Amino-Terminal Pro-B-Type Natriuretic Peptide Improves Discrimination for Incident Atherosclerotic Cardiovascular Disease Beyond Ambulatory Blood Pressure in Elderly Men

Per H. Skoglund, Jonas Höijer, Johan Ärnlöv, Björn Zethelius, Per Svensson

Abstract—Improvement of risk prediction for atherosclerotic cardiovascular disease (ASCVD) is needed. Both ambulatory blood pressure (ABP) and biomarkers amino-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein and cystatin C improve risk prediction but they have not been evaluated in relation to each other. We analyzed whether NT-proBNP, high-sensitivity C-reactive protein, or cystatin C improved risk prediction beyond traditional ASCVD risk factors combined with 24-hour systolic BP (SBP). Secondary aim was to evaluate whether ABP improved risk prediction when compared with models with the biomarkers. We followed up 907 70-year-old men, free of baseline disease, for incident ASCVD defined as fatal or nonfatal myocardial infarction or fatal or nonfatal stroke for a median of 10 years. Cox regression was used to estimate the association between variables in the models and incident ASCVD. Biomarkers were added to a model containing both traditional risk factors and ABP and the models were compared on C-statistics and net reclassification improvement. Twenty-four hour SBP improved discrimination for incident ASCVD when compared with office SBP in a traditional risk factor model (area under the receiver-operating characteristic curve, +2.4%). NT-proBNP further improved reclassification (+18.7%–19.9%; P<0.01) when added to ABP models, whereas high-sensitivity C-reactive protein and cystatin C did not. Twenty-four hour SBP significantly improved net reclassification when added to a traditional risk factor model that included NT-proBNP. The combination of 24-hour SBP and NT-proBNP improved discrimination and net reclassification for incident ASCVD when compared with office SBP in elderly men. NT-proBNP, but not high-sensitivity C-reactive protein or cystatin C, improved risk prediction and discrimination when added to a model that included ABP. (Hypertension. 2015;66:681-686. DOI: 10.1161/HYPERTENSIONAHA.115.05717.) ● Online Data Supplement

Key Words: aged ▪ B-type natriuretic peptide ▪ blood-brain barrier ▪ blood pressure monitoring, ambulatory ▪ C-reactive protein ▪ cardiovascular diseases ▪ cystatin c ▪ longitudinal studies

Cardiovascular diseases (CVDs) account for almost one third of all deaths globally.1 To identify individuals that would benefit the most from risk factor intervention, it is important to have tools that accurately predict the risk for atherosclerotic CVD (ASCVD). Current risk stratification is based on traditional risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking2 but models for a better risk stratification beyond that of traditional risk factor models are warranted. Ambulatory blood pressure (ABP) predicts CVD events better than office blood pressure (BP), and its use can add to risk stratification beyond that of traditional risk factor models.3,4 and it is increasingly used as a clinical tool for decisions on antihypertensive treatment. The biomarkers amino-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and cystatin C are also predictors for CVD events in various groups of patients and subjects.5 A positive correlation to ABP has previously been reported for all of the 3 biomarkers.6–8 However, it has not been reported whether the predictive value of ABP partly can be explained by variations in these biomarkers, and conversely whether these biomarkers separately predict ASCVD events independently of ABP. Results from a study in patients with peripheral arterial disease suggest that both NT-proBNP and hs-CRP are predictive of ASCVD events independently of ambulatory pulse pressure (APP); however, cystatin C is not.9 In another study in hypertensive patients, NT-proBNP was associated with mortality, adjusted for ABP but no discriminatory analysis was reported.10 To our knowledge, no other studies have
investigated the predictive value of NT-proBNP, hs-CRP, or cystatin C when adjusted for ABP and no studies have reported on the relation to incident ASCVD. The aim of this study was to investigate whether the association between the CVD risk biomarkers NT-proBNP, hs-CRP, and cystatin C and incident ASCVD is independent of traditional CVD risk factors and ABP and vice versa in a population-based cohort of elderly men. A secondary aim was to evaluate whether a new predictive model based on traditional risk factors together with ABP and with the addition of biomarker combinations improved risk discrimination and net reclassification.

Method
The Uppsala Longitudinal Study of Adult Men (ULSAM) was initiated in 1970 when all 50-year-old men born in 1920 to 1924 living in Uppsala, Sweden, were invited to participate in a study that aimed to identify risk factors for cardiovascular disease. The study is described in detail at www.pubcare.uu.se/ULSAM. The present study was based on data from follow-up in 1991 to 1995 when subjects reached ≈70 years of age. From the original patient inclusion, 1681 were still alive, living in Uppsala and 1221 of the subjects participated in the 1991 to 1995 follow-up. All patients with missing values in ABP or any of the investigated variables were excluded, leaving 1024 subjects. Before the baseline examination, 117 subjects had been hospitalized because of coronary heart disease, heart failure, or cerebrovascular disease (International Classification of Diseases-Ninth Revision, 410, 411.8, 428, 431, 433, 434 and International Classification of Diseases-Eighth Revision: 410, 411, 431, 432, 433, 434) or surgical codes (Swedish classification of interventions and procedures) for percutaneous coronary intervention or coronary artery bypass graft used as proxy for coronary heart disease (KVA: FNA, FNB, FNC, FND, FNE, FNF, FNG and before 1996; 3066, 3067, 3080, 3105, 3127, 3158) and were defined as having CVD at baseline and were excluded resulting in 907 subjects for final analyses.

BP Measurements
BP was measured in the right arm with a sphygmomanometer using the appropriate cuff size. Recordings were taken with the subject in the supine position after resting for 10 minutes.

ABP was measured with Accutracker II (Suntech Medical Instruments, Raleigh, NC).

Details of BP measurements are presented in the online-only Data Supplement.

Laboratory Examination
Laboratory methods are presented in the online-only Data Supplement.

Survival and Hospitalization Data
The end point was a new event of ASCVD defined as fatal or nonfatal myocardial infarction or fatal or nonfatal stroke. Event data were obtained from the Swedish Hospital Discharge and Cause of Death Registries according to the International Classification of Diseases-Tenth Revision: I21, I22, I61, I63, I64 and International Classification of Diseases-Ninth Revision: 410, 411.8, 431, 433 and 434. Only main discharge and main death diagnosis were used to identify events. All observations were censored at 10 years after the baseline visit (1991–1995).

Ethical Approval
The study was approved by the ethics committee of Uppsala University: DNR: 251/90. All participants gave informed consent.

Statistical Method
A basic ASCVD risk model was used that included the traditional CVD risk factors age, smoking, diabetes mellitus, treatment for hypertension, lipid-lowering medication, body mass index, cholesterol, high-density lipoprotein cholesterol, and office SBP, all of which have previously been used as risk factors in the ULSAM cohort (basic ASCVD risk model). The basic ASCVD risk model was altered by adding ABP variables one at a time and by exchanging office SBP for ABP variables one at a time. Cox regression was used to estimate the association between the variables in the models and incident ASCVD. For each of these models, a measure of predictive power, Harrell’s C, was calculated. Two ABP models (24-hour SBP and 24-hour PP) were chosen for further analyses. The biomarkers were added, alone and in combinations, to the basic ASCVD risk model and to the chosen ABP models and new models were created. Finally, the new models were compared with the same model that also included 24-hour SBP and 24-hour PP, respectively. The variables NT-proBNP, hs-CRP, and cystatin C were logarithmic transformed because of skewness. All continuous variables presented in the models were standardized, with the consequence that the interpretation of the regression coefficients was in terms of 1 change in SD. Observations with missing values on at least 1 covariate were excluded from the analysis. Schoenfeld residuals were used to test the assumptions of proportional hazards.

Two other measures of difference in discriminations between the models were used, category-free net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) for survival data according to Uno et al. When comparing 2 models in cNRI, a model is considered better in terms of predictability if individuals without events move to a lower risk and individuals with events move to a higher risk. IDI is based on predictive probabilities of events within the 2 event groups. A new model is considered better if the estimated probability of events is higher for individuals with events and lower for individuals without events. P values <0.05 were considered statistically significant. All statistical analyses were made with the statistical software Stata (version 13) and R (version 3.1).

Results
Baseline characteristics are displayed in Table 1. Median follow-up time was 10 years. All variables fulfilled the assumption of proportional hazards. All variables were predictive of outcome in crude analysis except for age (P=0.31), lipid-lowering medication (P=0.79), and body mass index (P=0.23; Table 2). All ABP variables were significant predictors in adjusted analyses (range; 24-hour SBP [hazard ratio, 1.35; P<0.001] to night PP [hazard ratio, 1.20; P=0.003]). Hazard ratios for all adjusted ABP variables and C-statistics for the different ABP models are presented in Table S1 in the online-only Data Supplement. The performance of the 2 ABP (24-hour SBP model [ASBPm] and 24-hour PP model; APP hazard ratio, 1.25; P=0.002) models that were chosen for further analyses with biomarkers compared with the basic ASCVD risk factor model is shown in Table 3. The AUC for the ASBPm was higher when compared with the basic ASCVD risk model but net reclassification was not significantly improved. The addition of any of the biomarkers to the basic ASCVD risk model did not improve AUC. However, the addition of NT-proBNP improved reclassification. The comparisons between the ABP-biomarker models and the ABP models are shown in Table 3. No significant improvement in C-statistics was observed when we compared combined ABP-biomarker models with the ASBPm or 24-hour PP model, respectively (Table 3). However, the addition of NT-proBNP, but not the other biomarkers, significantly improved net reclassification as well as IDI when compared with both to the ASBPm and to the 24-hour PP model (Table 3).
Table 1. Baseline Characteristics at 71 Years of Age: The Uppsala Longitudinal Study of Adult Men Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>n/mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.0 (0.61)</td>
<td>69.4–73.6</td>
</tr>
<tr>
<td>Smoker (yes)</td>
<td>185 (20.4)</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>584 (64.4)</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>132 (14.6)</td>
<td>...</td>
</tr>
<tr>
<td>Treatment for hypertension (yes)</td>
<td>287 (31.6)</td>
<td>...</td>
</tr>
<tr>
<td>Lipid medication (yes)</td>
<td>76 (8.4)</td>
<td>...</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2 (3.4)</td>
<td>16.7–46.3</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.80 (0.99)</td>
<td>2.43–8.97</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.30 (0.35)</td>
<td>0.51–3.05</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>96.6 (56.4, 188)</td>
<td>5–3992</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>1.81 (0.92, 3.8)</td>
<td>0.16–47.8</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>1.19 (1.07, 1.32)</td>
<td>0.75–4.87</td>
</tr>
<tr>
<td>SBP office, mm Hg</td>
<td>147.1 (18.5)</td>
<td>100–222</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>135.7 (16.5)</td>
<td>101–208</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>76.6 (7.9)</td>
<td>55–109</td>
</tr>
<tr>
<td>24-h PP, mm Hg</td>
<td>59.0 (12.3)</td>
<td>34–146</td>
</tr>
<tr>
<td>24-h SBP night, mm Hg</td>
<td>121.4 (19.2)</td>
<td>86–218</td>
</tr>
<tr>
<td>24-h DBP night, mm Hg</td>
<td>67.8 (8.8)</td>
<td>45–98</td>
</tr>
<tr>
<td>24-h PP night, mm Hg</td>
<td>53.5 (14.5)</td>
<td>30–165</td>
</tr>
</tbody>
</table>

Values expressed as n (%) for categorical variables and as mean (SD) or median (interquartile range) for continuous variables. BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PP, pulse pressure; and SBP, systolic blood pressure.

To determine the additive effect of ABP to models including biomarkers, we compared the ASBPM and the 24-hour PP model biomarker models to the basic ASCVD risk model with the corresponding biomarker combination. None of the combined ABP-biomarker models improved AUC to the corresponding basic ASCVD-biomarker risk models (Table 4). However, the addition of 24-hour SBP to a basic ASCVD risk model with NT-proBNP improved net reclassification (+19.2%; P=0.042) but not when added to any of the other biomarker models. IDI did not improve when we added 24-hour SBP or 24-hour PP to the basic ASCVD risk model combined with biomarkers (Table 4).

Discussion

In this study, we investigated whether the biomarkers NT-proBNP, hs-CRP, and cystatin C provided independent predictive information when added to a basic risk prediction model with and without ABP. The addition of 24-hour SBP improved prediction of incident ASCVD when compared with office SBP in elderly male subjects but did not improve net reclassification. However, when we added NT-proBNP net reclassification improved. A novel finding of this study was that NT-proBNP had additional predictive value when added to an ABP model, whereas hs-CRP and cystatin C did not. Furthermore, 24-hour SBP had additive predictive value to a traditional risk factor model including NT-proBNP.

ABP provides a more accurate measurement of BP values than office BP and in addition, a BP profile for 24 to 48 hours reveals both masked hypertension and nondipping patterns. ABP monitoring is commonly used for patients with large variability in BP readings in the office and when there is a suspicion of white-coat hypertension or masked hypertension. However, according to the current European guidelines, ABP should be considered in more BP evaluations or even routinely used because of the additive information it provides in treatment decisions and in monitoring treatment effect. ABP is also superior to office BP as a predictive marker for future CVD events. A positive correlation between ABP and the biomarkers NT-proBNP, hs-CRP, and cystatin C has been observed in different populations. Furthermore, in cross-sectional studies, associations between the level of natriuretic peptides and either nondipping or nondipping BP load,9 as well as cardiac hypertrophy or dysfunction have been reported. Despite the knowledge of such associations, few studies have investigated whether NT-proBNP, hs-CRP, and cystatin C predict incident ASCVD independently of ABP. To our knowledge, only Paget et al10 have showed NT-proBNP to be independent of ABP as a predictor of outcome. However, their study population was younger and consisted of hypertensive patients in a specialized clinical setting. Furthermore, their outcome consisted of all-cause death, whereas in our study, the outcome was all ASCVD events, which hampers comparisons.

The finding that NT-proBNP improved risk discrimination to ABP is not surprising. Earlier studies show a strong
association between NT-proBNP and CVD and CVD death. However, an earlier study showed that biomarkers including NT-proBNP had minimal additive value in risk classification when added to traditional risk factor model in a community-based setting. In the present study, we showed that NT-proBNP did have additive value in risk assessment when added to a model consisting of traditional risk factors and ABP and also when added together with ABP to a

Table 3. C-statistics and Reclassification Analyses of Different Risk Predictions Models Including Biomarkers and Office or Ambulatory Blood Pressure and Basic Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th>Model</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>AUC</th>
<th>cNRI</th>
<th>IDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic CVD risk factor model*</td>
<td>1.24</td>
<td>1.04 to 1.48</td>
<td>0.015</td>
<td>0.664</td>
<td>0.621 to 0.708</td>
<td>...</td>
</tr>
<tr>
<td>+log(NT-proBNP)</td>
<td>1.46</td>
<td>1.22 to 1.74</td>
<td>&lt;0.001</td>
<td>0.021</td>
<td>−0.006 to 0.048</td>
<td>15.6</td>
</tr>
<tr>
<td>+log(hs-CRP)</td>
<td>1.18</td>
<td>0.99 to 1.41</td>
<td>0.062</td>
<td>0.005</td>
<td>−0.008 to 0.017</td>
<td>20.1</td>
</tr>
<tr>
<td>+log(cystatin C)</td>
<td>1.17</td>
<td>0.99 to 1.39</td>
<td>0.069</td>
<td>0.006</td>
<td>−0.007 to 0.019</td>
<td>5.7</td>
</tr>
<tr>
<td>24-h SBP model</td>
<td>1.35</td>
<td>1.17 to 1.57</td>
<td>&lt;0.001</td>
<td>0.024</td>
<td>0.003 to 0.046</td>
<td>16.0</td>
</tr>
<tr>
<td>24-h PP model</td>
<td>1.25</td>
<td>1.09 to 1.43</td>
<td>0.027</td>
<td>0.013</td>
<td>−0.006 to 0.031</td>
<td>3.2</td>
</tr>
<tr>
<td>Basic CVD risk factor model and ABP</td>
<td></td>
<td></td>
<td></td>
<td>0.688</td>
<td>0.645 to 0.732</td>
<td>...</td>
</tr>
<tr>
<td>+log(NT-proBNP)</td>
<td>1.49</td>
<td>1.25 to 1.77</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>−0.010 to 0.043</td>
<td>18.7</td>
</tr>
<tr>
<td>+log(hs-CRP)</td>
<td>1.16</td>
<td>0.97 to 1.39</td>
<td>0.104</td>
<td>−0.000</td>
<td>−0.010 to 0.010</td>
<td>17.5</td>
</tr>
<tr>
<td>+log(cystatin C)</td>
<td>1.18</td>
<td>1.00 to 1.40</td>
<td>0.051</td>
<td>0.000</td>
<td>−0.011 to 0.012</td>
<td>7.6</td>
</tr>
<tr>
<td>+All biomarkers</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
<td>−0.012 to 0.036</td>
<td>19.3</td>
</tr>
<tr>
<td>24-h PP model</td>
<td></td>
<td></td>
<td></td>
<td>0.677</td>
<td>0.633 to 0.720</td>
<td>...</td>
</tr>
<tr>
<td>+log(NT-proBNP)</td>
<td>1.49</td>
<td>1.25 to 1.78</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>−0.010 to 0.043</td>
<td>19.9</td>
</tr>
<tr>
<td>+log(hs-CRP)</td>
<td>1.17</td>
<td>0.98 to 1.40</td>
<td>0.084</td>
<td>0.001</td>
<td>−0.010 to 0.012</td>
<td>17.5</td>
</tr>
<tr>
<td>+log(cystatin C)</td>
<td>1.18</td>
<td>1.00 to 1.39</td>
<td>0.057</td>
<td>0.003</td>
<td>−0.009 to 0.016</td>
<td>7.8</td>
</tr>
<tr>
<td>+All biomarkers</td>
<td></td>
<td></td>
<td></td>
<td>0.020</td>
<td>−0.006 to 0.046</td>
<td>18.5</td>
</tr>
</tbody>
</table>

AUC is based on Harrell’s C. CIs for the difference in c-statistics between models is calculated by bootstrap resampling. AUC indicates area under the receiver-operating characteristic curve; CI, confidence interval; cNRI, category free net reclassification improvement; CVD, cardiovascular disease; HR, hazard ratio (apply for a 1 SD increase in the variable added to the model); hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PP, pulse pressure; and SBP, systolic blood pressure.

*Basic CVD risk factor model consists of SBP office, serum cholesterol, high-density lipoprotein, body mass index, age, treatment for hypertension (yes/no), diabetes mellitus (yes/no), lipid-lowering treatment (yes/no), and smoking status (yes/no).

However, an earlier study showed that biomarkers including NT-proBNP had minimal additive value in risk classification when added to traditional risk factor model in a community-based setting. In the present study, we showed that NT-proBNP did have additive value in risk assessment when added to a model consisting of traditional risk factors and ABP and also when added together with ABP to a

Table 4. Comparisons of the Additive Value of Ambulatory Blood Pressure to Models With Biomarker and Basic Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC Diff</th>
<th>95% CI</th>
<th>%</th>
<th>P Value</th>
<th>Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic CVD risk factor model* and log(NT-proBNP)</td>
<td>0.685 (ref)</td>
<td>0.642 to 0.729</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>+24-h SBP</td>
<td>0.013</td>
<td>−0.004 to 0.030</td>
<td>19.2</td>
<td>0.042</td>
<td>0.014</td>
<td>−0.003 to 0.034</td>
</tr>
<tr>
<td>+24-h PP</td>
<td>0.007</td>
<td>−0.007 to 0.021</td>
<td>8.8</td>
<td>0.433</td>
<td>0.005</td>
<td>−0.011 to 0.021</td>
</tr>
<tr>
<td>Basic CVD risk factor model and log(hs-CRP)</td>
<td>0.669 (ref)</td>
<td>0.626 to 0.712</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>+24-h SBP</td>
<td>0.019</td>
<td>−0.000 to 0.039</td>
<td>13.6</td>
<td>0.138</td>
<td>0.008</td>
<td>−0.009 to 0.027</td>
</tr>
<tr>
<td>+24-h PP</td>
<td>0.009</td>
<td>−0.009 to 0.026</td>
<td>1.2</td>
<td>0.924</td>
<td>0.001</td>
<td>−0.017 to 0.016</td>
</tr>
<tr>
<td>Basic CVD risk factor model and log(cystatin C)</td>
<td>0.670 (ref)</td>
<td>0.627 to 0.713</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>+24-h SBP</td>
<td>0.019</td>
<td>−0.001 to 0.039</td>
<td>16.4</td>
<td>0.097</td>
<td>0.011</td>
<td>−0.007 to 0.030</td>
</tr>
<tr>
<td>+24-h PP</td>
<td>0.010</td>
<td>−0.007 to 0.027</td>
<td>3.0</td>
<td>0.778</td>
<td>0.003</td>
<td>−0.015 to 0.018</td>
</tr>
<tr>
<td>Basic CVD risk factor model and all biomarkers</td>
<td>0.689 (ref)</td>
<td>0.646 to 0.732</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>+24-h SBP</td>
<td>0.011</td>
<td>−0.004 to 0.027</td>
<td>19.8</td>
<td>0.052</td>
<td>0.013</td>
<td>−0.003 to 0.033</td>
</tr>
<tr>
<td>+24-h PP</td>
<td>0.008</td>
<td>−0.006 to 0.021</td>
<td>7.7</td>
<td>0.491</td>
<td>0.005</td>
<td>−0.011 to 0.021</td>
</tr>
</tbody>
</table>

Office blood pressure is exchanged for either 24-h SBP or 24-h PP in each basic CVD risk factor model with biomarkers. AUC is based on Harrell’s C. CIs for the difference in c-statistics between models is calculated by bootstrap resampling. AUC indicates area under the receiver-operating characteristic curve; CI, confidence interval; cNRI, category free net reclassification improvement; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PP, pulse pressure; and SBP, systolic blood pressure.

*Basic CVD risk factor model consists of SBP office, serum cholesterol, high-density lipoprotein, body mass index, age, treatment for hypertension (yes/no), diabetes mellitus (yes/no), lipid-lowering treatment (yes/no), and smoking status (yes/no).
traditional risk factor model. Thus, there are differences in design but also differences in the studied populations that may contribute to the different findings of the 2 studies. There is a
known correlation between NT-proBNP and ABP; however, in a recent study, we showed that NT-proBNP was a predictive
marker independent of ABP in patients with peripheral ar
terial disease.9 Zethelius et al9 have previously reported additive
value of a panel of biomarkers (including NT-proBNP)
when added to a traditional CVD risk model, both in risk prediction and in discrimination with CVD death as outcome.
NT-proBNP is highly associated with congestive heart failure
because NT-proBNP is secreted from cardiac myocytes when
stimulated by myocardial stretch. Therefore, the association
with CVD and CVD death in clinically healthy patients with
elevated NT-proBNP may be because of preclinical congestive
heart failure related to hypertensive and atherosclerotic
heart disease. Hence, in a clinical setting where ABP has been
performed, our results suggest that NT-proBNP may have
additional value to identify high-risk patients and affect treat-
ment decisions.

In our study, hs-CRP alone did not improve prediction
or discrimination beyond that of traditional risk factors (Table 3). This was an unexpected finding considering that
many previous studies have shown hs-CRP to be an indepen-
dent predictive marker for incident CVD.23 The use of hs-CRP
in risk stratification in addition to traditional risk factors has
also been suggested in recent guidelines.2 A previous study in
elderly men showed that hs-CRP was correlated to ABP.1 In a
study in patients with peripheral arterial disease, hs-CRP was
a predictor for CVD events independent of APP and the addi-
tion of hs-CRP improved risk discrimination in this setting.3
Despite previously reported positive associations between hs-
CRP and incident CVD, there is still debate whether CRP has
a role in predictive CVD models.23

Cystatin C is used for estimating kidney function through
estimating glomerular filtration rate. Kidney function is asso-
ciated with CVD and cystatin C has been shown to be a pre-
dictive marker for CVD.24,25 As for hs-CRP, cystatin C did not
improve prediction or discrimination in our study.

In our elderly cohort, many patients died from other
causes than ASCVD, which resulted in a high degree of cen-
sored observations, which might have lowered the power of
the study. It is also well known that the test of difference in
Harrell’s C has low statistical power when the base model
already has reasonably good predictability.26 Therefore,
Pencina et al26 developed 2 additional measures of predictive
power, NRI, and IDI. NRI is based on having predefined risk
categories but results heavily depend on relevant cutoffs in
order for patients to change risk categories when comparing
models. Therefore, Uno et al11 further developed a category-
free NRI that was used in the current study. This new reclas-
sification method also considers time-to-event data.

In the 2013 American College of Cardiology/American
Heart Association Guideline on the Assessment of Cardio-
vascular Risk,2 incident ASCVD was introduced as a new outcome. Incident ASCVD, defined as nonfatal myo-
cardial infarction or coronary heart disease death or fatal or
nonfatal stroke, differs from earlier CVD end points by now
including ischemic stroke. Previous studies have had different
variations in end points not all including stroke, which makes
comparisons difficult. In the current study, the outcome in
the 2013 American College of Cardiology/American Heart
Association Guideline on the Assessment of Cardiovascular
Risk was used, although we used a more narrow definition of
coronary heart disease death, only including fatal myocardial
infarction, in order not to introduce ascertainment bias and
improve the internal validity of this end point.

In this study, we tested several different models in differ-
ent combinations that increase the possibility of type I errors,
which may limit the interpretation of the results. Other limi-
tations are the lack of variety in age, (in general one of the
strongest predictors for ASCVD events) and that the cohort
only consisted of men. Although this limits the findings of our
study, it may enable the identification of new associations,
as the effects of age and sex are limited or nonexistent. Our
results need to be confirmed in populations with both sexes
and with a wider age distribution. Another limitation is that
cost-effectiveness analysis was not performed because of the
overall high absolute risk in this population.

Perspectives

Our results support the use of both NT-proBNP and ABP to
improve risk prediction in elderly male patients. NT-proBNP
and ABP are widely available and not harmful with possible
benefit for the patients as treatment may reduce risk for future
ASCVD events. However, our results need to be confirmed
in further studies including cost-effectiveness analyses with
estimates of the number needed to screen, before they can be
recommended in clinical practice.

Sources of Funding

This study was supported by grants from Karolinska Institutet Grants
and the Swedish Society of Medicine (SLS-412071).

Disclosures

Results and views of the present study represent the authors and are
not necessarily any official views of the Medical Products Agency
where one author (B. Zethelius) is employed. The authors declare no
conflicts of interest.

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**Novelty and Significance**

**What Is New?**

- Amino-terminal pro-B-type natriuretic peptide improves risk prediction and discrimination beyond ambulatory blood pressure for incident atherosclerotic cardiovascular disease in elderly men.

- Ambulatory blood pressure improves risk prediction and discrimination beyond amino-terminal pro-B-type natriuretic peptide for incident atherosclerotic cardiovascular disease in elderly men.

**What Is Relevant?**

- Ambulatory blood pressure monitoring is better than office blood pressure when predicting cardiovascular disease.

- Few studies have evaluated novel biomarkers in relation to traditional risk factors and ambulatory blood pressure.
Amino-Terminal Pro-B-Type Natriuretic Peptide Improves Discrimination for Incident Atherosclerotic Cardiovascular Disease Beyond Ambulatory Blood Pressure in Elderly Men

Per H. Skoglund, Jonas Höijer, Johan Årnlöv, Björn Zethelius and Per Svensson

_Hypertension._ 2015;66:681-686; originally published online July 6, 2015; doi: 10.1161/HYPERTENSIONAHA.115.05717

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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NT-proBNP IMPROVES DISCRIMINATION FOR INCIDENT
ATHEROSCLEROTIC CARDIOVASCULAR DISEASE BEYOND
AMBULATORY BLOOD PRESSURE IN ELDERLY MEN

Per Skoglund, Jonas Höijer, Johan Ärnlöv, Björn Zethelius,

Per Svensson

Supplemental material
**Ambulatory blood pressure measurement**
The device was fitted to the patients’ non-dominant arm by a skilled lab technician. Systolic BP (SBP) and diastolic BP (DBP) were measured every 30 min during daytime (0600-2300) and every hour during night time over 24 hours. From November 1993, BP was measured every 20 minutes during the whole 24-hour period. Limited editing was done excluding all readings of zero, DBP >170 mm Hg, SBP >270 mm Hg or < 80 mm Hg and all readings with pulse pressure (PP) less than 10 mm Hg.

**Office blood pressure**
The values was recorded twice and to the nearest even figure and presented as means of the two values for each BP. SBP and DBP was defined as Korotkoff phases I and V, respectively. Hypertension prevalence was defined as a supine SBP of 140 mmHg or greater and/or DBP of 90 mmHg or greater and/or treatment with anti-hypertensive drugs for hypertension. Men treated with these drugs for other reasons, i.e. congestive heart failure, were thus not included in this definition. Hypertension treatment was defined as treatment with antihypertensive drugs.

**Laboratory examination**
Serum Cystatin C and hs-CRP measurements were performed by latex enhanced reagent (Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec analyzer (Dade Behring). The assays were performed at the Department of Clinical Chemistry, University Hospital, Uppsala, which is accredited according to 17025 by Swedac. Plasma NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). Biomarker analysis was based on frozen samples stored at -70° C for a mean (SD) of 11±2 years. Plasma glucose in samples from the oral glucose tolerance test was measured by the glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany). Cholesterol and triglyceride concentrations were analyzed in serum and in the isolated lipoprotein fractions by enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method for use in a Monarch apparatus (Instrumentation Laboratories, Lexington, USA). HDL particles were separated by precipitation with magnesium chloride/phosphotungstate. LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45·serum triglycerides in mmol/L). Diabetes was diagnosed according to the 1985 WHO criteria.\(^1\)
References

Table S1

C-statistics and hazard ratios for adjusted cardiovascular risk models for different ambulatory blood pressure variables at 71 years of age the ULSAM cohort

<table>
<thead>
<tr>
<th>Model</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic CVD risk factor model*</td>
<td>1.24</td>
<td>1.04-1.48</td>
<td>0.015</td>
<td>0.664</td>
<td>0.621-0.708</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ 24h SBP</td>
<td>1.33</td>
<td>1.11-1.58</td>
<td>0.002</td>
<td>0.687</td>
<td>0.644-0.730</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ 24h DBP</td>
<td>1.26</td>
<td>1.06-1.51</td>
<td>0.009</td>
<td>0.679</td>
<td>0.636-0.722</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ 24h PP</td>
<td>1.19</td>
<td>1.02-1.40</td>
<td>0.027</td>
<td>0.678</td>
<td>0.635-0.721</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night SBP</td>
<td>1.26</td>
<td>1.08-1.47</td>
<td>0.003</td>
<td>0.683</td>
<td>0.639-0.726</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night DBP</td>
<td>1.25</td>
<td>1.05-1.49</td>
<td>0.011</td>
<td>0.670</td>
<td>0.626-0.714</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night PP</td>
<td>1.16</td>
<td>1.01-1.33</td>
<td>0.030</td>
<td>0.677</td>
<td>0.634-0.721</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Basic CVD risk model* without office SBP

<table>
<thead>
<tr>
<th>Model</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 24h SBP</td>
<td>1.35</td>
<td>1.17-1.57</td>
<td>&lt;0.001</td>
<td>0.688</td>
<td>0.645-0.732</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ 24h DBP</td>
<td>1.32</td>
<td>1.13-1.55</td>
<td>0.001</td>
<td>0.678</td>
<td>0.634-0.722</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ 24h PP</td>
<td>1.25</td>
<td>1.09-1.43</td>
<td>0.002</td>
<td>0.677</td>
<td>0.633-0.712</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night SBP</td>
<td>1.30</td>
<td>1.13-1.49</td>
<td>&lt;0.001</td>
<td>0.682</td>
<td>0.637-0.726</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night DBP</td>
<td>1.31</td>
<td>1.12-1.54</td>
<td>0.001</td>
<td>0.667</td>
<td>0.622-0.712</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ night PP</td>
<td>1.20</td>
<td>1.07-1.36</td>
<td>0.003</td>
<td>0.674</td>
<td>0.630-0.719</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

24h, 24 hour; AUC, area under the receiver-operating characteristic curve; CI, confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; HR, hazard ratio; PP, pulse pressure; SBP, systolic blood pressure

* basic CVD risk factor model consists of SBP office, serum cholesterol, HDL, BMI, age, treatment for hypertension (yes/no), diabetes, (yes/no), lipid lowering treatment (yes/no) and smoking status (yes/no)

Adjusted HRs and CIs are presented for the BP variable stated, and for office SBP in the basic CV risk factor model.

AUC is based on Harrell’s C.