

Impact of Systemic Hypertension on the Diagnostic Performance of B-Type Natriuretic Peptide in Patients With Acute Dyspnea

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Hypertension may affect the diagnostic performance of B-type natriuretic peptide (BNP). The objective of the present study was to assess the impact of a history of hypertension or blood pressure elevation on admission on the diagnostic performance of BNP in the diagnosis of heart failure (HF) in patients with acute dyspnea. BNP levels were measured using a rapid point-of-care device in 1,586 patients with acute dyspnea. In patients with HF, BNP levels did not differ between those with and without histories of hypertension. Conversely, in patients without HF, a history of hypertension was associated with higher median BNP levels (38 pg/ml [interquartile range 13 to 119] vs 21 pg/ml [interquartile range 7 to 64], $p < 0.001$). The areas under the receiver-operating characteristic curves were 0.88 and 0.93 for those with and without histories of hypertension, respectively ($p < 0.001$). Blood pressure elevation on admission did not affect the diagnostic accuracy of BNP (areas under the curve 0.90 in the 2 groups). In conclusion, although a history of hypertension is associated with higher BNP levels in patients with acute dyspnea without HF, the impact on the overall diagnostic performance of BNP is modest. Accordingly, BNP performs well as an indicator of HF in patients presenting in emergency departments regardless of a history of hypertension or elevated blood pressure on admission. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;104:966–971)

Arterial hypertension and left ventricular hypertrophy have been associated with increased plasma B-type natriuretic peptide (BNP) concentrations.¹ A history of hypertension could thus theoretically obscure the association between BNP and heart failure (HF) and reduce the diagnostic performance of BNP. Moreover, it is conceivable that acute pressure overload, commonly seen in patients presenting with acute dyspnea, may cause acute BNP elevation. Accordingly, the objective of the present study was to investigate whether a history of hypertension, or actual blood pressure elevation on admission, affects the diagnostic performance of BNP as a diagnostic marker of HF in patients with acute dyspnea.

Methods

The Breathing Not Properly Multinational Study was a 7-center diagnostic test evaluation trial conducted from April 1999 to December 2000.² The study's main aim was to evaluate the utility of BNP measurement for diagnosing HF in the emergency department. A total of 1,586 patients, all presenting with acute dyspnea in the emergency department, were enrolled. Of the cohort, 99 patients had no recorded data of medical histories of hypertension, leaving 1,487 patients for analysis of the effects of a history of hypertension. Three patients did not have complete data for blood pressure, leaving 1,583 in this subgroup. Patients presenting with acute myocardial infarctions or renal failure (estimated creatinine clearance < 15 ml/min and those receiving dialysis therapy), those aged < 18 years, those unable to give informed consent, and those with dyspnea due to obvious noncardiac origins (e.g., penetrating lung injury) were excluded. All patients were examined according to common clinical practice by an emergency physician. This included a thorough medical history and physical examination. A research assistant collected the patients' electrocardiograms, laboratory test results, and current medication information. Blood samples for subsequent BNP analysis were collected before the initiation of medical therapy.

The diagnosis of (1) dyspnea due to acute HF, (2) a history of HF but current dyspnea due to a noncardiac cause, or (3) dyspnea due to a noncardiac cause was made by 2 experienced cardiologists at each center. For the purposes of this study, the

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Table 1
Patient characteristics according to history of hypertension status

Variable	History of Hypertension		p Value
	No (n = 608)	Yes (n = 879)	
Final diagnosis of heart failure	210 (34.5%)	477 (54.3%)	<0.001
Age (years)	61 (45–75)	68 (56–77)	<0.001
Men	362 (60.0%)	475 (54.0%)	0.038
Previous heart failure	139 (22.9%)	364 (41.4%)	<0.001
Previous myocardial infarction	114 (19.2%)	248 (31.1%)	<0.001
Diabetes mellitus	73 (12.1%)	280 (34.1%)	<0.001
Atrial fibrillation/flutter	57 (9.4%)	88 (10.0%)	0.723
Body mass index (kg/m ²)	25.4 (22.3–30.4)	28.1 (24.2–33.5)	<0.001
Systolic blood pressure (mm Hg)	130 (114–147)	147 (128–165)	<0.001
Diastolic blood pressure (mm Hg)	75 (66–85)	80 (68–93)	<0.001
Mean arterial pressure (mm Hg)	93.3 (83–105)	102.7 (89.3–115.7)	<0.001
Heart rate (beats/min)	91 (80–109)	88 (74–103)	<0.001
Creatinine (mg/dl)	1.0 (0.8–1.2)	1.1 (0.8–1.4)	<0.001
BNP >100 pg/ml	268 (44.1%)	558 (63.5%)	<0.001
BNP (pg/ml)	66.6 (14.2–358.3)	253.7 (45.8–795.7)	<0.001
Medications at home			
Angiotensin-converting enzyme inhibitors	110 (18.5%)	348 (40.9%)	<0.001
β blockers	84 (14.1%)	234 (27.7%)	<0.001
Calcium channel blockers	60 (10.1%)	259 (30.7%)	<0.001
Digoxin	86 (14.5%)	173 (20.3%)	0.005
Other antiarrhythmic agents	29 (4.9%)	66 (7.8%)	0.031
Diuretics	199 (33.3%)	496 (57.9%)	<0.001

Data are expressed as number (percentage) or as median (IQR).

2 latter groups were pooled. The 2 cardiologists were blinded to the BNP results. Because not all patients underwent the same battery of diagnostic tests, no formal criteria for the diagnosis of HF were used by the 2 cardiologists. To classify patients into 1 of the 3 categories, the cardiologists did, however, have access to the emergency department sheets and information obtained after the initial assessment in the emergency department. This could include chest x-ray, reported by a radiologist; additional medical history; and echocardiographic reports or radionuclide or contrast ventriculographic reports. Echocardiography was performed in 709 of 1,586 patients, of whom 492 were diagnosed with HF. Echocardiographic examinations were performed according to the local practices of the participating academic centers (i.e., without formalization of echocardiographic methods across centers). Because the HF category could include patients with systolic HF and those with nonsystolic HF, no specific value for the left ventricular ejection fraction was used to distinguish patients with and without final diagnoses of HF. The 2 cardiologists were also presented with calculated Framingham scores for congestive HF and the National Health and Nutrition Examination Survey (NHANES) congestive HF scores. These calculations were based on case reports. For the non-HF group, confirmation of the diagnosis was based on normal chest x-ray findings (i.e., absence of radiographic cardiomegaly); evident chronic obstructive pulmonary disease, pneumonia, trauma, or lung cancer; and normal heart function assessed by echocardiography, radionuclide ventriculography, or contrast ventriculography. The most common causes of acute dyspnea in patients without HF or with histories of HF were chronic obstructive pulmonary disease, asthma, pneumonia, and ane-

mia. The 2 cardiologists agreed initially in their assessments in 1,420 of 1,586 patients.

The study protocol was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained from all participants. The study adhered to the principles outlined in the Declaration of Helsinki. All procedures followed were in accordance with institutional guidelines.

Five milliliters of venous blood was collected from each patient into ethylenediaminetetraacetic acid Vacutainer tubes (Becton, Dickinson & Company, Franklin Lakes, New Jersey). BNP concentrations were measured using the Triage BNP test (Biosite Diagnostics, Inc., San Diego, California). The characteristics of this sandwich fluorescence immunoassay for the rapid quantitative determination of BNP in whole blood and plasma have been described previously.^{2–4} Three consecutive BNP tests were performed, and the mean of these is presented.

The Breathing Not Properly study protocol did not specify a formal procedure for blood pressure recording. Accordingly, blood pressure was measured according to the routine procedures of the emergency departments of the participating centers. Absolute blood pressure values were used, and no rounding to 0 or 5 was performed.

A history of hypertension was ascertained by interviewing each patient. This study used the European Hypertension Society's⁵ definition of hypertension: systolic blood pressure \geq 140 mm Hg and/or diastolic blood pressure \geq 90 mm Hg. The acute setting of the Breathing Not Properly study did not strictly fulfill the criteria for diagnosing hypertension.⁵ We therefore use the term "elevated blood pressure" in this report.

Thus, the following subgroups were defined: (1) self-reported history of hypertension versus no history of hypertension and (2) elevated versus no elevated blood pressure on admission.

SPSS for Windows version 16.0 (SPSS, Inc., Chicago, Illinois) was used for all statistical analyses. Continuous data are presented as median (interquartile range [IQR]) and categorical data as percentages. Between-group differences were assessed using the Mann-Whitney U test and the chi-square test or Fisher's exact test, as appropriate, for continuous and categorical data, respectively. Spearman's rank correlations and linear regression analyses were used to assess relations between continuous variables. A 2-sided p value <0.05 was considered significant.

Sensitivity, specificity, accuracy, positive and negative predictive values, and positive and negative likelihood ratios for the detection of acute HF were calculated. Receiver-operating characteristic (ROC) curves were generated and used to assess the overall diagnostic accuracy of BNP. The areas under the ROC curves were calculated with 95% confidence intervals (CIs), and the optimal discriminatory cut-off value was estimated using MedCalc version 9.5.2.0. Comparisons of 2 areas under ROC curves were conducted in MedCalc with reference to the algorithms of Hanley and McNeil.⁶

Results

Patient characteristics according to the presence or absence of a history of hypertension are listed in Table 1, and patient characteristics according to the presence or absence of elevated blood pressure on admission are listed in Table 2. Median circulating BNP levels were significantly higher in patients with versus without histories of hypertension (254 pg/ml [IQR 46 to 796] vs 67 pg/ml [IQR 14 to 358], $p < 0.001$). However, this could be attributed mainly to a higher prevalence of a final diagnosis of HF in the patients with histories of hypertension (54% vs 35%, $p < 0.001$).

In patients with HF, median BNP levels did not differ significantly between those with and those without histories of hypertension (599 pg/ml [IQR 287 to 1,178] vs 562 pg/ml [230 to 1,121], $p = 0.34$). In patients without HF, median circulating levels of BNP were significantly higher in those with histories of hypertension than in those without such histories (38 pg/ml [IQR 13 to 119] vs 21 pg/ml [7 to 64], $p < 0.001$). Using BNP as the predictor variable and the presence of acute HF as the outcome variable, the introduction of a history of hypertension and elevated blood pressure on admission in logistic regression models only marginally influenced the odds ratio estimates for BNP and the explanatory power of the models (data not shown). The association between a history of hypertension and BNP levels was attenuated but remained significant ($p = 0.017$) after adjustment for age, gender, and body mass index. Circulating BNP levels in patients with final diagnoses of HF or no HF stratified according to the presence or absence of a history of hypertension are depicted in Figure 1. To assess the overall diagnostic performance of BNP in patients with and without histories of hypertension, ROC analysis was performed. The area under the ROC curve for patients with histories of hypertension was significantly lower than for those without such histories (0.88 [95% CI 0.85 to 0.90] vs 0.93 [95% CI 0.91 to 0.95], $p < 0.001$; Figure 2). The

Table 2

Patient characteristics according to the presence or absence of elevated blood pressure* on admission

Variable	Elevated Blood Pressure		p Value
	No (n = 740)	Yes (n = 843)	
Final diagnosis of heart failure	314 (42.4%)	427 (50.7%)	0.005
Age (years)	64 (49–76)	67 (54–78)	<0.001
Men	444 (60.0%)	437 (51.8%)	0.001
Previous heart failure	245 (33.1%)	281 (33.3%)	0.957
Previous myocardial infarction	193 (29.1%)	192 (25.1%)	0.094
Hypertension	317 (45.9%)	562 (70.8%)	<0.001
Diabetes mellitus	175 (25.7%)	192 (25.3%)	0.856
Atrial fibrillation/flutter	125 (18.9%)	131 (17.1%)	0.407
Body mass index (kg/m ²)	26.1 (23–31)	27.8 (24–33)	<0.001
Systolic blood pressure (mm Hg)	120 (107–130)	156 (146–174)	<0.001
Diastolic blood pressure (mm Hg)	68 (60–76)	89 (79–99)	<0.001
Mean arterial pressure (mm Hg)	84.7 (77–93)	110 (103–121)	<0.001
Heart rate (beats/min)	90 (75–107)	90 (76–105)	0.752
Creatinine (mg/dl)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.230
BNP >100 pg/ml	399 (53.9%)	497 (59.0%)	0.047
BNP (pg/ml)	130.7 (21–588)	170.7 (33–734)	0.012
Medications at home			
Angiotensin-converting enzyme inhibitors	219 (30.3%)	265 (32.7%)	0.322
β blockers	145 (20.1%)	197 (24.3%)	0.049
Calcium channel blockers	137 (19.0%)	193 (23.9%)	0.021
Digoxin	157 (21.8%)	136 (16.6%)	0.011
Other antiarrhythmic agents	58 (8.1%)	47 (5.9%)	0.105
Diuretics	340 (47.0%)	401 (48.9%)	0.475

Data are expressed as number (percentage) or as median (IQR).

* Systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg.

optimal BNP cut-off points, as assessed by ROC analysis, were 194 and 115 pg/ml for patients with and without histories of hypertension, respectively. Diagnostic accuracy at different cut-off values of BNP is listed in Table 3.

Median circulating blood levels of BNP were significantly higher in patients with elevated blood pressure than in those without elevated blood pressure (171 pg/ml [IQR 33 to 734] vs 131 pg/ml [IQR 21 to 588] pg/ml, $p = 0.012$; Table 2). A final diagnosis of HF was significantly more common (51% vs 42%, $p = 0.005$) in those patients presenting with elevated blood pressure than in those without elevated blood pressure. Circulating BNP levels in patients with final diagnoses of HF or no HF stratified according to the presence or absence of elevated blood pressure on admission are depicted in Figure 3. In patients without HF, the median BNP level did not differ significantly between those with elevated blood pressure and those without elevated blood pressure (32 vs 28 pg/ml, $p = 0.18$). Likewise, in patients with final diagnoses of HF, the median BNP level did not differ significantly between those with elevated

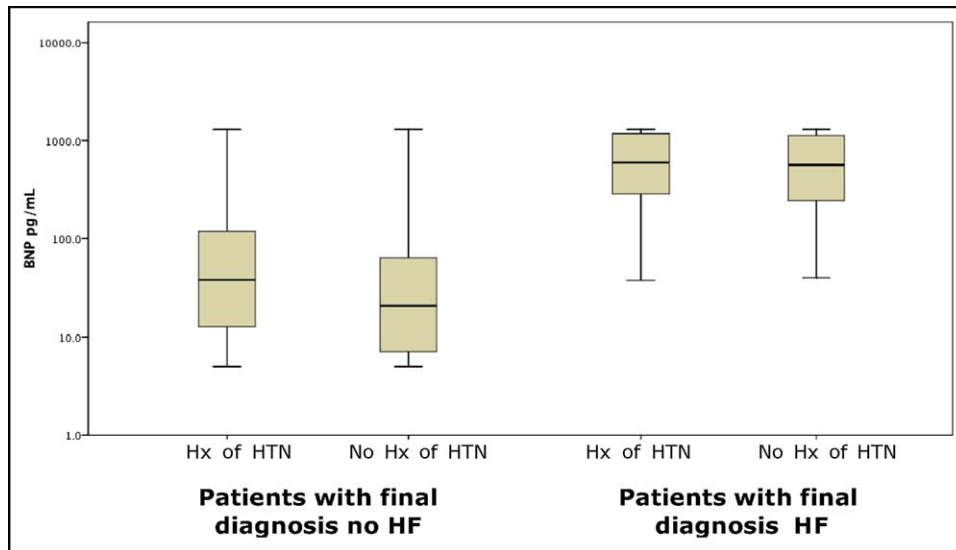


Figure 1. BNP levels in patients with dyspnea stratified according to final diagnosis and to the presence or absence of a history (Hx) of hypertension (HTN).

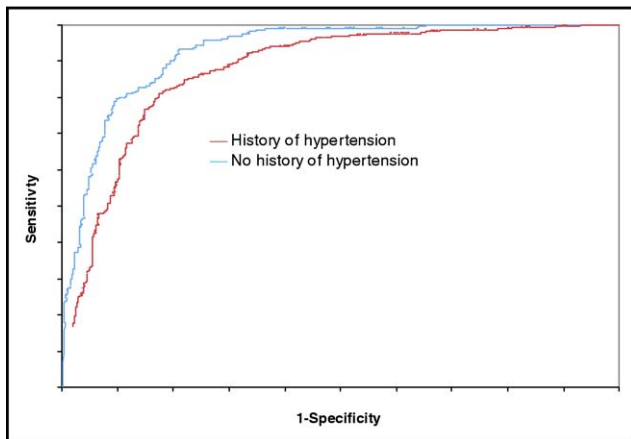


Figure 2. Overall diagnostic accuracy of BNP according to the presence or absence of a history of hypertension.

blood pressure and those without elevated blood pressure (616 vs 588 pg/ml, $p = 0.75$). In accordance with these results, no correlation was observed between BNP levels and systolic ($r = 0.05$, $p = 0.06$) or diastolic ($r = 0.04$, $p = 0.09$) blood pressure. Moreover, the areas under the ROC curves were nearly identical for the 2 groups (0.900 [95% CI 0.877 to 0.919] vs 0.897 [95% CI 0.873 to 0.918], $p = 0.89$; Figure 4). Optimal cut-off points were estimated to be 150 and 205 pg/ml for those with and without elevated blood pressure, respectively. Overall diagnostic accuracy for the diagnosis HF at different cut-off values of BNP in patients with and without elevated blood pressure on admission is listed in Table 4. In the 2 groups, accuracy reached a plateau between 100 and 200 pg/ml.

Discussion

The main findings of this study are that in patients with acute dyspnea with HF, a history of hypertension does not affect BNP levels, whereas in patients without HF, a history of hypertension is associated with higher BNP levels. The

association between a history of hypertension and BNP levels was attenuated but remained significant after adjustment for age, gender, and body mass index. Although the diagnostic accuracy of BNP was significantly lower in patients with histories of hypertension than in those without such histories, the difference was modest and due partly to confounding by age and gender. However, our results suggest that the optimal discriminatory BNP value for the diagnosis of HF is slightly higher in patients with histories of hypertension than for those without histories of hypertension.

Long-standing hypertension is associated with hypertrophy, fibrosis, and eventually diastolic and systolic dysfunction of the left ventricle.⁷ Because the main stimulus for BNP production from cardiac ventricles and atria is wall stretch,⁸ it is not surprising that a history of hypertension and left ventricular hypertrophy is associated with increased BNP levels in population-based studies.⁹ In addition, increased left ventricular mass per se may contribute to increased BNP levels.¹ No previous study has examined the effect of a history of arterial hypertension on the performance of BNP levels in patients with acute dyspnea, a patient group in which several extracardiac and cardiac factors other than left ventricular failure may cause elevated BNP levels¹⁰ and thus theoretically obscure the association between hypertension and BNP levels. Our data demonstrate that a history of hypertension is associated with modestly but significantly increased circulating BNP levels in patients with acute dyspnea without final diagnoses of HF. The presence of elevated blood pressure on presentation did not affect BNP levels, even in patients without final diagnoses of HF. The lack of a correlation between BNP and blood pressure values supports the notion that actual blood pressure does not represent a major stimulus for BNP production. The reason the effect of a history of hypertension was not demonstrable in patients with final diagnoses of HF can probably be ascribed to the fact that left ventricular failure

Table 3
Decision statistics at different cut-off values for patients with and without histories of hypertension

BNP Cutoff	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
History of hypertension					
50	0.97	0.56	0.75	0.93	0.79
100	0.9	0.72	0.81	0.85	0.83
120	0.88	0.76	0.83	0.82	0.82
140	0.86	0.78	0.84	0.81	0.83
160	0.85	0.8	0.85	0.8	0.83
180	0.83	0.83	0.87	0.78	0.83
200	0.82	0.85	0.88	0.78	0.83
300	0.74	0.88	0.89	0.72	0.8
No history of hypertension					
50	0.98	0.7	0.65	0.98	0.8
100	0.9	0.83	0.75	0.94	0.85
120	0.87	0.85	0.76	0.92	0.85
140	0.83	0.88	0.79	0.9	0.86
160	0.82	0.89	0.81	0.9	0.87
180	0.8	0.92	0.85	0.89	0.88
200	0.79	0.93	0.86	0.89	0.88
300	0.68	0.95	0.89	0.84	0.85

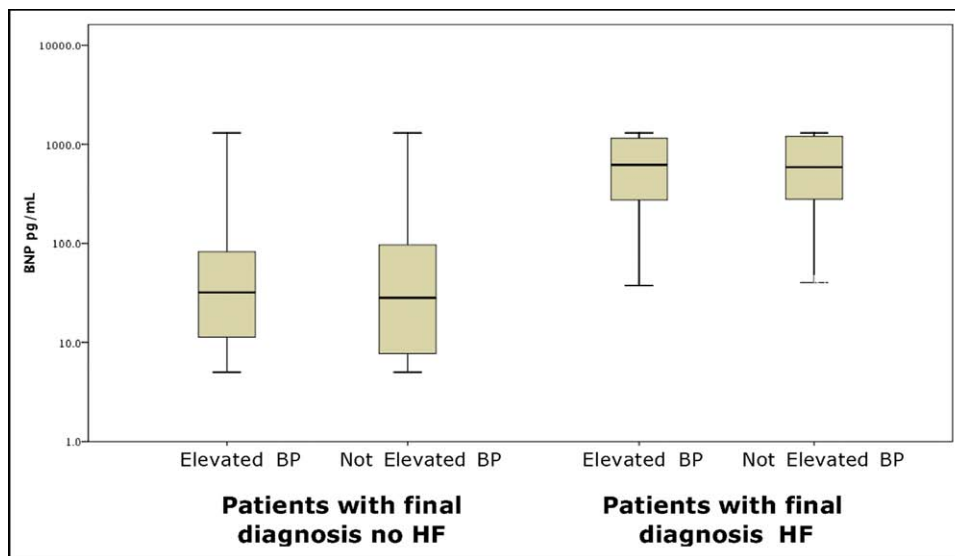


Figure 3. BNP levels in patients with dyspnea stratified according final diagnosis and to the presence or absence of elevated blood pressure (BP) on admission.

represents a much stronger stimulus for BNP production, thus obscuring the impact of hypertension.

In accordance with the observation that a history of hypertension is associated with increased circulating BNP levels in patients without final diagnoses of HF, the overall diagnostic accuracy was slightly lower and the optimal diagnostic cutoff defined by ROC analysis slightly higher in patients with than in those without histories of hypertension. However, the clinical impact of the observation of a higher, mathematically derived cutoff in patients with histories of hypertension is likely to be minor, because in the clinical setting, higher sensitivity may be more desirable than marginally better overall diagnostic accuracy. Accordingly, on the basis of the present data, we that believe it is justified to use the established BNP cutoff of 100 pg/ml for the diagnosis of HF in patients with acute dyspnea, regardless of a history of hypertension or not.

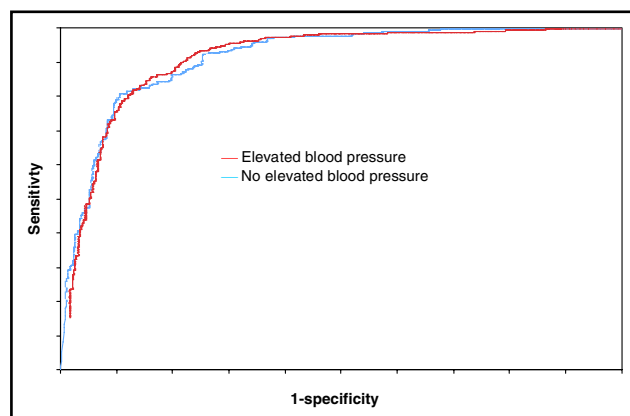


Figure 4. Overall diagnostic accuracy of BNP according to the presence or absence of elevated blood pressure on admission.

Table 4
Decision statistics at different cut-off values for patients with and without elevated blood pressure

BNP Cutoff	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Elevated blood pressure					
50	0.97	0.61	0.73	0.96	0.80
100	0.91	0.78	0.82	0.89	0.85
120	0.88	0.8	0.83	0.86	0.84
140	0.87	0.82	0.84	0.85	0.84
160	0.85	0.84	0.86	0.83	0.85
180	0.82	0.87	0.87	0.82	0.84
200	0.81	0.87	0.88	0.81	0.84
300	0.72	0.91	0.9	0.75	0.81
No elevated blood pressure					
50	0.97	0.63	0.68	0.96	0.78
100	0.89	0.76	0.75	0.9	0.82
120	0.87	0.78	0.77	0.88	0.82
140	0.84	0.81	0.79	0.86	0.83
160	0.84	0.84	0.81	0.86	0.84
180	0.82	0.87	0.83	0.86	0.85
200	0.81	0.89	0.85	0.85	0.85
300	0.73	0.91	0.87	0.81	0.83

Potential limitations of our study are that no distinction was made between systolic and diastolic HF and that a history of hypertension was either self-reported or based on information from medical records.

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