Predictive role of BNP/NT-proBNP in non-heart failure patients undergoing catheter ablation for atrial fibrillation: An updated systematic review

Nikolaos Papageorgiou[1*], Rui Providência[1*], Debbie Falconer[2], Tanakal Wongwarawipat[2], Dimitris Tousoulis[3], Wei Yao Lim[1], Anthony W. Chow[1], Richard Schilling[1], Pier D. Lambiase[1]

*equally contributed

[1] Electrophysiology Department, Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom

[2] Royal Free Hospital, London, United Kingdom

[3] 1st Cardiology Department, Athens University Medical School, Athens, Greece

Word count: 2174

Corresponding Author:
Dr Nikolaos Papageorgiou MD PhD FESC
Barts Heart Centre, St Bartholomew's Hospital
West Smithfield
London, EC1A 7BE
Tel: (+44) 020 3765 8000
Fax: (+44) 020 7791 9670
Email: drnpapageorgiou@yahoo.com

Abstract

Atrial fibrillation (AF) is a growing public health issue, associated with significant morbidity and mortality. The majority of patients are managed pharmacologically, but more than ever are being offered ablation as a potentially curative strategy. However, ablation even with low, it is still not free of complications risk, while AF itself will recur in a significant proportion of patients. Non-invasive, easily accessible markers/indexes that would help us better stratify patients depending on the likelihood of success would allow us to select the most appropriate patients for the procedure, reducing the recurrence rate and exposure to potentially life-threatening risks of ablation.

There has been much attention paid to brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as possible predictive markers of successful ablation. Several studies have demonstrated an association between higher pre-ablation levels of these peptides, and a greater likelihood of AF recurrence. Therefore, there may be a role for measuring brain natriuretic peptides levels when selecting which patients are suitable for ablation.

Keywords: Atrial fibrillation, ablation, brain natriuretic peptide, N-terminal BNP, recurrence

Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, and the prevalence is increasing as our population ages [1,2]. Symptomatic patients experience shortness of breath, palpitations and dizziness. Not only do they report a reduced quality of life, but they have a five-fold increased risk of stroke and a two-fold increased risk of death compared with their counterparts in sinus rhythm[2]. AF is characterized by rapid and irregular contractions of the atrium caused by multiple re-entrant circuits, variable in wavelength [1]. They are initiated by rapidly firing foci, often located in the pulmonary veins[3-4].

Catheter ablation is a potentially curative procedure, removing the need for long-term use of antiarrhythmic drugs. It is especially effective in paroxysmal AF (PAF) [[5]]. However, 5% of patients undergoing ablation will experience significant complications including transient ischaemic attack, stroke and pericardial tamponade [[6]]. The recurrence rate of AF has been reported to be as high as over 60% in non-paroxysmal AF, and over 30% in paroxysmal AF [[7]]. There are already established markers that help to predict the outcome including age and atrial size, but the search is underway for more indicators that will allow patients to be better selected for the procedure, reducing the incidence of recurrence. Brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are secreted from cardiomyocytes in response to stretching of the heart muscle cells [[8]]. Measuring the level of these peptides is easy, and BNP is already used in clinical practice to aid the diagnosis of heart failure. NT-proBNP is a prohormone of BNP which has a longer half-life and more stable plasma concentration. Both BNP and NT-proBNP are associated with AF, even in the absence of cardiac failure [[9-10]], and there is growing body of evidence demonstrating that pre-ablation levels of the peptides can predict the likelihood of AF recurrence following the procedure. This link proposes a role for BNP and NT-proBNP in optimising patient selection for ablation.

In the present article, we will review the relationship between natriuretic peptides and atrial fibrillation, followed by the most recent trials measuring the association between pre-ablation peptide levels and AF recurrence in non-heart failure (HF) patients.

Association between natriuretic peptides and atrial fibrillation

The relationship between natriuretic peptides and HF is well established, but more recently focus has switched to their association with other pathological conditions, including AF. Several studies have shown that AF is linked with elevated concentrations of both BNP and NT-proBNP, even in patients without a history of HF [9, 11-14]. Although natriuretic peptides are mainly secreted by the ventricular myocytes, Inoue et al found that in AF, BNP is actually secreted in the atrium [15]. Atrial overload and remodelling that occurs in AF is thought to underlie the elevation in BNP levels. Patients with persistent AF (persAF) have higher levels than those with paroxysmal AF, possibly as their atria have undergone more remodelling [16].

BNP levels have been shown to normalise after successfully treating AF by both electrical cardioversion [17-19] and catheter ablation [20-21]. Furthermore, this decrease in BNP was sustained for at least 3 months following a successful ablative procedure [22].

In patients undergoing pre-operative assessment, elevated baseline levels of BNP and NT-proBNP have been associated with increased risk of AF following coronary artery bypass grafting [23-24], cardiac surgery [25] and thoracic surgery [26]. Horie et al also found BNP predicted the development of chronic AF after pacemaker insertion in patients with sick sinus syndrome [27].

The predictive value of natriuretic peptides has been investigated in patients undergoing cardioversion. Their role here remains controversial, as some groups found the peptides successfully predicted successful cardioversion [28-30], whilst others found no association between NT-proBNP and rhythm stability [31-32].

Several studies have found natriuretic peptides can positively predict stroke risk in patient with atrial fibrillation [[33]]. The RE-LY study demonstrated patients in the highest quartile of NT-proBNP level had an increased risk of stroke, when compared with the group of patients with the lowest (2.3%/year vs 0.92%/ year respectively) [34]. The ARISTOTLE trial found the same association, and when added to the CHADS2VASC score, NT-proBNP actually increased the accuracy of stroke risk stratification [[35]].

Predictive Role of Natriuretic peptides

Brain natriuretic peptide (BNP)

Based on 7 related studies involving 500 patients, our analysis demonstrates that the group who experienced AF recurrence had a significantly higher pre-ablation BNP level than the group who maintained sinus rhythm. Of note, there was significant heterogeneity between studies (figure 1).

Studies favouring the association between high BNP levels and AF recurrence include Xing et al, who found there was a significant difference in BNP levels in the AFR (AF recurrence) group and NAFR (no AF recurrence) group (98.7 vs 49.3 pg/ml respectively). They also found BNP levels fell to within normal range in patients who had successful procedures. In the AFR group, BNP then increased to levels comparable to that of pre-ablation, whilst BNP levels remained low in the NAFR group[21]. An earlier study by Degener (table 1) with 73 patients established the same link, finding pre-ablation BNP levels were the only independent predictor of 3 month pulmonary vein isolation outcome[6]. Although not included in our analysis (as no data on standard deviations were available), Shin et al found similar results in their study of 68 patients. Pre-ablation BNP levels in the AFR group were 144pg/ml, compared with 68 pg/ml in the NAFR group ($p<0.05$) when studying outcomes 3 months after ablation[36]. An interesting observation was made by Mohanty et al. In a much larger study involving 568 patients, they found BNP was predictive of outcome in men, but not in women[37]. Though the exact cause for this is unclear, they suggest contributing factors may include later referrals for women undergoing ablation, by which time there is already more advanced structural remodelling of the atrium. The patients in this study had undergone pulmonary vein isolation, and there is evidence to suggest there is a higher prevalence of extra-pulmonary vein trigger sites in women than men[38].

However, not all studies have agreed with the above findings. Pillarisetti studied patients with PAF and persAF, some of whom presented for ablation in SR. They found BNP was related to rhythm (higher in patients presenting in AF compared with SR), but it did not relate to the likelihood of a successful outcome. Restoration of SR from AF resulted in a drop in BNP but there was no decrease in BNP in the group who presented in SR, suggesting it is a marker of atrial function rather than outcome[39]. Similarly, Machino-Ohtsuka found no significant correlation between BNP level and ablation outcome. They did, however, find BNP was significantly correlated with left atrial stiffness, and that the AFR group had a significantly higher left atrial stiffness index than the NAFR group[40]. Neither study by Yamada et al found a link between baseline BNP and ablation outcome[41-42], though they did find a significant reduction in BNP levels following a successful ablation, though not an unsuccessful one. Kurosaki also found that baseline BNP levels were not predictive of outcome, but a decrease in the levels after ablation was[43].

N-terminal prohormone of brain natriuretic peptide (NT-proBNP)

Coexisting in the circulation with BNP, NT-proBNP levels can be easily determined due to its longer half-life, higher quantity, and more stable concentration in the blood, making it an attractive alternative to BNP[44]. Based on 5 related studies involving 684 patients, our analysis shows that the group having recurrence of AF had a significantly higher pre-ablation levels of NT-proBNP. There is again a significant heterogeneity between studies (figure 2).

In 2009, Hwang et al demonstrated that NT-proBNP levels were an independent predictor of AF recurrence in a group of patients with PAF and persAF after multivariate analysis (table 2). Interestingly, NT-proBNP levels were also added to a model containing conventional risk factors for recurrence such as age and LA volume, and was found to significantly improve the predictive value ($p=0.02$)[45]. Den Uijl et al. studied a similar patient cohort of 87 people and found the same association. During a 6 month follow up period, 24% of patients experienced AF recurrence. Higher NT-proBNP levels were an independent predictor of recurrence ($p=0.036$)[46]. An important study by Fan and colleagues included only patients with PAF. Baseline NT-proBNP levels were higher in the PAF group than in the healthy controls, as expected. Mean levels in the recurrent group were significantly higher (572 pg/ml) compared with the non-recurrent group (176 pg/ml). They determined a cut off of more than 423pg/ml was a significant risk factor for AF recurrence in this cohort[44]. Ma et al studied persAF and PAF patients as separate cohorts. In the persAF group, NT-proBNP was an independent predictor of AF recurrence whilst there was no significant correlation in the PAF group after multivariate analysis. Ma et al. suggested that this was because the pathological changes seen after prolonged AF (and therefore in the persistent group) meant the NT-proBNP levels were higher in this group of patients[16].

Importantly, some studies have failed to find a significant association between NT-proBNP and AF recurrence. Giannopolous et al performed a *post hoc* analysis of a prospective study of hypertensive patients with PAF. Baseline NT-proBNP levels were higher in patients with recurrence than in those who remained arrhythmia-free, but the association was rendered non-significant when adjusted for variables[47]. Arana-Rueda et al. found baseline levels were not significantly different (p=0.69) but a decrease in NT-proBNP levels of >30% after ablation was consistent with maintenance of SR 1 year following the procedure. The fall in BNP was also associated with a decrease in left atrial volume and left atrial pressure[48].

Critical approach

There are already established prognostic markers for successful ablation including age, atrial size and duration of AF, but recurrence of AF remains a significant problem [[36]]. Therefore, more tools are needed to better stratify patients for this procedure, reducing the recurrence rate and exposure to serious complications. It is feasible to assess the risk of recurrence using blood markers, and they may have potential for use in clinical practice [[49]].

The predictive quality of natriuretic peptides may be explained by the changes in the left atrium that occur in AF including increased LA pressure, augmented LA volume, fibrosis, hypertrophy and inflammation[16]. Therefore, a higher pre-ablation level of NT-proBNP might indicate underlying increased atrial fibrosis and remodelling, which would increase the risk of post-ablation recurrence [[44, 50]]. Notably, recurrence rate is higher in persistent AF than paroxysmal AF, which directly correlates with the higher natriuretic peptide levels seen in persistent AF.

Secondly, an increased AF burden (which predicts a poor ablation outcome [[47]]), has been associated with increased natriuretic peptide levels, even after adjusting for conventional confounders [[51]]. The pre-ablation peptide level may reflect recent AF burden, as suggested by Pillarisetti et al. and therefore the risk of post-ablation AF recurrence. Thirdly, BNP and NT-proBNP are widely recognized as a biomarkers of HF and raised levels could indicate poor cardiac function, which could trigger AF due to various mechanisms [[49]].

Limitations

There are, of course, limitations associated with the studies. These are mostly observational, rather than randomized controlled trials, and only a few of them use large sample sizes.

There is also significant heterogeneity among these studies, both for BNP and NT-proBNP. This may be partially explained by variation in the baseline characteristics of the participants such as age and the type of AF. Most studies include both PAF and persAF patients in their cohort. The follow-up duration also ranged from 3 to 23 months. Other clinical factors that might contribute to this heterogeneity include the use of anti-arrhythmic drugs before and after the procedure, ablation method as well as the method used to assess AF recurrence. This makes it quite difficult to apply the studies to individual patients.

Furthermore, there is no consensus on what values would predict a successful outcome. Cut-off values would have to account for a number of factors including type of AF, gender and echocardiographic findings, in order to be applied to a complex population.

Finally, the studies we have reviewed exclude patients with structural heart disease or reduced left ventricular systolic function. However, BNP or NT-proBNP can be influenced by other non-cardiac diseases such as pulmonary hypertension, chronic obstructive pulmonary disease and renal failure, all of which may have been present in the study populations even in their subclinical form.

Conclusions

There is strong evidence that BNP and NT-proBNP are associated with AF in the absence of heart failure. Their role as predictive markers of AF recurrence following ablation has been well-studied- many groups finding a strong association between raised levels and AF recurrence. These markers are an attractive prospect in assessing risk of relapse as they are easily obtained and relatively inexpensive.

However, there is still way to go before this can be applied to clinical practice. There are relatively few randomised, controlled trials and patient characteristics vary widely between studies. A number of other conditions can affect peptide levels and we must establish if the markers are still significantly predictive in the absence of confounding variables.

Conflicts of Interest: None to declare

Acknowledgements: None

Figure legends

Figure 1. Forest plot of studies assessing the predictive role of BNP levels in AF recurrence after ablation

Figure 2. Forest plot of studies assessing the predictive role of NT-proBNP levels in AF recurrence after ablation

Tables.

Table 1. Predictive role of BNP in AF recurrence after ablation

Table 2. Predictive role of NT-proBNP in AF recurrence after ablation

References:

[1. Nattel, S., New ideas about atrial fibrillation 50 years on. *Nature* **2002,** *415* (6868), 219-26.
2. Zoni-Berisso, M.; Lercari, F.; Carazza, T.; Domenicucci, S., Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* **2014,** *6*, 213-20.
3. Jais, P.; Haissaguerre, M.; Shah, D. C.; Chouairi, S.; Gencel, L.; Hocini, M.; Clementy, J., A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* **1997,** *95* (3), 572-6.
4. Haissaguerre, M.; Jais, P.; Shah, D. C.; Takahashi, A.; Hocini, M.; Quiniou, G.; Garrigue, S.; Le Mouroux, A.; Le Metayer, P.; Clementy, J., Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* **1998,** *339* (10), 659-66.
5. Verma, A.; Jiang, C. Y.; Betts, T. R.; Chen, J.; Deisenhofer, I.; Mantovan, R.; Macle, L.; Morillo, C. A.; Haverkamp, W.; Weerasooriya, R.; Albenque, J. P.; Nardi, S.; Menardi, E.; Novak, P.; Sanders, P.; Investigators, S. A. I., Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* **2015,** *372* (19), 1812-22.
6. Degener, S.; Pattberg, S. V.; Feuersenger, H.; Bansmann, P. M.; Shin, D. I.; Krummenauer, F.; Horlitz, M., Predictive value of B-type natriuretic peptide levels in patients with paroxysmal and persistent atrial fibrillation undergoing pulmonary vein isolation. *J Interv Card Electrophysiol* **2011,** *30* (3), 217-25.
7. Cheema, A.; Vasamreddy, C. R.; Dalal, D.; Marine, J. E.; Dong, J.; Henrikson, C. A.; Spragg, D.; Cheng, A.; Nazarian, S.; Sinha, S.; Halperin, H.; Berger, R.; Calkins, H., Long-term single procedure efficacy of catheter ablation of atrial fibrillation. *J Interv Card Electrophysiol* **2006,** *15* (3), 145-55.
8. Weber, M.; Hamm, C., Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* **2006,** *92* (6), 843-9.
9. Ellinor, P. T.; Low, A. F.; Patton, K. K.; Shea, M. A.; Macrae, C. A., Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. *J Am Coll Cardiol* **2005,** *45* (1), 82-6.
10. Rossi, A.; Enriquez-Sarano, M.; Burnett, J. C., Jr.; Lerman, A.; Abel, M. D.; Seward, J. B., Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. *J Am Coll Cardiol* **2000,** *35* (5), 1256-62.
11. Darkner, S.; Goetze, J. P.; Chen, X.; Henningsen, K.; Pehrson, S.; Svendsen, J. H., Natriuretic Propeptides as Markers of Atrial Fibrillation Burden and Recurrence (from the AMIO-CAT Trial). *Am J Cardiol* **2017**.
12. Silvet, H.; Young-Xu, Y.; Walleigh, D.; Ravid, S., Brain natriuretic peptide is elevated in outpatients with atrial fibrillation. *Am J Cardiol* **2003,** *92* (9), 1124-7.
13. Bai, M.; Yang, J.; Li, Y., Serum N-terminal-pro-brain natriuretic peptide level and its clinical implications in patients with atrial fibrillation. *Clin Cardiol* **2009,** *32* (12), E1-5.
14. Knudsen, C. W.; Omland, T.; Clopton, P.; Westheim, A.; Wu, A. H.; Duc, P.; McCord, J.; Nowak, R. M.; Hollander, J. E.; Storrow, A. B.; Abraham, W. T.; McCullough, P. A.; Maisel, A., Impact of atrial fibrillation on the diagnostic performance of B-type natriuretic peptide concentration in dyspneic patients: an analysis from the breathing not properly multinational study. *J Am Coll Cardiol* **2005,** *46* (5), 838-44.
15. Inoue, S.; Murakami, Y.; Sano, K.; Katoh, H.; Shimada, T., Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. *J Card Fail* **2000,** *6* (2), 92-6.
16. Ma, X. X.; Zhang, Y. L.; Hu, B.; Jiang, W. J.; Wang, M.; Zheng, D. Y.; Zhu, M. R.; Xue, X. P., Association between left atrial appendage emptying velocity, N-terminal plasma brain natriuretic peptide levels, and recurrence of atrial fibrillation after catheter ablation. *J Interv Card Electrophysiol* **2017,** *48* (3), 343-350.

17. Jourdain, P.; Bellorini, M.; Funck, F.; Fulla, Y.; Guillard, N.; Loiret, J.; Thebault, B.; Sadeg, N.; Desnos, M., Short-term effects of sinus rhythm restoration in patients with lone atrial fibrillation: a hormonal study. *Eur J Heart Fail* **2002,** *4* (3), 263-7.
18. Wozakowska-Kaplon, B., Effect of sinus rhythm restoration on plasma brain natriuretic peptide in patients with atrial fibrillation. *Am J Cardiol* **2004,** *93* (12), 1555-8.
19. Svennberg, E.; Henriksson, P.; Engdahl, J.; Hijazi, Z.; Al-Khalili, F.; Friberg, L.; Frykman, V., N-terminal pro B-type natriuretic peptide in systematic screening for atrial fibrillation. *Heart* **2017,** *103* (16), 1271-1277.
20. Yamada, T.; Murakami, Y.; Okada, T.; Yoshida, N.; Toyama, J.; Yoshida, Y.; Tsuboi, N.; Inden, Y.; Hirai, M.; Murohara, T., Plasma brain natriuretic peptide level after radiofrequency catheter ablation of paroxysmal, persistent, and permanent atrial fibrillation. *Europace* **2007,** *9* (9), 770-4.
21. Xing, S. Y.; Wang, H. L.; Dong, P. S.; Lai, L. H.; Zhu, J. H.; Zhao, J. F.; Shang, X. Y., Clinical significance and levels of blood brain natriuretic peptides in patients with persistent atrial fibrillation before and after catheter ablation. *Genet Mol Res* **2015,** *14* (2), 6953-9.
22. Date, T.; Yamane, T.; Inada, K.; Matsuo, S.; Miyanaga, S.; Sugimoto, K.; Shibayama, K.; Taniguchi, I.; Mochizuki, S., Plasma brain natriuretic peptide concentrations in patients undergoing pulmonary vein isolation. *Heart* **2006,** *92* (11), 1623-7.
23. Ata, Y.; Turk, T.; Ay, D.; Eris, C.; Demir, M.; Ari, H.; Ata, F.; Yavuz, S.; Ozyazicioglu, A., Ability of B-type natriuretic peptide in predicting postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. *Heart Surg Forum* **2009,** *12* (4), E211-6.
24. Iskesen, I.; Eserdag, M.; Kurdal, A. T.; Cerrahoglu, M.; Sirin, B. H., Preoperative NT-proBNP levels: a reliable parameter to estimate postoperative atrial fibrillation in coronary artery bypass patients. *Thorac Cardiovasc Surg* **2011,** *59* (4), 213-6.
25. Wazni, O. M.; Martin, D. O.; Marrouche, N. F.; Latif, A. A.; Ziada, K.; Shaaraoui, M.; Almahameed, S.; Schweikert, R. A.; Saliba, W. I.; Gillinov, A. M.; Tang, W. H.; Mills, R. M.; Francis, G. S.; Young, J. B.; Natale, A., Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. *Circulation* **2004,** *110* (2), 124-7.
26. Amar, D.; Zhang, H.; Shi, W.; Downey, R. J.; Bains, M. S.; Park, B. J.; Flores, R.; Rizk, N.; Thaler, H. T.; Rusch, V. W., Brain natriuretic peptide and risk of atrial fibrillation after thoracic surgery. *J Thorac Cardiovasc Surg* **2012,** *144* (5), 1249-53.
27. Horie, H.; Tsutamoto, T.; Minai, K.; Hayashi, M.; Kito, O.; Kinoshita, M., Brain natriuretic peptide predicts chronic atrial fibrillation after ventricular pacing in patients with sick sinus syndrome. *Jpn Circ J* **2000,** *64* (12), 965-70.
28. Ari, H.; Binici, S.; Ari, S.; Akkaya, M.; Koca, V.; Bozat, T.; Gurdogan, M., The predictive value of plasma brain natriuretic peptide for the recurrence of atrial fibrillation six months after external cardioversion. *Turk Kardiyol Dern Ars* **2008,** *36* (7), 456-60.
29. Lellouche, N.; Berthier, R.; Mekontso-Dessap, A.; Braconnier, F.; Monin, J. L.; Duval, A. M.; Dubois-Rande, J. L.; Gueret, P.; Garot, J., Usefulness of plasma B-type natriuretic peptide in predicting recurrence of atrial fibrillation one year after external cardioversion. *Am J Cardiol* **2005,** *95* (11), 1380-2.
30. Beck-da-Silva, L.; de Bold, A.; Fraser, M.; Williams, K.; Haddad, H., Brain natriuretic peptide predicts successful cardioversion in patients with atrial fibrillation and maintenance of sinus rhythm. *Can J Cardiol* **2004,** *20* (12), 1245-8.
31. Freynhofer, M. K.; Jarai, R.; Hochtl, T.; Bruno, V.; Vogel, B.; Aydinkoc, K.; Nurnberg, M.; Wojta, J.; Huber, K., Predictive value of plasma Nt-proBNP and body mass index for recurrence of atrial fibrillation after cardioversion. *Int J Cardiol* **2011,** *149* (2), 257-9.

32. Tveit, A.; Seljeflot, I.; Grundvold, I.; Abdelnoor, M.; Arnesen, H.; Smith, P., Candesartan, NT-proBNP and recurrence of atrial fibrillation after electrical cardioversion. *Int J Cardiol* **2009,** *131* (2), 234-9.
33. Ioannou, A.; Papageorgiou, N.; Falconer, D.; Rehal, O.; Sewart, E.; Zacharia, E.; Toutouzas, K.; Vlachopoulos, C.; Siasos, G.; Tsioufis, C.; Tousoulis, D., Biomarkers associated with stroke risk in atrial fibrillation. *Curr Med Chem* **2017**.
34. Hijazi, Z.; Oldgren, J.; Andersson, U.; Connolly, S. J.; Ezekowitz, M. D.; Hohnloser, S. H.; Reilly, P. A.; Vinereanu, D.; Siegbahn, A.; Yusuf, S.; Wallentin, L., Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation* **2012,** *125* (13), 1605-16.
35. Hijazi, Z.; Wallentin, L.; Siegbahn, A.; Andersson, U.; Christersson, C.; Ezekowitz, J.; Gersh, B. J.; Hanna, M.; Hohnloser, S.; Horowitz, J.; Huber, K.; Hylek, E. M.; Lopes, R. D.; McMurray, J. J.; Granger, C. B., N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol* **2013,** *61* (22), 2274-84.
36. Shin, D. I.; Deneke, T.; Gorr, E.; Anders, H.; Buenz, K.; Paesler, M.; Horlitz, M., Predicting successful pulmonary vein isolation in patients with atrial fibrillation by brain natriuretic Peptide plasma levels. *Indian Pacing Electrophysiol J* **2009,** *9* (5), 241-6.
37. Mohanty, S.; Mohanty, P.; Di Biase, L.; Rong, B.; Burkhardt, D.; Gallinghouse, J. G.; Horton, R.; Sanchez, J. E.; Bailey, S.; Zagrodzky, J.; Natale, A., Baseline B-type natriuretic peptide: a gender-specific predictor of procedure-outcome in atrial fibrillation patients undergoing catheter ablation. *J Cardiovasc Electrophysiol* **2011,** *22* (8), 858-65.
38. Patel, D.; Mohanty, P.; Di Biase, L.; Sanchez, J. E.; Shaheen, M. H.; Burkhardt, J. D.; Bassouni, M.; Cummings, J.; Wang, Y.; Lewis, W. R.; Diaz, A.; Horton, R. P.; Beheiry, S.; Hongo, R.; Gallinghouse, G. J.; Zagrodzky, J. D.; Bailey, S. M.; Al-Ahmad, A.; Wang, P.; Schweikert, R. A.; Natale, A., Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm* **2010,** *7* (2), 167-72.
39. Pillarisetti, J.; Reddy, N.; Biria, M.; Ryschon, K.; Nagarajan, D.; Murray, C.; Atkins, D.; Bommana, S.; Reddy, M. Y.; DiBiase, L.; Pimentel, R.; Berenbom, L.; Dawn, B.; Natale, A.; Lakkireddy, D., Elevated brain natriuretic peptide level in patients undergoing atrial fibrillation ablation: is it a predictor of failed ablation or a mere function of atrial rhythm and rate at a point in time? *J Interv Card Electrophysiol* **2014,** *40* (2), 161-8.
40. Machino-Ohtsuka, T.; Seo, Y.; Tada, H.; Ishizu, T.; Machino, T.; Yamasaki, H.; Igarashi, M.; Xu, D.; Sekiguchi, Y.; Aonuma, K., Left atrial stiffness relates to left ventricular diastolic dysfunction and recurrence after pulmonary vein isolation for atrial fibrillation. *J Cardiovasc Electrophysiol* **2011,** *22* (9), 999-1006.
41. Yamada, T.; Murakami, Y.; Okada, T.; Yoshida, N.; Toyama, J.; Yoshida, Y.; Tsuboi, N.; Inden, Y.; Hirai, M.; Murohara, T., Plasma brain natriuretic peptide level after hybrid therapy with pulmonary vein isolation and antiarrhythmic drugs for atrial fibrillation. *Int Heart J* **2008,** *49* (2), 143-51.
42. Yamada, T.; Murakami, Y.; Okada, T.; Okamoto, M.; Shimizu, T.; Toyama, J.; Yoshida, Y.; Tsuboi, N.; Ito, T.; Muto, M.; Kondo, T.; Inden, Y.; Hirai, M.; Murohara, T., Plasma atrial natriuretic Peptide and brain natriuretic Peptide levels after radiofrequency catheter ablation of atrial fibrillation. *Am J Cardiol* **2006,** *97* (12), 1741-4.
43. Kurosaki, K.; Tada, H.; Hashimoto, T.; Ito, S.; Miyaji, K.; Naito, S.; Oshima, S.; Taniguchi, K., Plasma natriuretic peptide concentrations as a predictor for successful catheter ablation in patients with drug-refractory atrial fibrillation. *Circ J* **2007,** *71* (3), 313-20.

44. Fan, J.; Cao, H.; Su, L.; Ling, Z.; Liu, Z.; Lan, X.; Xu, Y.; Chen, W.; Yin, Y., NT-proBNP, but not ANP and C-reactive protein, is predictive of paroxysmal atrial fibrillation in patients undergoing pulmonary vein isolation. *J Interv Card Electrophysiol* **2012,** *33* (1), 93-100.
45. Hwang, H. J.; Son, J. W.; Nam, B. H.; Joung, B.; Lee, B.; Kim, J. B.; Lee, M. H.; Jang, Y.; Chung, N.; Shim, W. H.; Cho, S. Y.; Kim, S. S., Incremental predictive value of pre-procedural N-terminal pro-B-type natriuretic peptide for short-term recurrence in atrial fibrillation ablation. *Clin Res Cardiol* **2009,** *98* (4), 213-8.
46. den Uijl, D. W.; Delgado, V.; Tops, L. F.; Ng, A. C.; Boersma, E.; Trines, S. A.; Zeppenfeld, K.; Schalij, M. J.; van der Laarse, A.; Bax, J. J., Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *Am Heart J* **2011,** *161* (1), 197-203.
47. Giannopoulos, G.; Kossyvakis, C.; Angelidis, C.; Efremidis, M.; Panagopoulou, V.; Letsas, K.; Bouras, G.; Vassilikos, V. P.; Goudevenos, J.; Tousoulis, D.; Lekakis, J.; Deftereos, S., Amino-terminal B-natriuretic peptide levels and postablation recurrence in hypertensive patients with paroxysmal atrial fibrillation. *Heart Rhythm* **2015,** *12* (7), 1470-5.
48. Arana-Rueda, E.; Pedrote, A.; Garcia-Riesco, L.; Arce-Leon, A.; Guerrero-Marquez, F.; Rodriguez-Rodriguez, J., [Clinical value of N-terminal pro-B-type natriuretic peptide measurement in the follow up of pulmonary vein ablation]. *Med Clin (Barc)* **2015,** *145* (6), 248-50.
49. Jiang, H.; Wang, W.; Wang, C.; Xie, X.; Hou, Y., Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Europace* **2017,** *19* (3), 392-400.
50. Thamilarasan, M.; Klein, A. L., Factors relating to left atrial enlargement in atrial fibrillation: "chicken or the egg" hypothesis. *Am Heart J* **1999,** *137* (3), 381-3.
51. Plitt, D. C.; Chung, E. H.; Mounsey, J. P.; Schwartz, J. D.; Pursell, I. W.; Gehi, A. K., Relation of atrial fibrillation burden and N-terminal pro-brain natriuretic peptide. *Am J Cardiol* **2013,** *111* (9), 1315-8.

Table 1. Predictive role of BNP in AF recurrence after ablation

Study	Population	No of patients undergoing ablation	Mean age (years)	BNP level pre-ablation (pg/ml) Mean+/- SD or Median (IQR)		P value
				No AF recurrence	AF recurrence	
Yamada, 2006 [42]	pAF	66	61	55.7 +/- 45.5	66.8 +/- 56.8	*
Kurosaki, 2007[43]	pAF and persAF	54	58	49 +/- 43	45 +/- 34	0.8
Yamada, 2008[41]	pAF, persAF,	28	55	56.8 +/- 23.1	74.3 +/- 47.8	0.32
Shin, 2009[36]	pAF, persAF	68	28-70	68.7**	144.1**	<0.05
Degener, 2011[6]	pAF, pers AF	73	53	72 (25-72)	159 (101-246)	<0.001
Mohanty, 2011[37]	pAF, persAF,	568	54	***	***	0.006 (males) 0.426 (females)
Machino-Ohtsuka, 2011[40]	pAF and persAF	155	61	49.8 +/- 54.3	55.3 +/- 39.2	0.54
Pillarisetti, 2014[39]	pAF and persAF	88	60	26 (13-50)	40 (32-55)	0.14
Xing, 2015[21]	persAF	36	64.3	49.3 +/- 22.1	98.7 +/- 45.3	<0.01

*No significant difference in baseline BNP for pAF and persAF
**Median
***High' BNP (>50 pg/ml) significantly associated with AF recurrence in men, 'High' BNP (>100 pg/ml) not significantly associated with AF recurrence in women. Mean values not available.
Abbreviations: AF: atrial fibrillation; BNP: brain natriuretic peptide; pAF: paroxysmal AF; persAF: persistent AF

Table 2: Predictive role of NT-proBNP in AF recurrence after ablation

Study	Population	No of patients undergoing ablation	Mean age (years)	NT-proBNP level pre-ablation (pg/ml) Mean +/- SD or Median (IQR)		P value
				No AF recurrence	AF recurrence	
Hwang, 2009[45]	pAF, persAF	73	52	122.6 (37.0-222.9)	602 (293-770.3)	<0.001
den Uijl, 2011[46]	pAF	87	55	84.6 (43.3-142.7)	156.4 (64.1-345.3)	0.036
Fan, 2012[44]	pAF	33	56	176+/- 188.73	572.72 +/- 234	<0.001
Giannopoulos, 2015[47]	AF	296	60	188 (146-320)	269 (199-361)	*
Arana-Rueda, 2015[48]	pAF, persAF	75	52	152 (82-432)	155 (56-553)	0.69
Ma, 2016[16]	pAF, persAF	120	64	pAF- 279.3 persAF- 358.5	pAF-614.7 persAF-832.3	* persAF-<0.001

*non-significant when adjusted for covariates
Abbreviations: AF: atrial fibrillation; BNP: brain natriuretic peptide; pAF: paroxysmal AF; persAF: persistent AF