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B-Type Natriuretic Peptide and Ventricular Dysfunction in the Prediction of Cardiovascular Events and Death in Hypertension.

Joe Gallagher *
Chris Watson *
Shuaiwei Zhou†
Fiona Ryan†
Mark Ledwidge *
Kenneth McDonald *

* School of Medicine & Medical Sciences, University College Dublin, Ireland
† Heartbeat Trust, Crofton Terrace, Dun Laoghaire, Co Dublin

Corresponding author:
Joe Gallagher, School of Medicine and Medical Sciences, University College Dublin, Ireland.
Tel: +353 53 9421336 Fax: +353 53 9422526 E-mail:jgallagher@ucd.ie

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Conflict of interest
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Abstract:

Background:

The prevalence and morbidity of hypertension continues to grow globally and improved methods of stratifying risk and identifying organ damage earlier are required. Methods such as echocardiography and population based risk scores are suggested by guidelines as approaches to aid in risk stratification. However, biomarkers such as natriuretic peptides may help provide such an approach.

Methods:

We analysed data from the STOP-HF cohort including participants with hypertension with and without a history of a cardiovascular event at baseline. We investigated the ability of ventricular dysfunction on echocardiography at baseline and of B-type natriuretic peptide levels in predicting future major adverse cardiovascular events (MACE) and death. We also investigated the use of SCORE to predict these events in the uncomplicated cohort.

Results:

In total 572 patients (427 with uncomplicated hypertension) were included. Thirty three patients had MACE or died during follow up. In a univariate analysis, BNP was predictive of MACE and death in all groups. Ventricular dysfunction was not predictive of MACE and death in any group. Both BNP and SCORE had predictive value in this category (Table 5). However, the magnitude and strength of the continuous association between BNP and...
events is higher and BNP adds significantly to the predictive value of SCORE as determined by likelihood ratios. The net reclassification improvement for BNP compared to stage B heart failure was 0.20.

Conclusion:

This study demonstrates that in patients with hypertension, BNP is superior to ventricular dysfunction on echocardiography in the prediction of risk of MACE and death in a community-based cohort of patients with complicated and uncomplicated hypertension.

Introduction

The prevalence of hypertension is estimated to be 30–45% in adults, with a steep increase with ageing. Since 1990 the impact of hypertension on mortality has increased by 2.1 million deaths\(^1\). Current guidelines suggest, as part of the evaluation of hypertension, that cardiovascular (CV) risk and organ damage is assessed to help stratify risk and identify those most likely to benefit from treatment. Estimating cardiovascular disease (CVD) risk is a major responsibility of primary care.

In assessing cardiovascular risk amongst individual patients with hypertension, European guidelines have focused on the Systematic COронary Risk Evaluation (SCORE) model that has been developed based on large European cohort studies. The model estimates the risk of dying from CV (not just coronary) disease over 10 years based on age, gender, smoking habits, total cholesterol and systolic blood pressure. In practice, this approach is limited by seeking to apply population-derived risk to individual hypertensive patients based on risk factors. Additional limitations include: the applicability of risk prediction charts outside the original population studied; temporal changes in population risk are challenging to identify and incorporate; the risk prediction in relatively young and older cohorts is less reliable; Importantly, the risk estimate is only applicable to those with uncomplicated hypertension.
Although there is much interest in adding new risk factors and biomarkers of risk to help address these limitations and target scarce resources to those who need it most, novel approaches have had limited incremental impact to date. Nonetheless, many international guidelines including 2-4 have stratified CV risk in different categories, based on blood pressure, CV risk factors, asymptomatic organ damage and the presence of diabetes, symptomatic CVD or chronic kidney disease, classifying patients as low, moderate, high and very high risk. In addition, guidelines suggest echocardiography should be considered in all hypertensive patients as it aids risk prediction, but recognize that access to this resource may be limited.

B Type Natriuretic peptide (BNP) is a protective cardiac hormone, which is increased in response to volume overload, haemodynamic stress and fibro-inflammation. Initially BNP was used in the diagnosis and management of heart failure 6,7. However, it has also been shown to provide valuable risk stratification in asymptomatic patients with CVD8-10 and can be easily measured in the community using point of care technology or in traditional laboratory settings.

The aim of this study is to examine the role of BNP and ventricular dysfunction on echocardiography in refining risk prediction in a community based population with hypertension and to examine the use of BNP and the SCORE risk prediction model in the subset with uncomplicated hypertension.

Methods:
The STOP HF cohort has been previously described8. In brief it consists of a cohort of patients recruited from 39 general practices on the east coast of Ireland with at least one CV risk factor or CVD but no symptomatic heart failure or known left ventricular dysfunction at baseline visit. All patients with a history of hypertension at baseline were eligible for inclusion. Patients with hypertension were divided into three categories – all hypertensives, uncomplicated hypertension and complicated hypertension. Uncomplicated hypertension refers to patients with a history of hypertension but no CV event at baseline. Patients with complicated hypertension are defined as those with a history of hypertension and a history of a CV event at baseline. All hypertensives included both these groups. Patients were
eligible to be included if they had at least two years of follow up at the time of data analysis. Ventricular dysfunction was defined according to the parameters outlined in the ESC guidelines on arterial hypertension and included having one or more of: 1) left ventricular ejection fraction <50%, 2) Left atrial volume index (LAVI) >34ml/m² and/or 3) Left ventricular mass index (LVMI) of >95 (women) >115 (men) g/m². The parameter of septal e’ was not available and lateral e’ <10 was present in 76.9% of patients. Given the high prevalence of lateral e’, this was excluded from analysis as it would impair the ability of echocardiography to predict major adverse cardiovascular events (MACE). MACE was defined as one or more of emergency hospital admission for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure at any point during follow up.

Summary statistics for continuous variables are presented as mean (standard deviation) and for binary variables as n (%). Statistical tests for differences on continuous variables between uncomplicated and complicated groups were Student t-test or Wilcoxon signed-rank test, depending on whether the variables were normally distributed. The Shapiro-Wilk test was used to test whether variables could be considered normally distributed with alpha set at 0.05. Statistical tests for differences on binary variables between two groups were the Chi-squared test or Fisher’s exact test, depending on whether the n in any cell in the 2x2 summary table was less than 5.

A two category net reclassification improvement (NRI) was calculated for the total cohort (A BNP of greater than or equal to 30pg/ml compared to stage B heart failure) and for the uncomplicated hypertension cohort (BNP greater than or equal to 20pg/ml for those with a SCORE value of 4% or less)

Univariate and multivariate stepwise logistic regression models were employed to quantify and test the relationships of B-type natural peptide (BNP) and echocardiography indicator with the outcome of MACE and death prevalence. Normal distribution for BNP was approximated by taking logarithm of positively
skewed BNP for analysis and odds ratios (ORs) were analysed by the echocardiography indicator and log-transformed BNP as well as other covariates, such as age and gender. Particularly for uncomplicated hypertension cohort, log-transformed BNP and SCORE were applied to present the odds ratio and area under curve (AUC) with corresponding 95% confidence intervals. Akaike information criterion (AIC) was used to compare the two models. Combined and univariate models were compared using the Likelihood Ratio test. All calculations were carried out using R language version 3.2.0. A 2-sided p value of <.05 was considered as statistical significance.

Ethical approval was obtained from the St Vincents University Hospital Group ethics committee.

Results:

In total, 572 participants were included in the analysis of which 146 had complicated hypertension at baseline. Just over half (54.5%) were male. (Table 1) Mean follow up was 4.0 years.

33 patients had incident MACE or died during follow up (Table 2)

The antihypertensive profile of the population is shown in Table 3.

In a univariate analysis, BNP was predictive of MACE and death in all groups while age was predictive in uncomplicated and all hypertensives. Ventricular dysfunction as defined above was not predictive of MACE and death in any group (Table 4). It is notable that many traditional modifiable CV risk factors e.g. smoking, lipid levels, random glucose, BMI and systolic blood pressure did not differ between complicated and uncomplicated hypertension (table 1) despite the much higher event rate in the complicated hypertension group. However BNP was significantly different between the groups.
In age adjusted analysis, BNP remains a predictor of MACE/death for all hypertensives and interestingly also for uncomplicated hypertension but not for complicated hypertension. Again ventricular dysfunction on echocardiography was not predictive of events. (Supplemental file tables 1 and 2)

We also sought to evaluate the use of SCORE compared to BNP both alone and together in the subset of patients with uncomplicated hypertension. Both BNP and SCORE had predictive value in this category (Table 5 and supplemental file table 3). The optimal threshold for BNP to predict MACE/death in the all hypertensive population was found to be 30pg/ml (Figure 1) and 20pg/ml in uncomplicated hypertension.

The net reclassification improvement in the total cohort of a BNP > 30pg/ml compared to stage B heart failure was 0.20. In the uncomplicated hypertension cohort the NRI for a BNP >20pg/ml compared to a SCORE value of 4% or less was 0.07. Both these findings support the use of BNP in both complicated and uncomplicated hypertension in comparison to echocardiography and SCORE. However further studies are needed to determine the optimal integration of BNP with echocardiography and SCORE in a risk assessment algorithm as similar to heart failure diagnosis a staged approach may be most appropriate.
Discussion

In an era of ageing populations, growing prevalence of chronic CVD and limited healthcare resources, more personalized approaches to risk stratification and CVD prevention in primary care are needed. While current guidelines acknowledge the limitation of reliably applying population risk to individual patients based on traditional risk factors this study demonstrates that in patients with hypertension, BNP is superior to ventricular dysfunction on echocardiography in the prediction of risk of MACE and death in a community-based cohort of patients with complicated and uncomplicated hypertension. Similarly BNP adds to the SCORE model in predicting risk of MACE and death.

In hypertension, the decision to start pharmacological treatment depends not only on blood pressure, but also on the total CV risk. Evidence of subclinical organ damage from hypertension predicts death independently of SCORE and may modify the decision to start treatment. Therefore echocardiography is recommended as part of an initial diagnostic work up to identify organ damage which also includes measures of renal damage (creatinine and albuminuria), ECG and fundoscopy in European guidelines.

Although electrocardiographic evidence of left ventricular hypertrophy has been shown to be independently associated with CVD risk, the European guidelines note that echocardiography is more sensitive than electrocardiography in diagnosing left ventricular hypertrophy and is useful to refine CV and renal risk. The guidelines suggest echocardiography should be considered in hypertensive patients in different clinical contexts and with different purposes. For example, in hypertensive patients at moderate total CV risk, it may refine the risk evaluation by detecting left ventricular hypertrophy (LVH) undetected by ECG; in hypertensive patients with ECG evidence of LVH it may more precisely assess the hypertrophy quantitatively and define its geometry and risk; in hypertensive patients with cardiac symptoms, it may help to diagnose underlying disease. However, the guidelines do recognize that a wider or more restricted use will depend on availability and cost. Given the large numbers involved and difficulties in accessing echocardiography even for symptomatic patients it is not likely or feasible that all hypertensives will have access to echocardiography.
Current guidelines state that the use of biomarkers to assess risk is not recommended\textsuperscript{12}. However, there is increasing evidence for their role in this regard and biomarkers have become a major focus of attempts to improve CV risk scores. Theoretically, biomarkers are attractive due to their ease of use and the fact that they integrate signals from different pathophysiological pathways, including cardiac, vascular, and renal health. A recent study has shown that the benefit of troponin I added to SCORE for the prediction of CV death and disease in a population free of CVD\textsuperscript{13}. The better definition of risk is a crucial requirement as the population of those with risk factors and CVD grows. Most deaths in the community occur in those at lower levels of risk because this group has more individuals compared to those at higher risk. New strategies for personalized public health measures based on strategies, such as biomarkers, are required to better stratify those at low to moderate levels of risk on population-based risk scores to allow us to target resources better in this cohort. Paget et al.\textsuperscript{14} demonstrated that NTproBNP is a useful prognostic marker in hypertension and highlighted that given its performance, together with the ease of measurement, low cost, and widespread availability should prompt a wide use of this marker for risk stratification in hypertension. This study confirms this finding and extends it to include data on the relative value of echocardiography in this cohort. Also, recent data from the SPRINT study\textsuperscript{15} demonstrates that antihypertensive therapy reduced heart failure events. Given the large numbers of people with hypertension in the community it is challenging to identify those most at risk of heart failure and thereby those who would most likely benefit from intensive therapy. Recent guidelines from the USA\textsuperscript{16} suggest the use of natriuretic peptides to identify those most at risk of heart failure and thereby targeting therapy to this group. The current study supports the use of this approach.

Refining risk prediction may be aided by the use of natriuretic peptides which have been shown in large populations to identify those at highest risk of CV events, and more specifically of incident heart failure\textsuperscript{17,9}. Indeed, studies have shown the superiority of this peptide in this regard over conventional risk indicators\textsuperscript{9,18}. Defining organ damage at the
biochemical level rather than awaiting structural or functional changes may allow an opportunity for clinicians to intervene earlier and help guide them as to which individuals require more intensive treatment. Two recent studies have used a natriuretic peptide guided strategy to target care to those most at risk of CVD with a reduction in CV events\textsuperscript{8,19}. Based on these studies the use of natriuretic peptide guided care is now suggested in at least one international guideline\textsuperscript{20}.

This study has a number of strengths and limitations. It is a community based study with a cohort of patients from general practice typical of the general population, reflected in the large number of patients with uncomplicated hypertension. They have been well characterized using echocardiography and event collection was undertaken at the practice level and only included hospitalization events to ensure accuracy of diagnosis. However this may have resulted in events such as new onset atrial fibrillation occurring in the community not being recorded as events. The high level of abnormal e’ values in this group highlights the need to ensure studies are conducted in unselected populations but also meant that this parameter was not evaluated in this study. In comparing the cohort in this study to the original STOP HF cohort it is noteworthy that the BNP level is lower in the uncomplicated hypertensive cohort than that seen in the original cohort. This is an expected finding as the original cohort included those with previous major adverse cardiovascular events and this is associated with higher BNP levels. Also blood pressure was lower in this hypertensive cohort than in the original STOP HF cohort. In the original STOP-HF cohort 40.3% were on two or more antihypertensive medications while in the hypertension cohort 57.5% were on two or more antihypertensive medications (p<0.001). Finally, the numbers of events over the follow up period are limited because of the large proportion of patients with uncomplicated hypertension and participation in collaborative specialist-family medicine chronic disease management programme.

**Conclusion:**

This study demonstrates that in patients with hypertension, BNP is superior to ventricular dysfunction on echocardiography in the prediction of risk of MACE and death in a
community-based cohort of patients with complicated and uncomplicated hypertension. Similarly BNP adds to the SCORE model in predicting risk of MACE and death. Based on the results of this study further work should be undertaken to determine the role of natriuretic peptides in refining risk in patients with hypertension and the development of strategies to integrate this approach with the use of population based risk estimates such as SCORE and the use of echocardiography to detect disease such as left ventricular systolic dysfunction.

References


Table 1. Baseline Participant Demographics

Note: 1. SD, standard deviation. 2. BNP, brain-type natriuretic peptide. 3. LVEF, left ventricular ejection fraction. 4. LVMI, left ventricular mass index. 5. LAVI, left atrial volume index.
<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Uncomplicated</th>
<th>Complicated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>572</td>
<td>427</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>MACE, No. (%)</td>
<td>16  (2.80)</td>
<td>7 (1.64)</td>
<td>9 (6.21)</td>
<td>0.01</td>
</tr>
<tr>
<td>RIP, No. (%)</td>
<td>17  (2.97)</td>
<td>11 (2.58)</td>
<td>6 (4.14)</td>
<td>0.5</td>
</tr>
<tr>
<td>MACE+RIP, No. (%)</td>
<td>33  (5.77)</td>
<td>18 (4.22)</td>
<td>15 (10.34)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 2. Post-baseline MACE and death
<table>
<thead>
<tr>
<th>Category</th>
<th>All</th>
<th>Uncomplicated</th>
<th>Complicated</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 antihypertensive medication</td>
<td>183 (32.0%)</td>
<td>143 (33.5%)</td>
<td>40 (27.6%)</td>
<td>0.23</td>
</tr>
<tr>
<td>2 antihypertensive medication</td>
<td>185 (32.3%)</td>
<td>135 (31.6%)</td>
<td>50 (34.5%)</td>
<td>0.581</td>
</tr>
<tr>
<td>3’ antihypertensive medication</td>
<td>144 (25.2%)</td>
<td>99 (23.2%)</td>
<td>45 (31.0%)</td>
<td>0.074</td>
</tr>
<tr>
<td>AA/MRA</td>
<td>5 (0.87%)</td>
<td>2 (.47%)</td>
<td>3 (2.1%)</td>
<td>0.202</td>
</tr>
<tr>
<td>AB</td>
<td>72 (12.6%)</td>
<td>54 (12.6%)</td>
<td>18 (12.4%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>362 (63.3%)</td>
<td>273 (63.9%)</td>
<td>89 (61.4%)</td>
<td>0.672</td>
</tr>
<tr>
<td>BB</td>
<td>213 (37.2%)</td>
<td>134 (31.4%)</td>
<td>79 (54.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCB</td>
<td>227 (39.7%)</td>
<td>168 (39.3%)</td>
<td>59 (40.7%)</td>
<td>0.836</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Diuretic other</td>
<td>137 (24.0%)</td>
<td>105 (24.6%)</td>
<td>32 (22.1%)</td>
<td>0.624</td>
</tr>
<tr>
<td>Loop</td>
<td>23 (4.02%)</td>
<td>10 (2.3%)</td>
<td>13 (9.0%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 3: Antihypertensive medication profile
<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>572</td>
<td>427</td>
<td>145</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( OR (95% CI) )</td>
<td>2.06</td>
<td>2.08</td>
<td>1.75</td>
</tr>
<tr>
<td>ln(BNP)</td>
<td>(1.50,2.83)</td>
<td>&lt;0.001</td>
<td>(1.05,2.91)</td>
</tr>
<tr>
<td>Echo</td>
<td>(0.95,3.90)</td>
<td>0.069</td>
<td>(0.61,5.81)</td>
</tr>
<tr>
<td>Age</td>
<td>(1.03,1.12)</td>
<td>&lt;0.001</td>
<td>(0.99,1.15)</td>
</tr>
<tr>
<td>Male</td>
<td>(0.44,1.82)</td>
<td>0.770</td>
<td>(0.16,1.45)</td>
</tr>
</tbody>
</table>

Table 4. Predicting future MACE/death using unadjusted BNP and indicator of echo parameters at baseline
Note: 1. “Echo” here is a binary variable, indicating any of these echocardiography parameters being present: left ventricular ejection fraction (LVEF) <= 50%, left ventricular mass index (LVMI) > 95g/ m² in women or >115g/ m² in men, left atrial volume index (LAVI) >= 34 ml/ m². 2. OR: odds ratio. 3. CI: confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>AUC (95% CI)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(BNP)</td>
<td>2.08 (1.36, 3.19)</td>
<td>&lt;0.001</td>
<td>70.0% (57.0%-82.9%)</td>
<td>141.72</td>
</tr>
<tr>
<td>SCORE</td>
<td>1.27 (1.02, 1.58)</td>
<td>0.03</td>
<td>64.5% (51.2%-77.9%)</td>
<td>148.95</td>
</tr>
</tbody>
</table>

Table 5 Predicting future RIP/MACE via various BNP and SCORE for uncomplicated hypertension patients
Note: 1. OR: odds ratio. 2. CI: confidence interval. 3. AUC: area under curve. 4. AIC: Akaike information criterion.
Figure 1

Row 1 – All hypertension, Row 2 - Uncomplicated hypertension Row 3 - SCORE in uncomplicated hypertension

All hypertension

Uncomplicated hypertension

SCORE in uncomplicated hypertension cohort