is that, in patients with lone AF, BNP correlates with AF burden (chronicity, altered hemodynamics, and anatomic remodeling with left atrial dilation) and is a strong and independent predictor of arrhythmia recurrence after AF ablation. This robust and graded association persisted even after adjustment for covariates associated with arrhythmia recurrence in univariate analyses. Importantly, BNP predicted recurrent arrhythmia more strongly than any previously described risk factors. The significance of this very strong association has yet to be determined, but the findings add significantly to our knowledge about the natriuretic peptide axis in patients with lone AF.

Members of the natriuretic hormones family have both regulatory and modulatory roles in the cardiovascular system. These include but are not limited to the modulation of baroreflexes, natriuresis, and vasodilation. In patients with systolic or diastolic dysfunction, natriuretic peptides are elevated, and have been associated with poor clinical outcomes. In AF patients, several studies reported elevated levels of natriuretic peptides even in the absence of heart disease. The effect of comorbidities predisposing to both the arrhythmia and BNP elevation is minimal in lone AF patients. The population of patients with AF in the absence of heart disease and comorbidities predisposing to the arrhythmia is therefore particularly interesting. In patients with lone AF, BNP levels are elevated even in sinus rhythm compared with healthy control subjects and patients with other supraventricular tachyarrhythmia. Furthermore, lower BNP levels in these patients were found to predict rhythm stability after successful cardioversion to sinus rhythm. Very few studies in the literature evaluated the natriuretic peptide axis in lone AF patients undergoing radiofrequency ablation of their arrhythmia. The main finding from these studies is that BNP levels are elevated at baseline and significantly decrease in patients who maintain sinus rhythm but not in those with recurrent arrhythmia.

The exact significance of elevated BNP levels in lone AF and their association with outcomes of cardioversion and ablation are not yet understood, but may reflect altered hemodynamics caused by atrial mechanical dyssynchrony and its effect on ventricular filling. In our study, BNP levels correlated with AF burden and also independently predicted arrhythmia recurrence. The observations by Ellinor et al suggest that BNP elevation in lone AF patients may have implications beyond the hemodynamic derangements caused by the arrhythmia. In their study, lone AF patients had discordant levels of atrial and B-type natriuretic peptide levels even in sinus rhythm. Their findings suggest that BNP is abnormally secreted in lone AF patients via a pathway other than atrial natriuretic peptide and is independent of the hemodynamic derangements that are usually associated with

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Table 2. Clinical Factors Associated With Recurrent Arrhythmia After Lone Atrial Fibrillation Ablation in Cox Proportional Hazards Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Covariate Adjusted*</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>1.41</td>
<td>0.021</td>
</tr>
<tr>
<td>Age, +1 y</td>
<td>1.02</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI, +1 kg/m²</td>
<td>1.11</td>
<td>0.001</td>
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<tr>
<td>Non–PAF vs PAF</td>
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<td>&lt;0.01</td>
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<tr>
<td>Duration of AF, +1 y</td>
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<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF, −1%</td>
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<td>0.02</td>
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<tr>
<td>Left atrial size, +1 cm²</td>
<td>1.08</td>
<td>&lt;0.001</td>
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<tr>
<td>Serum creatinine, +1 mg/dL</td>
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<td>0.14</td>
</tr>
<tr>
<td>HbA1c, +1 g/dL</td>
<td>1.03</td>
<td>0.06</td>
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<tr>
<td>Rhythm on day of ablation†</td>
<td>1.34</td>
<td>0.02</td>
</tr>
<tr>
<td>Natural log of BNP, +1 log</td>
<td>2.32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; BMI, body mass index; PAF, paroxysmal atrial fibrillation; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; HbA1c, glycated hemoglobin; and BNP, plasma B-type natriuretic peptide.

*Adjusted for covariates found to have a statistically significant relationship with arrhythmia recurrence in univariate analysis.

†AF versus sinus rhythm.

Figure 2. Cumulative event rate of recurrent arrhythmia after lone atrial fibrillation ablation during the study follow-up according to plasma B-type natriuretic peptide quintiles (log-rank P<0.01). Q1 through Q5 are the cumulative event rate curves in the first through fifth quintiles.
elevation of both peptides. This secretion pattern potentially represents a subclinical predisposition to the arrhythmia, with data suggesting that the source of BNP, typically secreted by ventricles, is the atria in lone AF patients. This elevation may reflect intrinsic atrial disease such as inflammation, fibrosis, or even subclinical atrial myocardial ischemia with microvascular dysfunction. In fact, an abnormal atrial substrate has been classically reported in lone AF patients. The determinants of elevated baseline BNP levels in our study were older age, longer duration of AF, larger atrial size, and nonparoxysmal AF, suggesting that BNP elevation may reflect a more advanced atrial disease in lone AF patients. An abnormal atrial substrate explains the relatively high recurrence rates with increasing quintiles after isolation of the pulmonary veins. Those patients with elevated BNP at baseline may benefit from more extensive atrial mapping and ablation at the time of the initial procedure.

The potential involvement of BNP in arrhythmogenesis is probable, but is not yet established. Our knowledge about the electrophysiological effects of BNP on the cardiac myocyte is limited, but the very few data in the literature addressing this issue suggest that it may be arrhythmogenic. B-type natriuretic peptide has been shown to inhibit the resting sympathetic activity of the heart, potentiating vagal activity through the cGMP pathway, which results in sustaining atrial fibrillatory rotors and potentially initiating and sustaining AF.

Several caveats should be noted for our study. Every effort was made to define a lone AF population with no comorbid conditions that can predispose to AF recurrences. However, we may have included patients with subclinical coronary disease or undiagnosed sleep apnea because no formal workup was done to rule out these conditions. Lone AF was therefore defined on the basis of clinical and echocardiographic criteria. It is important to mention that in our practice, all patients found to have symptoms suggestive of coronary disease or sleep apnea during routine clinical encounters before ablation are generally referred for diagnostic workup before PVI. In addition, 19 patients (2.6%) did not complete the planned 24 months of follow-up. However, these patients were accounted for in the final analyses (4 had recurrences and 15 remained arrhythmia free over a median follow-up of 22 months).

Conclusions

We found that BNP is a strong, independent predictor of arrhythmia recurrence after ablation of lone AF. Although elevated BNP levels may reflect increased AF burden, arrhythmia chronicity, and atrial anatomic remodeling, the strong association with arrhythmia recurrences persisted after adjustment for these covariates. Interestingly, in a population without heart disease and comorbidities predisposing to arrhythmia recurrences, BNP levels were stronger predictors for arrhythmia recurrence than any previously described risk factors. Elevated BNP levels may reflect increased cardiac chamber wall stress and/or intrinsic atrial disease in these patients, thus increasing the risk of arrhythmia recurrence.

Disclosures

None.

References


Table 3. Cox Proportional Hazards Regression Results for Plasma B-Type Natriuretic Peptide Categorized Into Quintiles as Predictors for Recurrent Arrhythmia after Lone Atrial Fibrillation Ablation

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Range of Quintiles, pg/mL</th>
<th>Patients With Recurrence, %</th>
<th>Recurrence Rate per 100 person-y</th>
<th>Unadjusted* HR 95% CI P‡</th>
<th>Covariate Adjusted† HR 95% CI P‡</th>
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<td>&lt;31</td>
<td>6.2</td>
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<tr>
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<td>10.2</td>
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<td>2.7</td>
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<tr>
<td>4</td>
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<td>18.71</td>
<td>6.8</td>
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<td>5</td>
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<td>37.0</td>
<td>22.89</td>
<td>8.4</td>
<td>5.7</td>
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</table>

HR indicates hazard ratio; CI, confidence interval.
*HRs for arrhythmia recurrence in increasing B-type natriuretic peptide quintiles compared with the first quintile.
†Adjusted for covariates found to have a statistically significant relationship with arrhythmia recurrence in univariate analysis.
‡P for trend across quintiles.
The exact pathophysiology of atrial fibrillation (AF) is obscured by the effects of the arrhythmia itself because it leads to both mechanical and electrical remodeling. This is particularly true for patients with lone AF, which is AF in the absence of heart disease or comorbidities predisposing to the arrhythmia. Plasma B-type natriuretic peptide is abnormally elevated in patients with lone AF, but the exact significance and prognostic implications of this elevation have yet to be determined. In the present study, we followed up 726 patients with lone AF undergoing first-time arrhythmia ablation over a median of 26 months after the ablation procedure. B-type natriuretic peptide levels were found to correlate with lone AF burden (chronicity, altered hemodynamics, and anatomic remodeling with left atrial dilation) and to be a stronger predictor of arrhythmia recurrence than previously described risk factors. This robust and graded association persisted (chronicity, altered hemodynamics, and anatomic remodeling with left atrial dilation) and to be a stronger predictor of arrhythmia recurrence after AF ablation than previously described risk factors. This robust and graded association persisted.
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