N-terminal pro-B-type natriuretic peptide level at long-term follow-up after atrial fibrillation ablation: A marker of reverse atrial remodeling and successful ablation

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Pro-BNP after AF ablation

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Abstract

Aims: We investigated the relationship between arrhythmia burden, left atrial volume (LAV) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) at baseline and after long-term follow-up of atrial fibrillation (AF) ablation.

Methods: We studied 38 patients (23 paroxysmal, six women, mean age 56±11) scheduled for AF ablation. LAV was calculated on the basis of computed tomography images at baseline and long-term follow-up, and arrhythmia burden was graded from self-reported frequency and duration of AF episodes.

Results: After a mean period of 22±5 months, 28/38 patients (11/15 persistent) were free from AF recurrence. At baseline there were no differences in mean LAV (125 vs. 130 cm^3, $p=0.7$) or median NT-pro-BNP (33.5 vs. 29.5 pmol/L, $p=0.9$) between patients whose ablation had been successful or otherwise. At long-term follow-up there was a marked decrease in LAV (105 vs. 134 cm^3, $p<0.05$) and level of NT-pro-BNP (7 vs. 17.5 pmol/L, $p<0.05$) in the successful ablation patients. NT-pro-BNP correlated with LAV both at baseline ($r=0.71$, $p<0.001$) and at follow-up ($r=0.57$, $p<0.001$). Arrhythmia burden correlated with both NT-pro-BNP ($r=0.47$, $p<0.01$) and LAV ($r=0.52$, $p<0.01$). A decrease in NT-pro-BNP at follow-up of > 25% of baseline value had a specificity of 0.89 and a sensitivity of 0.6 (receiver operator characteristics, accuracy 0.82) for ablation success.

Conclusions: NT-pro-BNP correlates with LAV and arrhythmia burden in AF patients and both NT-pro-BNP and LAV decrease significantly after successful ablation. A decrease in NT-pro-BNP of >25% from the baseline value could be useful as a marker of ablation success.

Keywords: Atrial fibrillation, ablation, natriuretic peptide, atrial volume, arrhytmia burden

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, and pulmonary vein (PV) isolation by radiofrequency ablation (RFA) has become the standard therapy for selected patients [1]. In paroxysmal AF, quite high success rates are reported with isolation of the PVs only [2], but in persistent and permanent AF extended ablation strategies may be required [3-4]. Triggers seem to be important for initiation of AF, but an arrhythmogenic substrate appears to be necessary for the perpetuation of long-lasting AF episodes [5-6]. Electro-anatomical remodelling of the atrial tissue leads to changes in atrial conduction, shortening of refractory period and atrial dilatation [7]. The increase in atrial size is correlated with the degree of atrial fibrosis [8] and may be used as a measure of the atrial remodelling process.

AF also causes changes in the endocrine functions of the atria, and AF patients have higher levels of natriuretic peptides [9-11]. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) correlates with left atrial (LA) size [12] and epidemiological studies have identified it as a predictor of the development of AF [13]. Successful ablation of AF may initiate a reverse remodelling process in the atria, and LA size and NT-proBNP may decrease after restoration of sinus rhythm [14-17].

In this study we aimed to investigate the relation between arrhythmia burden, left atrial size and NT-proBNP before AF ablation and after long-term follow-up in patients with normal left ventricular systolic function.

Methods

Patient characteristics

Thirty-eight consecutive patients with drug-refractory paroxysmal, persistent or longstanding persistent AF were included in the study. Demographics and clinical data were collected prior to the procedure (Table 1). Self-reported AF burden was graded according to a modified arrhythmia frequency and severity scale [18], with 1-10 points for each frequency and duration of AF episodes (range 2-20). They underwent their first electrophysiological study and RFA during the second half of 2007, and further procedures if necessary. Patients with impaired systolic heart function (left ventricular ejection fraction < 50%), renal failure (glomerular filtration rate < 60ml/min) or valvular diseases were excluded. At the end of the study patients were divided into two groups, with successful ablation or recurrence of AF. All patients provided written informed consent. The study was performed in accordance with the

Declaration of Helsinki, and was approved by the local ethics committee (Regional Ethics Committee of Western Norway).

Electrophysiological study and ablation procedure

Patients underwent electrophysiological study and RFA in a fasting, sedated state. Vascular access was obtained under local anaesthesia through the right and left femoral veins. In all patients, a 7F 20-pole steerable mapping catheter (Livewire™, St. Jude Medical Inc, St. Paul, MN) was positioned in the coronary sinus, looped around the tricuspid annulus. After transseptal puncture, a 10-pole circular mapping catheter (Lasso™, Biosense Webster, Diamond Bar, CA, USA or Optima™, St. Jude Medical Inc) was introduced into the LA through an 8.5F transseptal introducer. An irrigated RFA catheter (ThermoCool®, Biosense Webster or Navistar® ThermoCool, Biosense Webster) was advanced into the LA through the same puncture site without a second introducer. A three-dimensional mapping system (Ensite NavX™ (St. Jude Medical Inc.) or Carto™XP (Biosense Webster)) was employed to guide mapping and ablation.

All 38 patients underwent electrical isolation of all PVs, confirmed by a circular mapping catheter. Twenty-one patients underwent PV isolation only. The remainder were given additional ablation of the cavotricuspid isthmus line (n=2), mitral isthmus line and one line connecting the two superior veins (n=4), ablation on complex fractionated atrial electrograms (CFAE, n=6), or a combination of the approaches (n=5) at the operator's discretion. The RFA application time was 40-60 seconds at each site and energy was delivered with a cut-off temperature of 50° C. The maximum output and irrigation rates were 30-35 W, 15-20 mL/min (for PV isolation) and 30-40 W, 20 mL/min for linear or CFAE ablation (maximum 35 W in LA, 40 W in right atrium (RA)), respectively. A Stockert-Cordis (Biosense Webster) RFA generator was utilized.

Blood sampling

Blood samples from the antecubital vein were obtained in all patients one day before ablation, and again on the long-term follow-up visit. NT-proBNP was determined using an electrochemiluminescence immunoassay on a Modular E system (Roche Diagnostics, Mannheim, Germany). The analytical detection limit was 1 pmol/L.

Computed tomography (CT)

All patients underwent cardiac CT imaging on the day before the ablation procedure and at the final follow-up. Imaging was performed with a 64-slide scanner (Aquillion 64, Toshiba, Jpn) with or, in patients in AF during imaging, without ECG-gated techniques. We acquired data during one breath-holding, which began after a bolus injection of contrast (Iomeron

400mg I/mL). For ECG-gated images, we used 0.5 mm and for non-gated images 1.0 mm slide thickness.

LA three-dimensional reconstructions and calculations of LA volumes were performed using an automated algorithm in the Ensite NavX™ Verismo system (St. Jude Medical Inc.). Before the calculation of chamber volume, the pulmonary veins were excluded at the ostia. The LA auricle could not be reconstructed in all patients, and was therefore also excluded [19].

Follow-up

Patients were followed up as out-patients at our clinic or by their local hospitals and referring cardiologists. All patients underwent clinical examination and at least one Holter registration at three and six months after the procedure. Additional clinical examination was performed if indicated by symptoms. Recurrence was defined as more than one episode of AF lasting more than 30 seconds after a one-month blanking period. At the end of follow-up all patients were examined at our clinic with a further seven days of heart rhythm monitoring using a specially developed event recorder for AF detection (AF Alarm, Medtronic, MN), CT imaging and blood sampling.

Statistical analysis

For all statistical analyses the SPSS software package version 17.0 (SPPS Inc., IL, USA) was used. Discrete variables are reported as counts (percentages) and continuous variables as mean ± SD or median and range for non-normal distributed data. Statistical comparisons were performed using the χ^2 or Fisher exact test for discrete variables. Continuous variables were assessed for characteristics of distribution by use of the Kolmogorov-Smirnov test and NT-pro-BNP was identified as non-normal distributed. Comparisons were performed using Student's t-test for parametric data and Mann-Whitney-U test for non-parametric data. Correlations were calculated using linear regression analysis and Spearman's rank correlation tests. A p-value of <0.05 was considered to be statistically significant. A receiver operator characteristic curve and best cut-off were calculated and plotted using R version 2.12.0 (The R Foundation for Statistical Computing, Austria).

Results

Clinical and procedural data

Demographics and procedural data are shown in Table 1. There were no differences in the distribution of co-morbidity, pre-procedural echocardiography data or procedure time in the two groups. There were more women in the AF recurrence group; otherwise the demographic data were similar. At baseline, 23 (60%) patients were regarded as paroxysmal, 4 (11%) as persistent and 11 (29%) as longstanding persistent AF. All patients had tried at least one anti-arrhythmic drug at referral, but none were still using amoidarone. Mean AF burden was 13.7 ± 4.4 before ablation. One patient in the success group had a minor, asymptomatic PV narrowing (approximately 30% based on the CT reconstruction) at follow-up. No other procedure-related complications, such as cardiac tamponade, atrio-esophageal fistula or major bleeding were observed in any of the patients.

Clinical follow-up

At mean follow-up of 22 ± 5 months, fourteen patients (37%) had undergone an additional ablation procedure because of recurrence of AF, and the mean number of procedures performed per patient was 1.4 ± 0.5 (1.3 for paroxysmal and 1.6 for persistent AF, p=0.09). Anti-arrhythmic drugs were continued in all patients at least three months after ablation and then discontinued if freedom of AF. After the last procedure the mean follow-up time was 17 ± 7 months. At the end of the study, 28/38 patients (74%) (11/15 persistent/longstanding persistent – 73%) were free of AF recurrence, while two (one paroxysmal and one persistent AF) were still on anti-arrhythmic drugs. One patient with longstanding persistent AF at baseline was still in continuous but asymptomatic AF. Two patients with late recurrence of AF were scheduled for new ablation procedures. The remaining seven patients with recurrence experienced a lower AF burden and a better quality of life, and by the time of follow-up had not been referred for new procedures.

Natriuretic peptides and atrial size

Baseline median NT-pro-BNP for all patients was 32.0 (range 2-179) pmol/L and demonstrated a statistically significant decrease at long-term follow-up (9.5, range 1-127 pmol/L, p< 0.001). Mean left atrial volume was 126.4 ± 35.7 mL at baseline and fell to 113.5 ± 33.5 pmol/L after ablation, p< 0.001. There were no differences in mean atrial volume or NT-pro-BNP between patients with or without successful ablations at baseline, but at long-term follow-up there was a marked decrease in atrial volume and level of pro-BNP only in those whose ablation had been successful (Figure 1). NT-pro-BNP correlated with atrial volume at both baseline (y=0.79x – 61, r=0.71, p<0.001) and at follow-up (y=0.43x – 31, r=0.57, p<0.001).

There was also a small and statistically significant decrease in the anterior-posterior diameter of the LA after ablation (40.1 ± 5.9 vs. 41.7 ± 7.1 mm, p=0.03), but the difference between patients whose ablation had or had not been successful was not statistically significant (39.1 ± 6.1 vs. 42.6 ± 3.4 mm, p=0.15).

A decrease in the level of NT-pro-BNP at follow-up indicated successful ablation. The area under the curve for percentage reduction in NT-pro-BNP was 0.805 (Figure 2) and the best cut-off for percentage NT-pro-BNP reduction by maximizing accuracy was -25% (accuracy 0.82, sensitivity 0.6 and specificity 0.89); by minimizing distance from perfect classification it was -50% (accuracy 0.71, sensitivity 0.8, specificity 0.68).

The self-reported AF burden correlated with both NT-pro-BNP ($r=0.47$, $p<0.01$) and atrial volume ($r=0.52$, $p<0.01$) at baseline. When patients were stratified for AF burden, statistically significant increases in atrial volume and NT-proBNP were demonstrated with increasing AF burden (Figure 3).

Discussion

We measured the levels of NT-pro-BNP and LA volume at baseline and long-term follow-up after RFA for AF. Our findings demonstrate a correlation between self-reported arrhythmia burden, LA volume and NT-pro-BNP at baseline. At long-term follow-up there was a marked decrease in LA volume and NT-pro-BNP in patients whose ablation had been successful. Those with recurrence of AF showed no such differences.

NT-pro-BNP

NT-pro-BNP is the inactive, more stable pro-hormone of B-type natriuretic peptide. Hwang *et al* [12] showed that the measurement of NT-pro-BNP added incremental predictive value to LA size and diastolic function before AF ablation. In patients with preserved left ventricular systolic function, AF and LA size have been shown to be independent predictors of NT-proBNP [10, 20]. In our study, baseline values of NT-pro-BNP and LA size (including volume and echocardiographic LA diameter) did not differ in patients whose ablation had or had not been successful. The heart rhythm was not systematically recorded at the time of blood sampling. In patients with a resent onset of AF before blood sampling, this might have increased the measured NT-pro-BNP level. In accordance with previous studies [16, 21-22], baseline NT-pro-BNP values decreased significantly in patients after successful restoration of sinus rhythm. Patients with recurrence of AF had no significant reduction in median NT-pro-BNP after ablation. Some recurrent AF patients yet had a major reduction in AF burden after ablation, which might contribute to a reduction in NT-pro-BNP. We included patients with paroxysmal AF and relatively low AF burden (mean 13.7/20; range 8-20). Several of these patients had a baseline NT-pro-BNP well within the normal range, yet there was a statistically significant decrease of NT-pro-BNP in patients after successful ablation which correlated with the reduction in LA volume. Measurement of NT-pro-BNP at baseline and follow-up may therefore add value to the clinical evaluation of ablation success. NT-pro-BNP measured before ablation was not identified as a valid predictor of ablation outcome.

CT imaging

We used an automated algorithm based on three-dimensional co-ordinates from the reconstructions of the cardiac CT to calculate LA volumes. This method has not previously been published in studies of this type. The normal standard for calculating LA volume involves manually tracing each cross-sectional image of the CT scan [23]. The automated approach used in our study revealed a close correlation to this method. In clinical practice, LA diameter measured by echocardiography is the most widely used method of measurement , but Hof *et al* found a poor correlation between LA diameter and LA volume as measured using CT [24]. In our study, the difference in LA size between successful or unsuccessful ablated patients was only significant using atrial volumes, not LA diameters.

Atrial size

AF causes atrial remodelling and leads to enlargement of the atria [5-6]. These processes may be reversible. A reverse remodelling process takes place after successful restoration of sinus rhythm [25-26]. Reant *et al* described an improvement in left ventricular systolic and diastolic function and a decrease in LA size measured by echocardiography after catheter-based ablation [26]. In patients with recurrent AF, increases in LA dimensions have been shown [27], but our study does not reproduce this finding. Some of our patients whose ablation was unsuccessful experienced a marked decrease in AF burden, which may have influenced the degree of LA dilatation. Previous studies have demonstrated that a larger LA predicts worse outcome after AF ablation, that pre-procedural measurements of LA volume may be useful to identify patients for ablation restricted to PV isolation, and that patients with larger LA volumes need additional ablation [28]. Our study did not identify pre-ablation LA size as a valid predictor of ablation outcome.

The decrease in atrial size may be caused in part by the formation of atrial scars after ablation. Such scar formation should also occur in patients with recurrence of AF after ablation. Neither the total ablation time nor the proportion of patients with ablation additional to PV isolation were different in patients with or without AF recurrence in this study. It might therefore be reasonable to assume that the main contributor to the reverse remodelling seen after ablation is the restoration of sinus rhythm.

There is evidence that LA size predicts the cardiovascular outcome in a population [29]. Thromboembolization from the LA auricle is one of the most important causes of AF-related stroke events. Dilatation and impaired function of the auricle has been associated with thrombus formation. Moreover, the LA auricle undergoes reverse remodelling after successful AF ablation [30], which could theoretically indicate a decrease in thromboembolic risk after ablation. In the present study, the LA auricle was excluded from the volume calculations. Further studies of this topic are needed.

Recurrence of AF

There were more women in the recurrence group; otherwise there were no differences in baseline characteristics in patients with or without AF recurrence. There was a tendency to more ablation procedures in patients with successful ablation, but the difference was non-significant. However, this might indicate that a higher success rate could have been achieved with repeated procedures in patients with AF recurrence. Some patients nevertheless experience a significant clinical improvement even after ablation that was unsuccessful in curing AF. After ablation, asymptomatic AF might be present and twentyfour-hour Holter monitoring might not provide a true success rate [31]. All our patients had at least one additional seven-day event recording at long-term follow-up and a total of six asymptomatic AF episodes were revealed. One recurrent AF patient experienced a purely asymptomatic recurrence, other patients with registered asymptomatic episodes had known symptomatic AF.

Study limitations

This study was not randomized and patients received a different ablation approach based on their type of AF, but the demographical and procedural data were similar in patients whose outcomes were or were not successful. Atrial fibrillation during CT imaging excludes an ECG-gated technique, and in patients whose rhythms were different at baseline and follow-up this might have confounded the results.

Arrhythmia burden at baseline was based on a self-reported arrhythmia scale. Patients with asymptomatic AF episodes might therefore have underestimated their true AF burden.

Finally, there exists the possibility of measurement bias for volume estimations due to the inclusion of parts of the left atrial auricle or the PVs.

Conclusions

NT-pro-BNP correlates with atrial volume and arrhythmia burden in AF patients. Both NT-pro-BNP and atrial volume decrease significantly after successful ablation, but not in patients with recurrence of AF. A decrease in NT-pro-BNP of >25% from the baseline value may be useful as a indicator of ablation success.

Acknowledgements

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Conflict of interests

Consultant fees, St.Jude Medical (Chen and Solheim) and Nordic electrophysiological research grant, Biosense Webster (Schuster).

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Table 1. Baseline characteristics and procedural data

Patient characteristics	***Successful ablation N = 28***	***Recurrence of AF N = 10***	***P-* value**
Age (years)	56 ± 12	57 ± 11	0.90
Female (%)	2 (11)	4 (40)	0.04 *
Duration of AF (years)	10 ± 7	12 ± 8	0.52
Number of AADs	1.9 ± 1.0	2.0 ± 0.7	0.85
Paroxysmal AF (%)	19 (68)	6 (60)	0.47
AF burden	13.7 ± 3.9	13.7 ± 5.2	0.99
Hypertension (%)	11 (39)	4 (40)	0.62
Coronary heart disease (%)	3 (11)	1 (10)	0.72
Left ventricular ejection fraction (%)	61 ± 6	62 ± 5	0.75
Echocardiographic left atrial diameter (mm)	43 ± 6	45 ± 7	0.38
Number of ablation procedures	1.7 ± 0.8	1.2 ± 0.7	0.10
PVI only (%)	15 (54)	6 (60)	0.27
Procedure time (min)	236 ± 83	213 ± 58	0.42
Total ablation time (min)	54 ± 20	47 ± 14	0.33

AF=Atrial fibrillation, AAD=Anti-arrhythmic drug, PVI=Pulmonary vein isolation. AF burden = Self-reported frequency and duration of AF episodes, scored from 2 to 20.
*Statistically significant difference between groups.

Legends

Figure 1

Median plasma pro-brain natriuretic peptides (NT-pro-BNP) and mean left atrial volume (LAV) at baseline (BL) and follow-up (F-U). There were no differences in baseline values in patients with or without recurrence of atrial fibrillation (AF).

Figure 2

Receiver operator characteristics curve for percentage change in NT-pro-BNP. AUC = area under the curve.

Figure 3

Baseline median NT-pro-BNP and mean left atrial volume (LAV) in patient tertiles, based on self-reported atrial fibrillation burden (AFB) (first tertile AFB < 12, second tertile AFB 12-14, third tertile AFB > 15). The differences between the first and second tertile were not statistically significant (NT-pro-BNP p=0.14, LAV p=0.07), between the second and third tertile there were a statistically significant difference for NT-pro-BNP (p<0.05), but not for LAV (p=0.10).

Figure 1

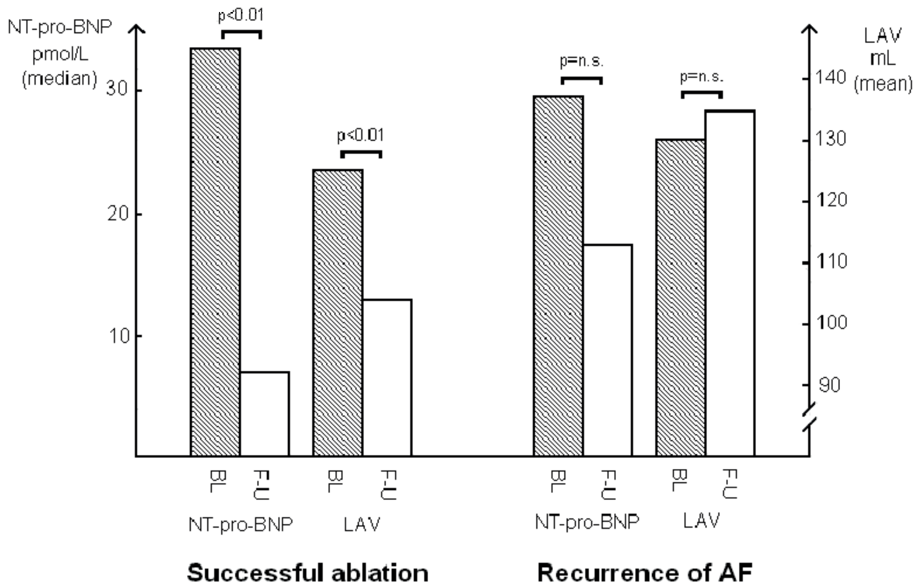
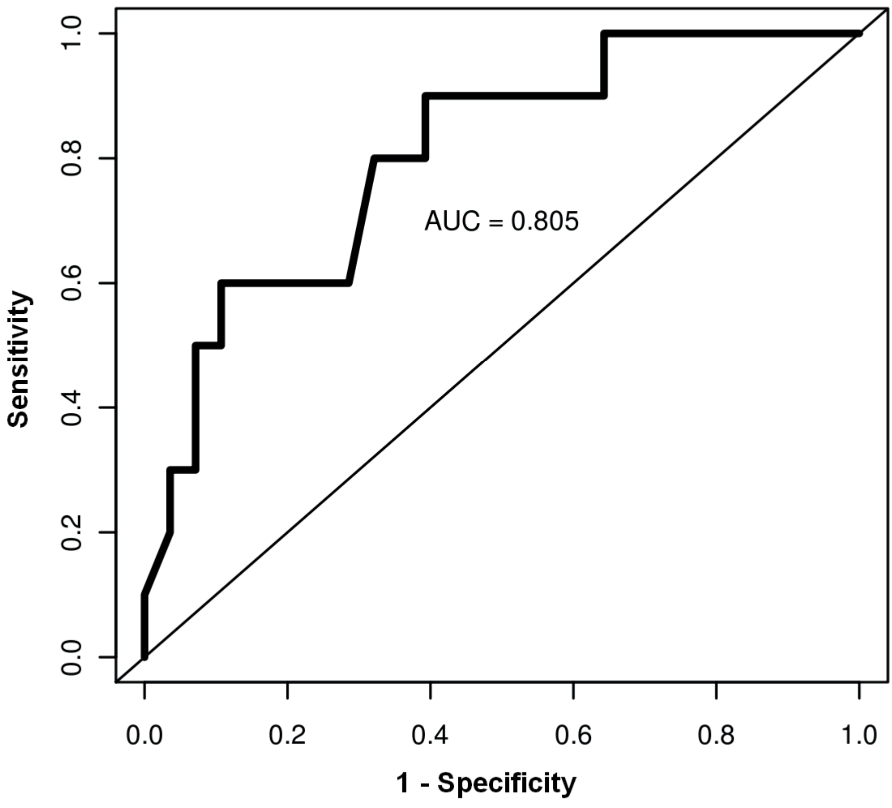

NT-pro-BNP
pmol/L
(median)
30
20
10
p<0.01
p<0.01
p=n.s.
p=n.s.
LAV
mL
(mean)
140
130
120
110
100
90
BL
F-U
BL
F-U
BL
F-U
BL
F-U
NT-pro-BNP
LAV
NT-pro-BNP
LAV
Successful ablation
Recurrence of AF

Figure 2


AUC = 0.805
Sensitivity
0.0
0.2
0.4
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0.8
1.0
1 - Specificity
0.0
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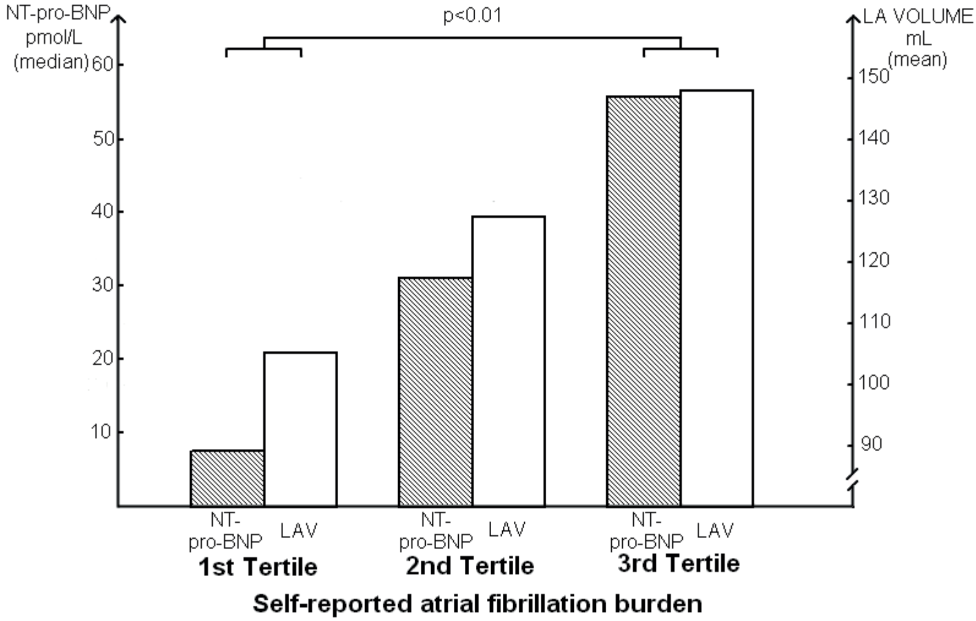
0.4
0.6
0.8
1.0

Figure 3


NT-pro-BNP
pmol/L
(median)
60
50
40
30
20
10
p<0.01
LA VOLUME
mL
(mean)
150
140
130
120
110
100
90
NT-
pro-BNP
LAV
1st Tertile
2nd Tertile
3rd Tertile
Self-reported atrial fibrillation burden