

Usefulness of N-terminal-pro B-type natriuretic peptide as a heart failure marker in patients undergoing percutaneous left atrial appendage occlusion

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Abstract

Background: The left atrial appendage is involved in secretion of N-terminal-pro B-type natriuretic peptide (NT-proBNP). Percutaneous left atrial appendage occlusion (LAAO) for prevention of stroke may cause variations in NT-proBNP release.

Aim: This study aimed to assess the diagnostic value of NT-proBNP after LAAO.

Methods: The study group comprised 53 patients in whom LAAO was performed. The patients with heart failure (HF) and reduced ejection fraction (EF) were allocated to group I (n = 16) whereas patients with no HF symptoms and EF > 40% were allocated to group II (n = 37). The symptomatic patients with EF > 40% were excluded. NT-proBNP values were measured prior to LAAO, at one–two days, and at three-month follow-up. EF, six-minute walk test (6MWT), and peak oxygen consumption (VO₂max) were assessed 24 h prior to LAAO and after three months.

Results: Prior to LAAO the NT-proBNP level was higher in group I, when compared to group II (3084.74 ± 559.53 pg/mL vs. 808.02 ± 115.83 pg/mL, p < 0.01). In both groups there was a nonsignificant increase in NT-proBNP level at one–two days after LAAO (3100.14 ± 690.08 pg/mL in group I and 1012.09 ± 166.71 pg/mL in group II). At the three-month follow-up a further increase of NT-proBNP level in group I (3852.73 ± 1025.78 pg/mL) and a decrease in group II (855.03 ± 107.49 pg/mL) was observed. The pairwise comparison between the means of 6MWT and VO₂max showed no significant changes during follow-up. At baseline, NT-proBNP level of 988 pg/mL presented 87.5% sensitivity and 75.7% specificity for prediction of HF. Three months after LAAO, it increased to 1358 pg/mL (sensitivity 81.2%, specificity 78.4%).

Conclusions: When diagnosing HF in atrial fibrillation patients, the higher cut-off value of NT-proBNP should be used. NT-proBNP remains an appropriate diagnostic marker of HF in patients after LAAO.

Key words: heart failure, left atrial appendage occlusion, NT-proBNP

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INTRODUCTION

The N-terminal-pro B-type natriuretic peptide (NT-proBNP) is a known marker of heart failure (HF). It was shown that the NT-proBNP levels are increased in HF and, on the other hand, the low levels rule out HF [1]. Therefore, different recommendations concerning the diagnosis of HF advise the use of NT-proBNP or other natriuretic peptides in routine, clinical settings.

It was also shown that alterations in natriuretic peptides have a prognostic value. The concentration of natriuretic peptides on admission for acute HF predicts inpatient mortality [2]. Despite the absolute NT-proBNP values, the extent of decrease in NT-proBNP concentrations during admission and the absolute NT-proBNP concentration at one month after discharge are independent prognostic markers [3].

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Table 1. Characteristics of studied population

	Overall population (n = 53)		Group I (n = 16)		Group II (n = 37)	
	N	%	N	%	N	%
Male	36	67.92	15	93.75	21	56.76
CHA ₂ DS ₂ VASc:						
1	1	1.89	0	0	1	2.70
2	7	13.21	2	12.50	5	13.51
3	10	18.87	1	6.25	9	24.32
4	13	24.53	5	31.25	8	21.62
5	7	13.21	2	12.50	5	13.51
6	13	24.53	4	25.00	9	24.31
7	1	1.89	1	6.25	0	0.00
8	1	1.89	1	6.25	0	0.00
HASBLED:						
2	6	11.32	1	6.25	5	13.51
3	27	50.94	7	43.75	20	54.05
4	15	28.3	5	31.25	10	27.03
5	4	7.55	2	12.5	2	5.40
6	1	1.89	1	6.25	0	0.00
Hypertension	44	83.02	11	68.75	33	89.19
Diabetes	20	38.46	5	31.25	15	40.54
Liver insufficiency	3	5.66	3	18.75	0	0.00
Renal insufficiency	17	32.08	8	50.00	9	24.32
Paroxysmal atrial fibrillation	22	46.81	7	43.75	20	54.05

In the normal heart, the endocrine capacity resides in the atria. In response to the stretch of atrial myocytes, different natriuretic hormones regulating fluid homeostasis and blood pressure are secreted [4]. The concentration of natriuretic peptides may be increased in diseases concerning solely the atria (e.g. atrial fibrillation [AF]) [5]. However, in the case of ventricular diseases, the natriuretic peptides are also secreted in ventricles.

The left atrial appendage occlusion (LAAO) procedures are emerging as a safe and efficient method of stroke prevention in AF patients [6, 7]. The concept of percutaneous LAAO is based on the insertion of a self-expanding device in the left atrial appendage (LAA). Independently of their constructional differences, all closure devices used for LAAO cause the expansion of the LAA wall, which may result in the release of natriuretic peptides. On the other hand, after LAAO, the closure devices are covered by endothelium and thus the LAA is free of the pressure overload that may occur in the left atrium in HF patients. In turn, these procedures may cause a reduction of the natriuretic peptide synthesis.

The aim of the current study was to assess if NT-proBNP may be used as a reliable marker for HF patients who have undergone LAAO.

METHODS

Study population

Left atrial appendage occlusion procedures were performed in 53 patients diagnosed with permanent or paroxysmal AF. All qualified patients also had a high risk of stroke based on the CHA₂DS₂VASc scoring system (score ≥ 2). Mean CHA₂DS₂VASc score was 4.25 ± 1.57 and mean HASBLED score was 3.38 ± 0.86 . According to European Society of Cardiology guidelines HF with reduced ejection fraction (EF) was diagnosed in patients with HF symptoms and left ventricular (LV) EF $< 40\%$ [8]. The patients with HF and reduced EF prior to LAAO were allocated to group I (n = 16) and the remaining patients with no HF symptoms to group II (n = 37). The symptomatic patients with EF $> 40\%$ were excluded from the study. The patients with HF with reduced EF received the optimal pharmacotherapy for at least two weeks prior to LAAO. Characteristics of the studied population are presented in Table 1.

Study design

Prior to the LAAO procedures, all patients had transthoracic and transoesophageal echocardiograms. The patients with a significant valvular disease or LAA anatomy unsuitable

for percutaneous occlusion were excluded from the study. Amplatzer Cardiac Plug or Amplatzer Amulet were used to occlude LAA. All procedures were performed under general anaesthesia.

The blood samples were drawn and the functional capacity tests were performed 24 h prior to LAAO and at the three-month follow-up visit. Additionally, the blood samples were also collected one–two days after the procedure.

NT-proBNP assessment

In all patients participating in the study, the concentration of NT-proBNP was assessed in the blood samples drawn from the cubital vein. The blood samples were collected in tubes coated with EDTA. Blood was then centrifuged at 3000 r/min within 1 h of collection, and NT-proBNP levels were determined using the enzyme-linked immunosorbent assay (ELISA) in the hospital laboratory. The upper reference range of plasma NT-proBNP concentration was 125 pg/mL.

Functional capacity assessment

Cardiopulmonary exercise tests were performed using a motorised treadmill while undergoing 12-lead electrocardiogram (ECG) monitoring (Mac[®] 5000, GE Healthcare). Prior to the testing, all patients were instructed on the use of the mouth-piece, and they were also familiarised with walking on the treadmill, for approximately 10 min, followed by 10 min of rest. Each test was preceded by a complete calibration of the gas concentrations with a three-litre syringe, using primary standard gases and flow.

During the test, the grade was increased every 2 min and participants were encouraged to walk for as long as possible, in order to achieve anaerobic threshold and respiratory exchange ratio > 1.1. Metabolic gas exchange was measured continuously during exercise and it was averaged over 30-s intervals. Peak VO_2 was defined as the highest oxygen uptake for a given 30 s interval, within the last 60 s of exercise.

Six-minute walk test

The six-minute walk test (6MWT) was performed according to the American Thoracic Society guidelines. The heart rate, blood pressure, and oxygen saturation were measured before the test. Afterwards, patients were asked to walk at their own pace along a 30-m hospital corridor. The patients were asked to walk as much distance as possible in 6 min. Patients were allowed to stop if it was necessary, but they were encouraged to resume walking as soon as possible, if they could. At the end of the six-minute walk, the vital signs and oxygen saturation were measured again.

Statistical analysis

The quantitative parameters were presented as means and standard error with 95% confidence interval (CI), and the qualitative variables were presented as frequencies and

percentages. When the same quantitative parameter was measured in the same subject at different time points, then the repeated measures analysis of variance (ANOVA) was used. The variance analysis was validated with the sphericity test of Mauchly. When appropriate, both the Greenhouse-Geisser and Huynh-Feldt estimates were used as correction factors that were applied to the degrees of freedom used to calculate the p-value for the observed value of F. The diagnostic performance of NT-proBNP before and after LAAO was evaluated using receiver operating characteristic (ROC) curve analysis. The statistical significance of the difference between ROC curves was tested with the method of DeLong.

Ethics

The study protocol was approved by the Local Ethics Committee. Prior to any procedures, patients were informed about the aim and design of the study, and written, informed consent was obtained from all participants.

RESULTS

The baseline NT-proBNP plasma concentration for overall population ranged from 5 pg/mL to 7863 pg/mL, with the mean value 1495 ± 233.99 pg/mL (95% confidence interval [CI] 1025.78–1964.89). In samples obtained one–two days after LAAO, the NT-proBNP level increased to 1642.45 ± 269.39 pg/mL (95% CI 1101.87–2183.02). The slightly higher NT-proBNP concentrations were also observed in blood samples obtained at the three-month follow-up, when mean NT-proBNP concentration was 1759.99 ± 365.56 pg/mL (95% CI 1026.45–2493.55). The mean difference for pairwise comparison of NT-proBNP prior to and shortly after LAAO was 147.12 ± 142.90 (p = 0.92), and for NT-proBNP prior to LAAO and three months after was 264.67 ± 189.80 (p = 0.51).

A separate analysis of baseline NT-proBNP for group I and II showed that NT-proBNP concentration was significantly higher in group I, when compared to group II (3084.74 ± 559.53 pg/mL; 95% CI 1892.14–4277.34 vs. 808.02 ± 115.83 pg/mL; 95% CI 573.11–1042.92; p < 0.01, respectively).

Compared to baseline, the NT-proBNP concentration was higher in group I shortly after LAAO (3100.14 ± 690.08 pg/mL; 95% CI 1629.27–4571.02) and three months later (3852.73 ± 1025.78 pg/mL; 95% CI 1666.33–6039.13). However, the pairwise comparisons between baseline and later assessments did not reveal significant differences. The mean difference in NT-proBNP between measurements taken at the first two time points was 15.41 (p = 0.96) and between baseline and three months follow-up was 767.99, with p = 0.22.

A slight increase was observed also in group II. For the measurements of NT-proBNP repeated shortly after LAAO, the concentration reached 1012.09 ± 166.71 pg/mL (95%

CI 673.99–1350.20), but three months after LAAO the mean value of NT-proBNP decreased to 855.03 ± 107.49 pg/mL (95% CI 637.04–1073.03). The pairwise comparison of measurements performed at the first time point and the following two periods showed no differences (respectively, mean difference of 204.08 pg/mL [$p = 0.19$ for the first pair] and mean difference of 47.02 pg/mL [$p = 0.53$ for the second pair]). The results of NT-proBNP assessments are shown in Figure 1.

The distance covered by 6MWT before LAAO was 311.37 ± 15.38 m for the overall population. The 6MWT repeated at three-month follow-up visit did not significantly change and the mean distance was 323.15 ± 18.11 m ($p = 0.34$). The analysis of results obtained in 6MWT, separately for group I and group II, did not show any changes at the follow-up visit, when compared to the baseline. The mean difference in pairwise comparison was 11.79 m (95% CI –36.15–12.58).

The analysis of peak VO_2 consumption on cardiopulmonary stress test showed a slight increase in peak VO_2 consumption for the overall population at three-month follow-up visit, when compared to the results obtained at baseline. Before LAAO, the peak VO_2 consumption was 15.18 ± 0.76 mL/kg/min and at three-month follow-up visit it was 15.4 ± 0.72 mL/kg/min ($p = 0.70$). The same was observed in the sub-analysis performed for group I and group II. Peak VO_2 consumption in group I prior to LAAO was 14.50 ± 0.94 mL/kg/min and after LAAO it was 15.81 ± 0.80 mL/kg/min ($p = 0.16$). Similarly, in group II, peak VO_2 consumption shifted from 15.48 ± 1.02 mL/kg/min to 15.22 ± 0.99 mL/kg/min ($p = 0.73$).

The baseline mean LVEF in the overall population was $45.49 \pm 2.13\%$ (95% CI 41.20–49.78), and the mean difference at three-month follow-up was 1.39%, which was statistically not significant ($p = 0.37$). EF was significantly lower in group I (mean EF $26.23 \pm 1.78\%$, 95% CI 22.46–30.08), when compared to group II (mean EF $53.97 \pm 1.30\%$, 95% CI 51.22–56.72; $p < 0.01$). After LAAO, EF did not change significantly in group I (mean difference of EF -3.67 ; $p = 0.052$) or in group II (mean difference of EF 3.62%; $p = 0.08$).

At baseline, NT-proBNP cut-off value of 988 pg/mL had 87.5% sensitivity and 75.7% specificity for prediction of HF, in the studied population (Fig. 2). The area under ROC curve for NT-proBNP at baseline was 0.87 (95% CI 0.75–0.95). When the NT-proBNP plasma concentration in blood samples taken at three-month follow-up visit was used for prediction of HF, it showed that a higher cut-off value of NT-proBNP (1358 pg/mL) had lower sensitivity — 81.2%. The area under the ROC curve (AUC) for NT-proBNP at the three-month follow-up visit was 0.74 (95% CI 0.74–0.94). The results are shown in Figure 3. However, the pairwise comparison of ROC curves for baseline and three-month follow-up visit showed no significant differences between both ROC curves. The dif-

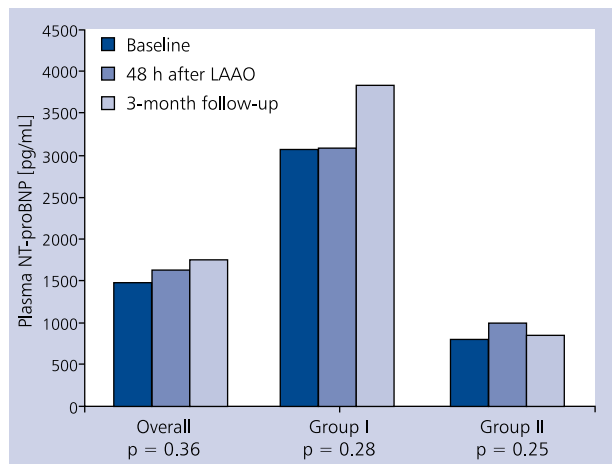


Figure 1. N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma concentration at baseline, 48 h after left atrial appendage occlusion (LAAO), and at three-month follow-up visit, and p value for within-subject effects

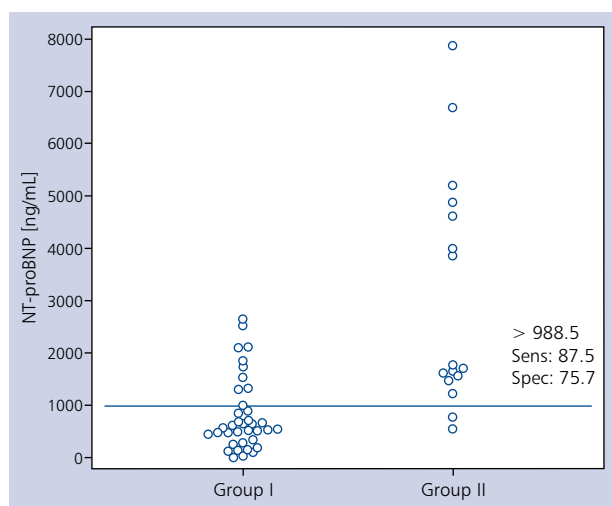


Figure 2. Diagnostic performance of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in samples taken at baseline

ference between both AUCs was 0.009 (95% CI –0.07–0.08; $p = 0.81$; Fig. 4).

DISCUSSION

NT-proBNP is considered to be a gold standard biomarker in the diagnosis and management of HF. The cut-off value of NT-proBNP in symptomatic patients differs depending on the initial symptoms. In the non-acute onset of HF symptoms, an exclusion point of NT-proBNP at 125 pg/mL is recommended [8]. Whereas, in the case of acute symptoms, a value of 300 pg/mL is thought to be abnormal. However, the increase of NT-proBNP concentration may occur in other conditions, including right ventricular overload, myocardial ischaemia,

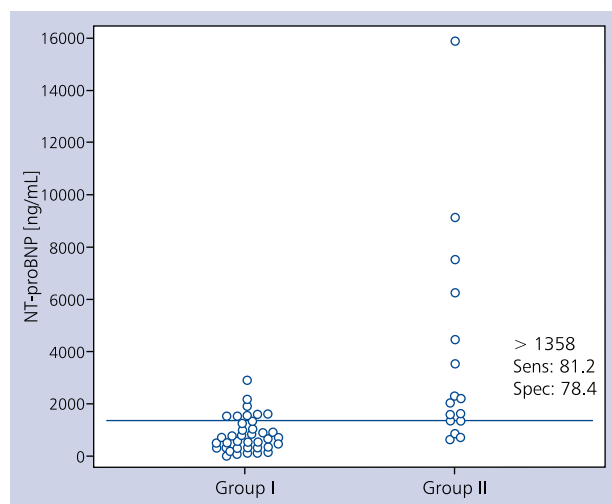


Figure 3. Diagnostic performance of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in samples taken at three-month follow-up visit

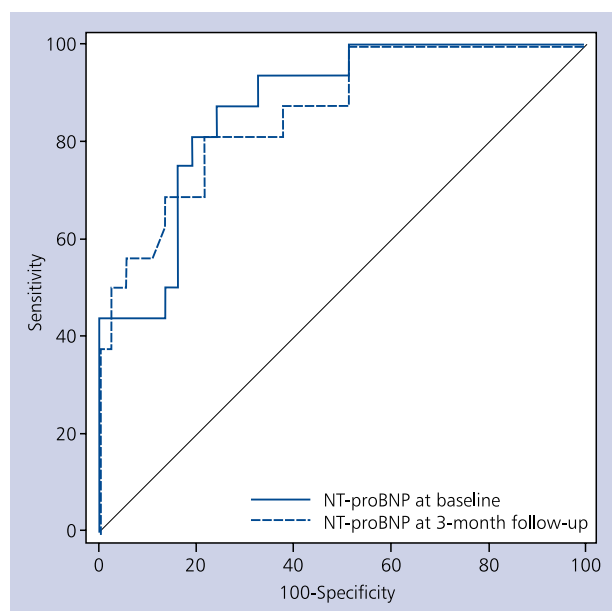


Figure 4. Pairwise comparison of receiver operating characteristic (ROC) for N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline and three-month follow-up visit

hypoxemia, renal dysfunction, liver cirrhosis, sepsis, and infection [9–12]. Even though NT-proBNP is increased in these conditions, it remains valuable in the HF diagnosis, but different cut-off values are suggested.

Various studies have shown that NT-proBNP level may increase in AF, as well [13]. In the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial, NT-proBNP was elevated in three-quarters of the patients with AF and at least one risk factor for stroke, and it was in-

dependently associated with an increased risk for stroke and mortality [14]. This may explain elevated NT-proBNP levels in the non-HF group in the present study as well. The fact that the patients referred for LAAO presented other comorbidities might be the explanation for the NT-proBNP elevation, independent of HF diagnosis.

It is interesting which consequences bring the occlusion of the LAA for both the heart haemodynamics as well as its hormonal function. In healthy subjects, the endocrine function of the heart is predominantly associated with the endocrine capacity of the atria. Stretching of the atrial walls results in secretion of the natriuretic hormones that regulate fluid homeostasis and blood pressure [4]. One should realise that the LAA has a considerable volume, with a greater compliance of its walls when compared with the rest of the atrium. Because of these features, it acts as a reservoir that attenuates the increase in the atrial pressure [15, 16]. Its occlusion changes the haemodynamics of the left atrium, and this change results in an increase of the atrial pressure and its dilatation. Moreover, the LAA contains stretch-sensitive receptors that are able to influence heart rate and natriuretic peptides secretion in response to the change in the atrial pressure. A quantitative analysis of the atrial natriuretic peptides (ANP) in the excised LAAs revealed that approximately 30% of all the cardiac ANP is secreted by the LAA [17]. All these factors may lead to alterations to the NT-proBNP secretion as a result of LAAO, and this questions the usefulness of NT-proBNP assessment in patients that have undergone such procedures.

Cruz-Gonzalez et al. [18] studied 34 patients with non-valvular AF, in whom LAAO was performed. The authors found no significant changes in BNP level in samples drawn 24 h after the procedure. However, LAAO resulted in a significant decrease in BNP levels at the first follow-up visit (45–60 days), when compared to the baseline measurements [18]. The population analysed in this study included only patients without HF and with preserved LV systolic function (EF 58.4% ± 4.5%). The patients who developed signs of HF during the observation were also excluded from analysis. The authors explained the decrease observed in the BNP values as a result of the isolation of the LAA from the haemodynamic changes occurring in the left atrium.

Discrepant results were obtained by Majunke et al. [19], who studied the alternation to the ANP and BNP secretion after percutaneous occlusion of LAA with a Watchman device. They reported that the occlusion of the LAA leads to a significant increase in ANP and BNP levels, immediately after the procedure, with a subsequent decrease of the levels in the samples drawn more than 24 h later [19]. The analysis included a wide variety of patients: patients with and without HF, as well as those with paroxysmal, persistent, and permanent AF were included. The increase in the concentration of ANP and BNP immediately after the LAAO has been explained as a result of a stretching in the walls of the LAA by the con-

trast dye and by the closure device. Twenty-four hours after the procedure, ANP and BNP values decreased significantly, when compared with baseline values. In this study, the influence of percutaneous LAA closure on secretion of natriuretic peptides has been analysed only in the early postprocedural phase. It was suggested that ANP and BNP values may further decrease over time due to advanced endothelialisation of the device surface and consecutive progress in the complete closure of the LAA.

In the present study, the changes in the concentration of NT-proBNP, which has different features than ANP and BNP, were analysed. Although produced simultaneously, the characteristics of BNP and NT-proBNP may have an influence on their concentration after LAAO. BNP is a smaller peptide and has a shorter plasma half-life than NT-proBNP (15–20 min vs. 1 h). For these reasons, BNP might show a better correlation with the rapid changes in the activation of the neurohormonal systems and haemodynamics than NT-proBNP. On the other hand, NT-proBNP degrades more slowly, has a higher circulating concentration, and is more stable, with less biological variability than BNP [20].

Analysis of NT-proBNP carried out for the entire study population showed that there was a slight increase in NT-proBNP values 48 h after LAAO. Similarly, the NT-proBNP results obtained three months after LAAO showed a further increase in a group of patients with impaired LVEF, when compared to both baseline values and values obtained 48 h after treatment, and a decrease of NT-proBNP values in patients without HF LVEF. However, these changes were not statistically significant.

The importance of NT-proBNP results is of particular value in relation to the functional assessment of the cardiovascular system. The results of the 6MWT as well as the peak oxygen consumption in the cardiopulmonary stress test performed before and three months after LAAO showed no statistically significant differences. There was even a trend toward higher values.

The answer to the question regarding the changes in the NT-proBNP concentration and the possible impact on the NT-proBNP interpretation in the diagnosis and monitoring of the patients with HF is reflected by receiver-operating curves. Although no significant differences in AUC for both curves were identified, the cut-off value for NT-pro BNP at baseline was 988 pg/mL, and this level presented a higher sensitivity (87.5%) than the value obtained after three months, when level was at 1358 pg/mL, with a sensitivity of 81.2%. The shift in cut-off value is relatively small if one refers to baseline values of NT-proBNP in the overall population.

Limitations of the study

The major limitation of this study is that we assessed a single natriuretic peptide, whereas various natriuretic peptides have different half-life. Moreover, the secretion of natriuretic peptides is better reflected by appropriate gene activation

than by assessment of the peptides themselves. It would also be valuable to broaden the analysis by examining the correlation of NT-proBNP with AF burden in patients suffering from paroxysmal AF.

CONCLUSIONS

This study shows that LAAO does not significantly influence the NT-proBNP secretion. It may be still used as a marker for HF in patients after LAAO. However, in patients with AF, different cut-off values may be more appropriate, for a better correlation with HF diagnosis.

Conflict of interest: Witold Streb: proctor St. Jude Medical, honorarium for lecturers for St. Jude Medical, Katarzyna Mitreġa: proctor St. Jude Medical, honorarium for lecturers for St. Jude Medical, Zbigniew Kalarus: proctor St. Jude Medical, honorarium for lecturers for St. Jude Medical.

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