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

Nikolaos Papageorgiou1*, Rui Providência1*, Debbie Falconer2, Tanakal Wongwarawipat2, Dimitris Tousoulis3, Wei Yao Lim1, Anthony W. Chow1, Richard Schilling1, Pier D. Lambiase1

*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

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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. 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. AF is characterized by rapid and irregular contractions of the atrium caused by multiple re-entrant circuits, variable in wavelength. They are initiated by rapidly firing foci, often located in the pulmonary veins.

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). However, 5% of patients undergoing ablation will experience significant complications including transient ischaemic attack, stroke and pericardial tamponade. 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. 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. 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, 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 patients 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{40}. Neither study by Yamada et al found a link between baseline BNP and ablation outcome\textsuperscript{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\textsuperscript{43}.

\textit{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\textsuperscript{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)\textsuperscript{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)\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 [\textsuperscript{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 [\textsuperscript{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\textsuperscript{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 [\textsuperscript{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 [\textsuperscript{47}]), has been associated with increased natriuretic peptide levels, even after adjusting for conventional confounders [\textsuperscript{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 [\textsuperscript{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:**


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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No of patients undergoing ablation</th>
<th>Mean age (years)</th>
<th>NT-proBNP level pre-ablation Mean +/- SD or Median (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hwang, 2009&lt;sup&gt;35&lt;/sup&gt;</td>
<td>pAF, persAF</td>
<td>73</td>
<td>52</td>
<td>No AF recurrence: 122.6 (37.0-222.9) AF recurrence: 602 (293-770.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>den Uijl, 2011&lt;sup&gt;36&lt;/sup&gt;</td>
<td>pAF</td>
<td>87</td>
<td>55</td>
<td>No AF recurrence: 84.6 (43.3-142.7) AF recurrence: 156.4 (64.1-345.3)</td>
<td>0.036</td>
</tr>
<tr>
<td>Fan, 2012&lt;sup&gt;44&lt;/sup&gt;</td>
<td>pAF</td>
<td>33</td>
<td>56</td>
<td>No AF recurrence: 176 +/- 188.73 AF recurrence: 572.72 +/- 234</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Giannopoulos, 2015&lt;sup&gt;47&lt;/sup&gt;</td>
<td>AF</td>
<td>296</td>
<td>60</td>
<td>No AF recurrence: 188 (146-320) AF recurrence: 269 (199-361)</td>
<td>*</td>
</tr>
<tr>
<td>Arana-Rueda, 2015&lt;sup&gt;48&lt;/sup&gt;</td>
<td>pAF, persAF</td>
<td>75</td>
<td>52</td>
<td>No AF recurrence: 152 (82-432) AF recurrence: 155 (56-553)</td>
<td>0.69</td>
</tr>
<tr>
<td>Ma, 2016&lt;sup&gt;16&lt;/sup&gt;</td>
<td>pAF, persAF</td>
<td>120</td>
<td>64</td>
<td>No AF recurrence: pAF-279.3 persAF-358.5 AF recurrence: pAF-614.7 persAF-832.3</td>
<td>*</td>
</tr>
</tbody>
</table>

*non-significant when adjusted for covariates

Abbreviations: AF: atrial fibrillation; BNP: brain natriuretic peptide; pAF: paroxysmal AF; persAF: persistent AF