Association Between Baseline Natriuretic Peptides and Atrial Fibrillation Recurrence After Catheter Ablation

A Meta-Analysis

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SUMMARY

Natriuretic peptides like B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro BNP) are reported to be increased in atrial fibrillation (AF) patients. However, the prognostic roles of BNP and NT-pro BNP in post-ablation AF recurrence remain inconclusive. We performed this meta-analysis to investigate the potential role of baseline natriuretic peptides in predicting AF recurrence after catheter ablation.

Electronic databases were searched for studies that evaluated the potential relationship between AF recurrence and baseline BNP or NT-pro BNP levels. The pooled standardized mean difference (SMD) and 95% confidence interval (CI) were calculated to quantify differences in BNP or NT-pro BNP levels between patients with and without AF recurrence.

Ten studies on BNP and 8 studies on NT-pro BNP were included, in which 411 of 1300 patients and 256 of 846 patients experienced AF recurrence, respectively. Overall, the pooled SMD of studies on BNP was 0.55 (95% CI: 0.26-0.84, $P < 0.001$) while the pooled SMD of studies on NT-pro BNP was 0.96 (95% CI: 0.62-1.30, $P < 0.0001$). Meta-regression was conducted by AF type, AF duration, follow-up period, left atrial dimension (LAD), and concomitant heart failure, after which subgroup analysis demonstrated only follow-up period (3 months or > 3 months) in the NT-pro BNP group might account for the heterogeneity. Sensitivity analyses indicated both the results were stable.

Meta-analysis of current eligible studies suggested that both increased baseline BNP and NT-pro BNP levels are associated with greater risk of AF recurrence after catheter ablation, which could be biomarkers for predicting AF recurrence. (Int Heart J 2016; 57: 183-189)

Key words: BNP, NT-pro BNP, Predictive

Atrial fibrillation (AF) is the most common arrhythmia and a rising global burden with progressive increases in prevalence, incidence, and AF-associated mortality during past decades.¹⁾ Catheter ablation for rhythm control was recommended in specific patient populations with paroxysmal, persistent, or long-standing persistent AF by the latest guideline.²⁾ However, relapse is still common since the single-procedure efficacy of AF ablation was estimated to be 60-80% in paroxysmal AF and 50-70% in persistent AF.³⁾ Since ablation techniques have been developed over time, the relapse rate might be partially due to the complicated pathological mechanisms and our limited knowledge of AF. Thus, stratification of patients who will sustain a better rhythm outcome after catheter ablation may be beneficial to clinical practice.

Natriuretic peptides (BNP, NT-pro BNP) are primarily secreted by myocytes in response to a number of stimuli, and have been widely used as important diagnostic and monitoring tools for cardiovascular diseases.⁴⁾ Meanwhile, it has been shown that AF patients had higher plasma natriuretic peptide concentrations than controls and the elevated natriuretic pep-

tide levels decreased when sinus rhythm was restored by transcatheter ablation.⁵⁻⁷⁾ Somehow, it is inconsistent whether increased natriuretic peptides are real predictors of AF recurrence or mere dysfunction of atrial rhythm and ventricular rate at certain time points.⁸⁾ Consequently, we conducted this meta-analysis that aimed to identify the association between baseline BNP or NT-pro BNP levels and AF recurrence after catheter ablation.

METHODS

Search Strategy and Selection Criteria: This meta-analysis was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.⁹⁾ Pubmed, Embase, Cochrane Central Register of Controlled Trials, and the ISI Web of Science were searched by two independent investigators (Y.H. Zhang and A. Chen) for English literature published up to September 1, 2015. The search items were “Natriuretic peptides”, “BNP”, “B-type natriuretic peptide”,

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“brain natriuretic peptide”, “NT-pro BNP”, “N-terminal pro-BNP”, “atrial fibrillation”, “catheter ablation”, “radiofrequency ablation”, “pulmonary vein isolation”, and “circumferential pulmonary vein ablation”. Reference lists of retrieved articles and relevant reviews were also screened to identify potential eligible studies. Disagreements were resolved by consensus.

The inclusion criteria were: 1) catheter ablation was performed for rhythm control in AF patients; 2) follow-up period was ≥ 3 months; and 3) baseline natriuretic peptide concentrations and AF recurrence rates were published. Studies were excluded as follows: 1) AF patients underwent rate control strategies or surgical ablation; and 2) sufficient data were not available and could not be acquired from corresponding authors.

Definitions: The classification of AF in included studies was described as paroxysmal AF (AF that terminates spontaneously or with intervention within 7 days of onset), persistent AF (continuous AF that is sustained > 7 days), and longstanding persistent AF (continuous AF of > 12 months duration) in terms of the duration of episodes.

The definitions of AF recurrence and freedom from AF recurrence after catheter ablation were accorded with authors' descriptions. Generally, after a post-ablation blanking period of 1-3 months, any atrial tachyarrhythmia or AF lasting > 30 seconds recorded by ECG or 24-hour Holter monitoring during the follow-up period was defined as AF recurrence. Accordingly, the other patients sustained in sinus rhythm or without detectable atrial arrhythmias were defined as non-recurrence patients.

Data extraction and quality assessment: The first author's name, publication year, main characteristics of the patients, AF type, AF duration, rhythm during blood sampling, left atrial dimension (LAD), baseline BNP or NT-pro BNP levels, ablation strategies, and rhythm outcome during the follow-up were extracted by two authors (Y.H. Zhang and L. Song) independently. If a study evaluated AF recurrence at different time points, we extracted the latest data. Corresponding authors were contacted by email for the missing data we needed in this meta-analysis.

For studies in which natriuretic peptide concentrations were expressed as medians and quartiles, we transformed these data into the mean and standard deviation (SD) as documented in the Cochrane Handbook.¹⁰ Briefly, the mean was assumed to be very similar to the median, and was used directly in meta-analysis. The interquartile range width was approximately 1.35 SD and SDs were transformed in this way.

The Newcastle-Ottawa Scale (NOS) with a maximum score of 9 was used to assess the quality of eligible non-randomized studies based on the components of Selection (0-4 points), Comparability (0-2 points), and Exposure or Outcome (0-3 points).¹¹ In general, a higher score indicates a better methodological quality. Additionally, consensuses were reached by authors during the discussion to resolve disagreements.

Statistical analysis: The standardized mean difference (SMD) and 95% confidence interval (CI) were used to assess the continuous data in our meta-analysis, as the detection methods and units of natriuretic peptide concentrations were varied. Meanwhile, a random-effects model was used for the relatively small sample size and potential clinical heterogeneity between studies. The significance of the pooled SMD was determined

by the z -test with a $P < 0.05$ being considered as statistically significant. Statistical heterogeneity was assessed using the I^2 statistic and $I^2 \geq 50\%$ was considered as a sign of significant heterogeneity between studies. Meta-regression and subgroup analyses were conducted to explore the potential source of heterogeneity. For potential publication bias we performed the Begg-adjusted rank correlation test. Statistical analyses were performed with Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Study selection: A total of 430 records were retrieved after a primary search, which were further evaluated according to the identification process shown in Figure 1. The remaining 289 studies were screened by titles and abstracts after duplicates were excluded, of which 42 potential eligible full-text articles were reviewed in detail. Finally, 18 studies that met the inclusion criteria were included in our meta-analysis. Among them, 10 studies^{8,12-20} evaluated the association between baseline BNP levels and AF recurrence after catheter ablation while the 8 other studies²¹⁻²⁸ investigated the potential role of NT-pro BNP.

Study characteristics: The demographic and clinical properties of eligible studies are presented in Table I and Table II, respectively. Circumferential or segmental pulmonary vein isolation (PVI) was performed in all patients, whereas additional linear ablation or complex fractionated atrial electrogram (CFAE) ablation was carried out for patients who remained in AF or sustained AF was inducible after initial PVI. In the studies on BNP, 411 of 1300 patients had AF recurrence during a mean follow-up period that ranged from 3 to 33.8 months. Meanwhile, after a mean follow-up time of 3 to 13.7 months, 256 of 846 patients had experienced recurrent AF in studies on NT-pro BNP. For quality assessment, all included studies were of relatively high quality with the NOS scores ranging from 6 to 8 points. Publication bias was assessed by the Begg-adjusted rank correlation test, which demonstrated no significant publication bias existed ($P > 0.05$). As we included a small number of studies for each group, formal assessment of publication

Figure 1. Flow diagram of the identification of eligible studies. SR indicates sinus rhythm and RFCA, radiofrequency catheter ablation.

Table I. Characteristics of Studies on BNP

Author (Year)	Design	Patients (Recurrence)	Male (%)	Age (years)	Paroxysmal AF (%)	AF Duration (years)	Concomitant HF (%)	Ablation procedure	Follow-up (months)	Rhythm during blood sampling	HR (bpm)	LAD (mm)	NOS
Date, <i>et al</i> (2006)	Retro	53 (21)	47 (89)	53.1 ± 10.0	53 (100)	5.2 ± 4.6	None	PVI	14	33 SR and 20 AF	NA	38.2 ± 4.9	8
Yamada, <i>et al</i> (2006)	Retro	66 (31)	54 (82)	61 ± 10	66 (100)	4 ± 3	None	PVI	> 3	NA	NA	35 ± 5	7
Nakazawa, <i>et al</i> (2009)	Pro	51 (24)	45 (88)	58.1 ± 10.6	39 (76)	4.9 ± 6.1	None	PVI	6	most cases in SR	72 ± 16	40 ± 4	7
Degener, <i>et al</i> (2011)	Pro	73 (19)	56 (77)	53 ± 13	45 (62)	2.7 ± 2.2	None	PVI	3	NA	NA	NA	8
Machino-Ohtsuka, <i>et al</i> (2011)	Retro	155 (45)	123 (79)	61 ± 9	100 (65)	5.4 ± 4.9	None	PVI	33.8 ± 12.2	NA	63 ± 12	38 ± 6	7
Naruse, <i>et al</i> (2011)	Retro	221 (87)	179 (81)	59 ± 11	127 (57)	5.8 ± 5.4	22 (10)	PVI PVI+LA	31.9 ± 7.6	NA	NA	NA	7
Okumura, <i>et al</i> (2011)	Pro	50 (21)	38 (76)	61.3 ± 9.4	28 (56)	5.9 ± 6.0	3 (6)	PVI PVI+CFAE	14.0 ± 16.2	NA	NA	NA	6
Im, <i>et al</i> (2013)	Pro	499 (122)	367 (74)	56.4 ± 11.3	266 (53)	NA	62 (12)	RFCA	25.2 ± 14.5	NA	NA	41.9 ± 6.8	6
Kimura, <i>et al</i> (2014)	Pro	44 (15)	38 (86)	59 ± 8	31 (70)	NA	7 (16)	PVI PVI+CFAE	9.7 ± 2.4	NA	NA	39 ± 6	7
Pillarisetti, <i>et al</i> (2014)	Pro	88 (26)	60 (68)	60 ± 8	29 (33)	NA	None	PVI PVI+CFAE	12	48 SR and 40 AF	NA	41.6 ± 9.8	8

Retro indicates retrospective; Pro, prospective; AF, atrial fibrillation; SR, sinus rhythm; HF, heart failure; PVI, pulmonary vein isolation; LA, linear ablation; CFAE, complex fractionated atrial electrogram; RFCA, radiofrequency catheter ablation; LAD, left atrial dimension; NOS, Newcastle-Ottawa Scale; NA, not applicable; and HR, heart rate. Values are mean ± SD or *n* (%).

Table II. Characteristics of Studies on NT-pro BNP

Author (year)	Design	Patients (recurrence)	Male (%)	Age (years)	Paroxysmal AF (%)	AF Duration (years)	Concomitant HF (%)	Ablation procedure	Follow-up (months)	Rhythm during blood sampling	HR (bpm)	LAD (mm)	NOS
Nilsson, <i>et al</i> (2009)	Retro	51 (29)	32 (63)	55.3 ± 10.3	34 (67)	5.2 ± 6.0	12 (24)	PVI	12	SR	NA	39 ± 5	7
Hwang, <i>et al</i> (2009)	Pro	73 (20)	64 (88)	53.5 ± 10.0	49 (67)	5.7 ± 5.1	None	PVI PVI+LA	3	NA	NA	42 ± 5	8
Den Uijl, <i>et al</i> (2011)	Pro	87 (21)	70 (80)	55 ± 9.0	78 (90)	5.4 ± 5.0	None	PVI	6.6 ± 3.0	SR	NA	NA	8
Fan, <i>et al</i> (2012)	Pro	33 (10)	23 (70)	56.4 ± 10.4	33 (100)	4.2 ± 4.0	None	PVI	3	NA	81.4 ± 9.8	34.2 ± 5.6	8
Fiala, <i>et al</i> (2014)	Pro	159 (29)	124 (77)	59 ± 9.0	0 (0)	2.3 ± 2.4	None	PVI PVI+LA	12	AF	NA	48.4 ± 5.5	8
Sasaki, <i>et al</i> (2014)	Pro	60 (29)	49 (82)	57.6 ± 10.9	32 (53)	4.3 ± 4.6	8 (13)	PVI PVI+LA	12.1 ± 1.0	NA	NA	NA	7
Giannopoulos, <i>et al</i> (2015)	Retro	296 (93)	207 (70)	60 ± 8.9	296 (100)	NA	None	PVI	13.7	NA	NA	43 ± 2	8
Parwani, <i>et al</i> (2015)	Pro	87 (25)	57 (65)	62 ± 9.0	47 (54)	NA	-*	PVI PVI+LA	12	NA	79 ± 23	44 ± 7	8

Retro indicates retrospective; Pro, prospective; AF, atrial fibrillation; SR, sinus rhythm; HF, heart failure; PVI, pulmonary vein isolation; LA, linear ablation; LAD, left atrial dimension; NOS, Newcastle-Ottawa Scale; NA, not applicable; and HR, heart rate. - * represents heart failure patients existed but without exact number. Values are mean ± SD or *n* (%)

bias with funnel plots might not be appropriate.

Baseline BNP and post-ablation AF recurrence: Of the 10 studies on BNP included,^{4,12,15,18,19} showed patients with AF recurrence after catheter ablation had significantly greater baseline BNP than those without AF recurrence. Overall, these data were synthesized with the other 6 studies^{8,13,14,16,17,20} and the pooled SMD was 0.55 (95% CI: 0.26-0.84, $P < 0.001$, Figure 2). However, heterogeneity testing revealed a significant heterogeneity ($I^2 = 79\%$). To explore the potential source of heterogeneity, we performed meta-regression by covariates including AF type ($P = 0.922$), AF duration ($P = 0.572$), LAD ($P = 0.583$), mean follow-up period ($P = 0.380$), and concomitant heart failure ($P = 0.830$). Since these underlying confounding factors could not explain the heterogeneity, we conducted sen-

sitivity analyses but found no significant change in heterogeneity or pooled SMD when any single study was excluded.

Baseline NT-pro BNP and post-ablation AF recurrence: All 8 studies demonstrated greater baseline NT-pro BNP concentrations in the recurrence group. Quantitative data synthesis showed the overall pooled SMD was 0.96 (95% CI: 0.62-1.30) with a z -test score for overall effect of 5.57 ($P < 0.0001$, Figure 3A). Meta-regression was also used to explore any significant heterogeneity ($I^2 = 74\%$) by covariates including AF type ($P = 0.640$), AF duration ($P = 0.656$), LAD ($P = 0.252$), mean follow-up period ($P = 0.018$), and concomitant heart failure ($P = 0.529$). Subsequently, subgroup analysis stratified by follow-up period (3 months or > 3 months) was conducted. The pooled SMD was 2.09 (95% CI: 1.57-2.60, $P < 0.00001$) and

Figure 2. Forest plot of pooled SMD in studies evaluated suggested increased BNP levels and postablation AF recurrence risk.

Figure 3. Forest plots of pooled SMD in studies evaluated suggested increased NT-pro BNP levels and postablation AF recurrence risk. **A:** Overall effect. **B:** Subgroup analysis by follow-up period of 3 months or > 3 months.

0.68 (95% CI: 0.51-0.84, *P* < 0.00001) for early recurrence within 3 months and late recurrence beyond 3 months, respectively (Figure 3B). Moreover, the sensitivity analyses showed no single study significantly changed the overall pooled effects when it was excluded, demonstrating the results were stable.

DISCUSSION

This meta-analysis identified 18 observational studies that investigated the potential association between baseline natriuretic peptides and AF recurrence after catheter ablation. The

present results suggested that patients with AF recurrence have greater baseline BNP or NT-pro BNP levels, indicating a predictive role for natriuretic peptides in the recurrence of AF after catheter ablation.

Atrial fibrillation is a complex arrhythmia associated with increased morbidity of stroke and heart failure, as well as poor prognosis and increased mortality.²⁹⁻³¹ Accordingly, the current therapeutic strategies for AF are focused on thromboembolism prevention and rate or rhythm control.² Since the ectopic activities from pulmonary veins were discovered to be triggers of AF by Haissaguerre, *et al*³² radiofrequency catheter ablation of pulmonary vein antrum has been proven to be an efficient

treatment for rhythm control in AF patients. Furthermore, PVI and additional linear ablation or CFAE ablation have exhibited superior outcomes compared to those of antiarrhythmic drugs in rhythm control.^{33,34)} However, the recurrence of AF after catheter ablation is common, especially during the first 3 months, which is usually defined as early recurrence. Early recurrence tends to be transient and has also been reported as a predictor for late recurrence or long-term rhythm outcome after successful catheter ablation.³⁵⁻³⁷⁾ Similarly, in our meta-analysis, subgroup analysis based on follow-up period showed a higher pooled SMD (2.09, 95% CI: 1.57-2.60) in the early recurrence group than the pooled SMD (0.68, 95% CI: 0.51-0.84) in the late recurrence group and the statistical heterogeneity was eliminated (Figure 3B). Thus, the follow-up period might be a potential stratification factor for further investigations, although the effect was not observed when the same subgroup analysis was conducted in currently eligible studies on BNP. Moreover, previous studies^{8,13,15,22,39)} have suggested that non-paroxysmal AF, longer duration of AF, and larger left atrial size might reflect higher AF burden, which is correlated with elevated natriuretic peptides levels. However, in our study, covariates including AF type, AF duration, LAD, mean follow-up period, and concomitant heart failure did not show significant differences on meta-regression. As a result, these factors might not be the sources of the heterogeneity in our study.

Circulating BNP and NT-pro BNP have been used as biomarkers for diagnosis, prognosis, and therapeutic monitoring in various cardiovascular diseases including heart failure, stable coronary artery disease (CAD), and acute coronary syndrome (ACS).^{4,38)} As for AF, elevated B-type natriuretic peptides might be strong predictors of recurrent arrhythmia after ablation, regardless of whether structural heart diseases existed.³⁹⁾ This might be due to the irregular ventricular rhythm or pathophysiology of atrial substrate including hypertrophy, fibrosis, and inflammation in AF patients. Meanwhile, it should be noted that whether or how the baseline rhythm and rate status of AF patients affect the association between natriuretic peptides and post-ablation AF recurrence remain inconsistent. A study by Pillarisetti, *et al*⁸⁾ suggested that elevated BNP levels just represented atrial rhythm and ventricular rates rather than being a conclusive predictor of short-term or long-term procedural success. However, Date, *et al*¹²⁾ reported that the heart rhythm (sinus or AF) at the time of blood sampling did not affect baseline BNP concentrations and Hussein, *et al*³⁹⁾ suggested that BNP is a strong, independent predictor of post-ablation AF recurrence after adjustment of cardiac or extracardiac parameters including heart rate, pre-ablation rhythm, left atrial size, age, AF duration, and the type of AF. In our meta-analysis, the studies included showed no significant differences in the baseline characteristics of age, gender, or baseline heart rate between the recurrence and non-recurrence groups. However, AF patients with concomitant heart failure were enrolled in 4 studies¹⁷⁻²⁰⁾ on BNP and 3 studies^{21,26,28)} on NT-pro BNP. The meta-regression or subgroup analysis based on concomitant heart failure failed to provide a clue to the origin of heterogeneity. In addition, the study of Naruse, *et al*¹⁷⁾ enrolled 54 (24%) patients with chronic kidney disease, while others excluded these patients or did not mention if they were excluded. Sensitivity analysis revealed this study did not eliminate the significant heterogeneity ($I^2 = 76\%$) and did not cause a significant change in the pooled SMD (0.60, 95% CI: 0.29-

0.91).

The concentrations of BNP and NT-pro BNP were measured by immunoradiometric assay or chemiluminescent enzyme immunoassay, with a unit of pg/mL being used, with the exceptions of Nilsson²¹⁾ who adopted pmol/L and Sasaki²⁶⁾ who adopted $\mu\text{g/mL}$. Thus, the pooled SMD was applied to reflect the overall effects between studies. The general rules of thumb described by Cohen suggested that a SMD of 0.2 represents a “small” effect, a SMD of 0.5 represents a “medium” effect, and a SMD of 0.8 represents a “large” effect.⁴⁰⁾ Accordingly, the pooled SMD of studies on BNP was 0.55, indicating a moderate difference of baseline BNP levels between the recurrence and non-recurrence groups. For NT-pro BNP, the pooled SMD was 0.96, which represented a significant difference in baseline NT-pro BNP levels between the recurrence group and non-recurrence group. Although the studies included on NT-pro BNP showed a more consistent result and the pooled SMD of NT-pro BNP was greater than BNP, we cannot directly draw the conclusion that NT-pro BNP is a better marker than BNP. The potential advantage of NT-pro BNP is a longer half-life than BNP, which could lead to higher circulating levels and slower fluctuations.³⁸⁾ A well-designed head to head comparative trial is required to determine whether NT-pro BNP is more valuable than BNP or not.

Although the results indicated a significant association between increased natriuretic peptide levels and post-ablation AF recurrence, some limitations should be taken into consideration. First, since valid data for baseline rhythm and heart rate of AF patients were not applicable in most studies, this meta-analysis was conducted to identify the univariate association of baseline natriuretic peptides with post-ablation recurrence. The role of other confounding clinical factors should be estimated in the future. Second, all studies included were observational studies rather than randomized control trials (RCT), some of which had a relatively small sample size (< 100). Third, significant heterogeneity existed in the quantitative syntheses with the random effect model that was used. As the results of the meta-regression and subgroup analyses showed above, it might be partially due to differences in the complicated clinical characteristics of the enrolled patients between studies. Fourth, the association between post-ablation AF recurrence risk and baseline natriuretic peptides was indicated by the pooled SMD indirectly. The SMD mainly expressed the size of the difference in natriuretic peptide levels in each study relative to the variability observed in that study. If further studies were available, the statistical power of the pooled risk ratio or odds ratio would be greater than SMD. Finally, publication bias cannot be completely excluded in this study as only a small number of studies were included. Meanwhile, effect estimates like SMD that are naturally correlated with standard errors can produce spurious asymmetry in a funnel plot.

Conclusion: Our meta-analysis indicated that increased baseline natriuretic peptides, both BNP and NT-pro BNP, are associated with greater risk of AF recurrence after catheter ablation. Considering the limitations described above, further well designed, larger, and long-term studies in specific populations are needed to elucidate the predictive value of baseline natriuretic peptides in AF patients undergoing catheter ablation.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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