

# Association Between Blood Pressure Level and the Risk of Myocardial Infarction, Stroke, and Total Mortality

## *The Cardiovascular Health Study*

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**Background:** Recent reports have drawn attention to the importance of pulse pressure as a predictor of cardiovascular events. Pulse pressure is used neither by clinicians nor by guidelines to define treatable levels of blood pressure.

**Methods:** In the Cardiovascular Health Study, 5888 adults 65 years and older were recruited from 4 US centers. At baseline in 1989-1990, participants underwent an extensive examination, and all subsequent cardiovascular events were ascertained and classified.

**Results:** At baseline, 1961 men and 2941 women were at risk for an incident myocardial infarction or stroke. During follow-up that averaged 6.7 years, 572 subjects had a coronary event, 385 had a stroke, and 896 died. After adjustment for potential confounders, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure were directly associated with the risk of incident myocardial infarction and stroke. Only SBP was associated with total mortality. Importantly, SBP was a better predictor of cardiovascular events than DBP or pulse pressure. In the adjusted model for myocardial

infarction, a 1-SD change in SBP, DBP, and pulse pressure was associated with hazard ratios (95% confidence intervals) of 1.24 (1.15-1.35), 1.13 (1.04-1.22), and 1.21 (1.12-1.31), respectively; and adding pulse pressure or DBP to the model did not improve the fit. For stroke, the hazard ratios (95% confidence intervals) were 1.34 (1.21-1.47) with SBP, 1.29 (1.17-1.42) with DBP, and 1.21 (1.10-1.34) with pulse pressure. The association between blood pressure level and cardiovascular disease risk was generally linear; specifically, there was no evidence of a J-shaped relationship. In those with treated hypertension, the hazard ratios for the association of SBP with the risks for myocardial infarction and stroke were less pronounced than in those without treated hypertension.

**Conclusion:** In this population-based study of older adults, although all measures of blood pressure were strongly and directly related to the risk of coronary and cerebrovascular events, SBP was the best single predictor of cardiovascular events.

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**I**N MIDDLE-AGED adults, the relationship between blood pressure level and risk of cardiovascular disease has aptly and traditionally been characterized as "continuous, graded, strong, independent, and etiologically significant."<sup>1</sup> This judgment reflects findings from numerous studies, including the Framingham Heart Study,<sup>2,3</sup> the screenees from the Multiple Risk Factor Intervention Trial,<sup>1,4</sup> and a major meta-analysis.<sup>5</sup> Although the relationship may be stronger for systolic blood pressure (SBP) than for diastolic blood pressure (DBP),<sup>3,4</sup> the association of blood pressure level with cardiovascular disease and the proven benefits of treatment with low-dose diuretics and  $\beta$ -blockers<sup>6</sup> have formed the basis of the current US national guidelines on the detection and treatment of high blood pressure.<sup>7</sup>

Several recent studies in older adults have raised questions about the shape of association between blood pressure and cardiovascular events. In a study of older adults from Italy,<sup>8</sup> SBP but not DBP was associated with total and cardiovascular mortality. In the Rotterdam Study,<sup>9</sup> blood pressure was linearly related to the risk of stroke in untreated participants; but in participants with treated hypertension, the relationship of both SBP and DBP to stroke risk was J-shaped with increased risks at high and low levels of blood pressure. Several other studies,<sup>10-13</sup> 2 of them including only subjects with isolated systolic hypertension,<sup>10,11</sup> emphasized the importance of pulse pressure as a predictor of cardiovascular events or mortality. In a meta-analysis of trials of isolated systolic hypertension,<sup>10</sup> for instance, SBP was directly

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## PARTICIPANTS AND METHODS

### SETTING

The CHS is a prospective cohort study of risk factors for coronary heart disease and stroke in men and women 65 years and older. In June 1990, 4 field centers completed recruitment of 5201 participants. In June 1993, the recruitment of an additional 687 African Americans was completed using similar methods. Each community sample was obtained from random samples of the Medicare eligibility lists, and those eligible to participate included all persons who were living in the household of each individual sampled from the Health Care Financing Administration lists and who (1) were 65 years or older, (2) were noninstitutionalized, (3) expected to remain in the area for 3 years, and (4) gave informed consent and did not require a proxy respondent. Among those contacted and eligible, 57.3% were enrolled. The CHS design and recruitment experience are described in detail elsewhere.<sup>17,18</sup>

### BASELINE EXAMINATION

The baseline examination consisted of a home interview and a clinic examination. Participants answered standard questionnaires that assessed a variety of risk factors, including smoking, physical activity, and medical history of cardiovascular conditions and procedures.<sup>17</sup> Self-reported medical conditions such as myocardial infarction, angina, and stroke were validated.<sup>19</sup> Medications were assessed by inventory at the home interview.<sup>20</sup>

Participants were asked to come to the clinic examination after an 8- to 12-hour overnight fast. All examinations were scheduled in the morning. Seated blood pressure measurement followed by venipuncture was performed early in the examination. Blood pressure was measured in the right arm of seated participants after a 5-minute rest using an appropriately sized cuff and a Hawksley random-zero sphygmomanometer (model 7076; Hawksley and Sons Limited, Sussex, England) in 1989-1990 and a standard mercury sphygmomanometer in 1992-1993. Duplicate measures of supine blood pressure in the right arm and both

posterior tibial arteries were assessed by an 8-MHz Doppler probe attached to a stethoscope, and the ratio of SBPs was used to calculate the ankle-arm index. Anthropomorphic measures included weight and height. Blood samples from the fasting venipuncture were analyzed at the Central Blood Analysis Laboratory for levels of glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides, and standardized according to the Centers for Disease Control and Prevention as previously described.<sup>17,21</sup> Low-density lipoprotein cholesterol was calculated according to the Friedewald equation.<sup>22</sup>

Carotid sonography was performed with sonographic units (Toshiba SSA-270A; Toshiba America Medical Systems, Tustin, Calif). A single longitudinal lateral view with measurements taken at the distal 10 mm of the far wall of the right and left common carotid arteries and 3 views with measurements centered on the site of maximum wall thickening of the proximal right and left internal carotid arteries were recorded and read by the Ultrasound Reading Center.<sup>23</sup> The maximal intimal medial thickness was the average of the discrete maximum separately for the both common and both internal carotid arteries.

Subjects were excluded from the analysis if they had had (1) a myocardial infarction, stroke, or congestive heart failure prior to entry into CHS<sup>19</sup>; or (2) missing data at baseline on key variables, including blood pressure, diabetes, carotid ultrasound, or smoking status.

### FOLLOW-UP AND CLASSIFICATION OF EVENTS

Participants were contacted every 6 months, and the contacts alternated between a telephone interview and a clinic examination, which included an electrocardiogram. At each contact, participants were asked about cardiovascular events and all hospitalizations. Discharge summaries and diagnoses were obtained for all hospitalizations. For all potential incident cardiovascular events, additional information, including history of chest pain, cardiac enzyme levels, and serial electrocardiograms for potential myocardial infarction events and onset set of symptoms, duration of deficits, and findings on computed tomography or magnetic resonance imaging examinations for potential stroke events,

and DBP was inversely related to the risks of various cardiovascular events. In trial participants with isolated systolic hypertension,<sup>14</sup> pulse pressure was a more important predictor of cardiovascular events than mean pressure. Finally, using Framingham data, Port and colleagues<sup>15</sup> recently challenged the linear association between blood pressure and total mortality.

In the last decade, researchers and guidelines have increasingly recognized the importance of SBP rather than DBP, especially in older adults.<sup>7,16</sup> Clinicians and current guidelines do not use pulse pressure to define treatable levels of blood pressure. Using data from the Cardiovascular Health Study (CHS), a population-based cohort study of risk factors for cardiovascular disease in older adults,<sup>17</sup> we assessed the association of SBP, DBP, and pulse pressure with the risks of myocardial infarction, stroke, and total mortality. The analysis included a systematic search for several nonlinear relationships that have recently been described.<sup>9,15</sup>

## RESULTS

Ineligible for this analysis were (1) 348 men and 211 women who, at baseline, had a previous history of myocardial infarction; (2) 108 men and 92 women who had a previous stroke; and (3) 49 men and 86 women who had previous congestive heart failure. Another 29 men and 63 women were excluded because of missing data on blood pressure (n=15), diabetes status (n=49), carotid ultrasound (n=22), or smoking status (n=6). Of 5888 participants in CHS, 1961 men and 2941 women who were at risk of a first myocardial infarction or stroke were included in this analysis and followed up for an average of 6.7 years.

**Table 1** summarizes the baseline risk factors in subjects according to level of SBP. Level of SBP was associated with a number of risk factors, including age, carotid intimal medial thickness, race, and diabetes. In this

was collected. All potential myocardial infarction and stroke events were reviewed and classified by the CHS Cardiovascular Events Committee or the CHS Stroke Committee, respectively. The algorithms for classifying myocardial infarction<sup>24</sup> and stroke<sup>25</sup> have been published. Myocardial infarction in this analysis included myocardial infarction by serial electrocardiography, hospitalized nonfatal myocardial infarction, fatal myocardial infarction, and definite fatal coronary heart disease. Stroke included fatal and nonfatal stroke.

For analyses of myocardial infarction or stroke, event times were computed as the time to the first event. Subjects could have an incident myocardial infarction and an incident stroke during follow-up, and these subjects were included as events in both analyses. For subjects without a myocardial infarction or stroke, censoring times were calculated according to the last date of follow-up or the date of death. For analyses of total mortality, event times were times to death, and censoring times were the dates of last follow-up.

#### DEFINITION OF VARIABLES AND METHODS OF STATISTICAL ANALYSIS

Although participants with a prebaseline myocardial infarction or stroke were excluded, some had a history of coronary heart disease, defined as a history at baseline of angina, coronary angioplasty, or coronary artery bypass surgery. Clinical cardiovascular disease was defined as a history at baseline of coronary heart disease, carotid endarterectomy, or peripheral vascular disease surgery. Diabetes was defined as a fasting glucose level of 6.99 mmol/L or higher ( $\geq 126$  mg/dL)<sup>26</sup> or the use of insulin or oral hypoglycemic agents, and impaired fasting glucose was defined as a level of 6.10 mmol/L or higher ( $\geq 110$  mg/dL). Treated hypertension at baseline was defined, regardless of blood pressure level, as a person who reported a history of high blood pressure and who was using medications that are usually used to treat hypertension. Pulse pressure was the difference between systolic and diastolic blood pressures. Blood pressure categories were defined according to the traditional stages of hypertension: optimal

(<120/80 mm Hg), normal (<130/85), high-normal (<140/90), stage 1 hypertension (<160/100), and the combination of stages 2 and 3 hypertension ( $\geq 160/100$ ).<sup>7</sup> In part because the mean level of DBP was "optimal" by criteria of the Sixth Report of the Joint National Committee,<sup>7</sup> and in part because there is no standard "clinical" approach to categorizing pulse pressure, we defined another set of blood pressure categories by quintiles according to blood pressure levels in subjects who had had an event.

We used a statistical software package for data analysis (SPSS for Windows version 10; SPSS Inc, Chicago, Ill). Techniques included analysis of variance for continuous variables,  $\chi^2$  tests for categorical variables, and Cox proportional hazards models for multivariate analysis.<sup>27</sup> All *P* values represent 2-sided tests. These analyses were based on the updated CHS database, which incorporated minor corrections through April 13, 1999.

#### APPROACH TO MULTIVARIATE ANALYSIS

In preliminary analyses, we used centered linear plus quadratic terms to screen SBP, DBP, and pulse pressure for quadratic associations between level of blood pressure and the risk of myocardial infarction, stroke, and total mortality. These analyses were done in the entire population and separately in subjects with treated hypertension. Significant deviations from the linear model were further explored using spline models.<sup>28</sup> The spline models assessed whether, across the range of blood pressure values, 2 lines with different slopes provided a better description of the blood pressure cardiovascular-disease event association than a single linear term.

In models that used continuous measures of blood pressure, each measure was divided by its standard deviation to facilitate comparisons among systolic, diastolic, and pulse pressures. Analyses were stratified on the presence or absence of treated hypertension. Based on previous work<sup>29</sup> and sensitivity analyses, Cox models were adjusted for major risk factors, including age, sex, current smoking, diabetes, clinical cardiovascular disease, and maximum common carotid intimal medial wall thickness. Neither total nor high-density lipoprotein cholesterol was related to risk.<sup>29</sup>

population-based sample as a whole, 45.2% reported a history of hypertension, 35.5% had treated hypertension, and the mean blood pressure was 136.3/71.0 mm Hg with a mean pulse pressure of 65.3 mm Hg.

At baseline, the prevalence of stage 1 or greater hypertension was higher for SBP (40.3%) than for DBP (4.8%; **Table 2**). Table 2 also presents the event rates per 1000 person-years of myocardial infarction, stroke, and total mortality according to the traditional stages of hypertension. In general, event rates increased across levels of SBP and DBP.

In **Table 3**, the association between level of blood pressure and the incidence of myocardial infarction is represented both for continuous measures and for quintiles. In adjusted models (1 to 3), the hazard ratio (HR) associated with a 1-SD change in blood pressure was higher for SBP (HR=1.24 per 21.4 mm Hg, adjusted) than for either DBP (HR=1.13 per 11.2 mm Hg) or pulse pressure (HR=1.21 per 18.5 mm Hg). For DBP (model 3),

high levels, although 95.2% were within the normal range, were nonetheless associated with an increased risk of myocardial infarction. The addition of DBP or pulse pressure to the model with SBP did not improve the model fit (models 4 and 5). The model with both pulse pressure and DBP (model 6) did improve the fit compared with either model alone (models 2 and 3). The analysis by quintiles suggested a generally increasing or linear association of the risk of myocardial infarction with levels of blood pressure, including DBP, and there was little evidence of a J-shaped curve for any of the blood pressure measures.

In subjects with treated hypertension (**Table 4**), the association between level of blood pressure and risk of myocardial infarction was less pronounced than in subjects without treated hypertension. The adjusted HR for SBP was 1.13 (95% confidence interval [CI], 1.00-1.28) in participants with treated hypertension and 1.31 (95% CI, 1.18-1.46) in those without treated hypertension.

**Table 1. Characteristics of Participants by Systolic Blood Pressure Level\***

Characteristic	Systolic Blood Pressure Category, mm Hg					Total
	<120	≥120 to <130	≥130 to <140	≥140 to <160	≥160	
No.	1112	889	927	1298	676	4902
Age, y†	71.4 (4.9)	72.0 (5.4)	72.1 (5.1)	73.3 (5.7)	74.6 (5.9)	72.6 (5.5)
Weight, kg†	70.7 (14.1)	72.7 (14.6)	74.2 (14.9)	73.4 (14.5)	71.6 (15.1)	72.5 (14.6)
Height, cm†	165.4 (9.4)	165.2 (9.3)	165.2 (9.6)	163.7 (9.3)	163.6 (9.6)	164.6 (9.4)
Body mass index, kg/m <sup>2</sup> †	25.7 (4.3)	26.5 (4.7)	27.0 (4.6)	27.3 (4.8)	26.6 (4.9)	26.6 (4.7)
Physical activity, kJ/wk‡	7866 (8908)	7799 (8899)	7644 (8678)	6740 (7945)	7071 (8883)	7406 (8623)
Systolic blood pressure, mm Hg†	110.1 (7.4)	124.7 (2.8)	134.5 (2.9)	148.3 (5.6)	173.6 (12.6)	136.3 (21.4)
Diastolic blood pressure, mm Hg†	63.3 (8.3)	68.3 (8.7)	71.0 (9.7)	74.7 (10.5)	80.1 (11.9)	71.0 (11.2)
Pulse pressure, mm Hg†	46.8 (9.5)	56.4 (8.9)	63.5 (10.0)	73.7 (11.1)	93.6 (15.8)	65.3 (18.5)
Total cholesterol, mmol/L	5.44 (1.04)	5.49 (0.99)	5.49 (0.98)	5.50 (1.01)	5.57 (0.99)	5.50 (1.00)
HDL cholesterol, mmol/L†	1.43 (0.42)	1.42 (0.40)	1.40 (0.39)	1.43 (0.40)	1.46 (0.42)	1.43 (0.41)
LDL cholesterol, mmol/L	3.30 (0.95)	3.31 (0.93)	3.32 (0.91)	3.32 (0.91)	3.37 (0.90)	3.32 (0.92)
Triglycerides, mmol/L†	1.46 (0.68)	1.57 (0.81)	1.60 (0.84)	1.59 (0.88)	1.59 (0.96)	1.56 (0.83)
Fasting glucose, mmol/L†	5.78 (1.43)	6.10 (2.23)	6.15 (2.11)	6.16 (1.86)	6.34 (2.03)	6.09 (1.93)
Ankle-arm index†	1.11 (0.15)	1.10 (0.14)	1.08 (0.15)	1.06 (0.16)	1.00 (0.19)	1.07 (0.16)
Maximum IMT, mm						
Common carotid†	1.00 (0.19)	1.03 (0.19)	1.06 (0.20)	1.08 (0.22)	1.13 (0.22)	1.05 (0.21)
Internal carotid†	1.30 (0.50)	1.34 (0.53)	1.37 (0.53)	1.45 (0.56)	1.58 (0.60)	1.40 (0.55)
History of CVD	11.4	10.6	11.4	12.4	11.9	11.6
Angioplasty	1.1	0.5	0.3	1.2	0.9	0.8
Bypass surgery	1.8	2.1	2.6	2.0	1.8	2.1
Angina	9.4	9.8	9.5	10.1	9.5	9.7
Carotid endarterectomy	0.5	0.9	0.9	1.3	0.9	0.9
PVD surgery	1.5	0.6	1.6	1.5	1.2	1.3
Women	60.5	58.5	58.7	61.6	59.8	60.0
African American†	10.3	13.9	14.6	17.2	18.9	14.8
Self-reported hypertension†	25.2	34.9	46.0	55.4	71.0	45.2
Treated hypertension†	20.9	28.2	35.7	43.1	54.0	35.5
Using insulin or oral hypoglycemic agents†	5.2	5.7	7.6	8.3	11.5	7.4
Diabetes or IFG†	20.9	28.2	29.2	30.9	33.9	28.2
Current smoker†	14.0	15.0	11.3	10.0	9.3	12.0
≥High school education†	75.6	72.0	70.6	71.6	70.1	72.2
Self-reported health very good or excellent†	46.1	44.2	42.5	38.3	35.2	41.5
Married‡	71.4	65.3	66.8	64.4	64.1	66.6

\*Data are given as mean CVD, cardiovascular disease; (SD) or percentage of subjects. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; IMT, intimal medial thickness; PVD, peripheral vascular disease; and IFG, impaired fasting glucose. To convert from kilojoules per week to kilocalories per week, divide by 4.184. To convert from millimoles per liter to milligrams per deciliter, divide by 0.0259 for cholesterol, by 0.0555 for glucose, and by 0.0113 for triglycerides.

†P < .001.

‡P < .05.

These HRs were marginally different ( $P = .056$ ), and the myocardial infarction incidence rates by quintile of SBP for those with and without treated hypertension are illustrated in **Figure 1A**. For subjects with treated hypertension, DBP and pulse pressure were minimally associated with the risk of myocardial infarction after adjustment.

**Table 5** summarizes the association between blood pressure and stroke incidence. In adjusted models (1 to 3), the HR associated with a 1-SD change in blood pressure was largest for SBP (HR = 1.34) and higher for DBP (HR = 1.29) than for pulse pressure (HR = 1.21). While SBP was the single best predictor, 2-term models improved the fit compared with model 1 ( $\chi^2_1 = 5.2$ ,  $P = .02$ ). Analysis by quintiles of blood pressure again suggests a generally linear relationship for all 3 measures. In model 4, both SBP and DBP were directly related to the risk of stroke. In participants with treated hypertension, the adjusted HR for SBP was 1.19 (95% CI, 1.03-1.37), and in those without treated hypertension, it was 1.43 (95% CI, 1.25-1.63). These HRs were different ( $P = .02$ ), and the

stroke incidence rates by quintile of SBP for those with and without treated hypertension are illustrated in **Figure 1B**.

**Table 6** summarizes the association between blood pressure and total mortality. In adjusted models, the HRs associated with a 1-SD change in blood pressure were generally small, and the association achieved conventional levels of statistical significance for SBP (HR = 1.08) and DBP (HR = 1.07) but not for pulse pressure (HR = 1.05). The addition of pulse pressure to the models with SBP or DBP did not improve the fit significantly (models 5 and 6). Although the analysis by quintiles suggests the possibility of a J-shaped relationship of the risk of myocardial infarction with quintiles of diastolic or pulse pressure, the HR estimates were generally close to 1.00, and few CIs excluded the null.

In additional analyses, we used the addition of a quadratic term to the linear models to screen the 3 blood pressure measures for quadratic associations with the risk of myocardial infarction, stroke, and total mortality both in the whole sample and in subjects with treated hyper-

**Table 2. Rates (per 1000 Person-Years) of Myocardial Infarction, Stroke, and Total Mortality by Traditional Levels of Systolic and Diastolic Blood Pressure\***

BP Category	BP Range	N	Myocardial Infarction			Stroke			Total Mortality		
			n	PY	Rate	n	PY	Rate	n	PY	Rate
<b>Systolic</b>											
Optimal	<120	1112	72	7518	9.6	47	7533	6.2	166	7673	21.6
Normal	≥120 to <130	889	81	5791	14.0	46	5860	7.9	157	5973	26.3
High-normal	≥130 to <140	927	124	6059	20.5	67	6149	10.9	153	6336	24.2
Stage 1	≥140 to <160	1298	180	8112	22.2	135	8127	16.6	247	8486	29.1
≥Stage 2	≥160	676	115	3965	29.0	90	3980	22.6	173	4197	41.2
<b>Diastolic</b>											
Optimal	<80	3834	423	24 879	17.0	268	25 042	10.7	697	25 759	27.1
Normal	≥80 to <85	516	72	3240	22.2	48	3278	14.6	103	3402	30.3
High-normal	≥85 to <90	317	42	1947	21.6	42	1936	21.7	54	2047	26.4
Stage 1	≥90 to <100	196	30	1156	26.0	21	1174	17.9	33	1219	27.1
≥Stage 2	≥100	39	5	223	22.5	6	219	27.4	9	237	37.9

\*BP indicates blood pressure; N, number of persons; n, number of events; and PY, person-years.

**Table 3. Risk of Myocardial Infarction by Blood Pressure Level and Quintiles of Blood Pressure in All 4902 Subjects\***

BP Range	Unadjusted Model			Adjusted Model†			
	HR (95% CI)	χ <sup>2</sup>	P	HR (95% CI)	χ <sup>2</sup>	P	
<b>Linear term</b>							
1. Systolic BP	SD = 21.4	1.37 (1.27-1.48)	62.1	<.001	1.24 (1.15-1.35)	28.3	<.001
2. Diastolic BP	SD = 11.2	1.14 (1.05-1.24)	9.5	.002	1.13 (1.04-1.22)	8.3	.004
3. Pulse pressure	SD = 18.5	1.33 (1.24-1.43)	52.2	<.001	1.21 (1.12-1.31)	20.6	<.001
<b>2-Term models</b>							
4a. Systolic BP	SD = 21.4	1.40 (1.28-1.53)	63.0	<.001	1.25 (1.13-1.37)	28.3	<.001
4b. Diastolic BP	SD = 11.2	0.96 (0.87-1.05)			1.00 (0.91-1.10)		
5a. Systolic BP	SD = 21.4	1.29 (1.11-1.50)	63.0	<.001	1.24 (1.07-1.45)	28.3	<.001
5b. Pulse pressure	SD = 18.5	1.07 (0.92-1.25)			1.00 (0.85-1.17)		
6a. Diastolic BP	SD = 11.2	1.14 (1.05-1.24)	63.0	<.001	1.12 (1.03-1.21)	28.3	<.001
6b. Pulse pressure	SD = 18.5	1.34 (1.24-1.44)			1.21 (1.11-1.31)		
<b>Quintiles</b>							
<b>7. Systolic BP</b>							
1	≤125	1.00 Reference	77.0	<.001	1.00 Reference	44.4	<.001
2	>125 to ≤135	1.63 (1.26-2.11)			1.45 (1.12-1.88)		
3	>135 to ≤147	1.64 (1.27-2.11)			1.37 (1.06-1.77)		
4	>147 to ≤160	2.53 (1.96-3.27)			2.19 (1.70-2.84)		
5	>160	2.69 (2.08-3.49)			1.98 (1.52-2.58)		
<b>8. Diastolic BP</b>							
1	≤62	1.00 Reference	13.0	.01	1.00 Reference	10.5	.03
2	>62 to ≤69	0.93 (0.72-1.20)			0.98 (0.76-1.27)		
3	>69 to ≤75	1.10 (0.85-1.42)			1.13 (0.88-1.46)		
4	>75 to ≤82	1.26 (0.97-1.63)			1.34 (1.03-1.73)		
5	>82	1.42 (1.09-1.85)			1.37 (1.05-1.79)		
<b>9. Pulse pressure</b>							
1	≤56	1.00 Reference	68.5	<.001	1.00 Reference	32.4	<.001
2	>56 to ≤65	1.64 (1.28-2.12)			1.46 (1.13-1.88)		
3	>65 to ≤73	1.87 (1.44-2.42)			1.65 (1.27-2.15)		
4	>73 to ≤86	2.21 (1.72-2.83)			1.83 (1.42-2.37)		
5	>86	2.65 (2.05-3.44)			1.98 (1.50-2.60)		

\*There were 572 events. BP indicates blood pressure; HR, hazard ratio; and CI, confidence interval.

†Adjusted for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery.

tension. In these 18 models, the squared term improved the model fit in only 1 model—the association between level of SBP and the risk of myocardial infarction; the  $\chi^2$  value for the addition of the squared term was 8.67 with 1 df ( $P = .003$ ). In this fitted quadratic model, the risk of myocardial infarction appeared to increase with higher levels of SBP and then “decrease” at highest levels of SBP.

The pattern is apparent in Table 3, where the adjusted HR increases to 2.19 in the fourth quintile and then decreases slightly to 1.98 in the fifth quintile.

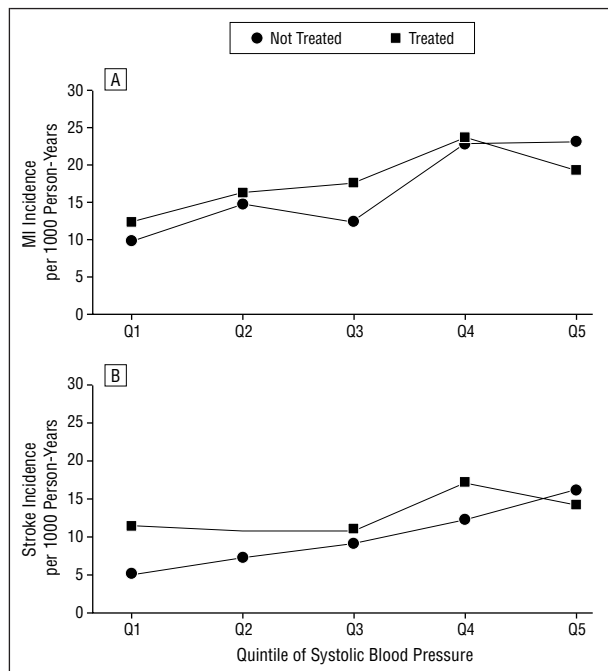
We also used spline models to assess nonlinear associations. Based on the work by Port and colleagues,<sup>15</sup> we allowed the HRs (slopes) to vary above and below the 75th percentile of SBP (153 mm Hg in our sample;

**Table 4. Risk of Myocardial Infarction by Blood Pressure Level in Participants With and Without Treated Hypertension\***

BP		Unadjusted Model			Adjusted Model†		
		HR (95% CI)	$\chi^2$	P	HR (95% CI)	$\chi^2$	P
<b>With Treated Hypertension (1738 Subjects, 233 Events)</b>							
Linear term							
1. Systolic BP	SD = 21.4	1.21 (1.07-1.36)	8.8	.003	1.13 (1.00-1.28)	3.9	.048
2. Diastolic BP	SD = 11.2	1.07 (0.95-1.22)	1.2	.27	1.07 (0.95-1.22)	1.3	.26
3. Pulse pressure	SD = 18.5	1.18 (1.05-1.33)	7.3	.007	1.11 (0.98-1.26)	2.6	.10
<b>Without Treated Hypertension (3164 Subjects, 339 Events)</b>							
Linear term							
1. Systolic BP	SD = 21.4	1.47 (1.33-1.63)	50.1	<.001	1.31 (1.18-1.46)	23.3	<.001
2. Diastolic BP	SD = 11.2	1.16 (1.03-1.29)	6.5	.01	1.15 (1.03-1.28)	5.9	.02
3. Pulse pressure	SD = 18.5	1.42 (1.28-1.57)	42.9	<.001	1.27 (1.14-1.42)	17.4	<.001

\*BP indicates blood pressure; HR, hazard ratio; and CI, confidence interval.

†Adjusted for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery.



**Figure 1.** Adjusted incidence of myocardial infarction (MI) (A) and stroke (B) by quintiles of systolic blood pressure and hypertensive treatment status.

**Table 7).** In model 1, SBP was entered as a linear term so that the HRs were forced to be the same on either side of the cut point. In model 2, the HRs were allowed to vary on either side of the 153 mm Hg. In the fully adjusted model for myocardial infarction, the HR associated with a 1-SD increase in SBP, when less than 153 mm Hg, was 1.49 (95% CI, 1.27-1.75); yet for SBP greater than or equal to 153 mm Hg, the HR was 0.93 (95% CI, 0.76-1.14). These HRs differed significantly. In both age-, sex-, and fully adjusted models, the spline model represented a significant improvement in the model fit ( $\chi^2$  values of 10.8 and 10.7, respectively;  $P = .001$ ). **Figure 2** represents both the linear and the spline models.

In subjects with treated hypertension, the HRs for myocardial infarction, below and above SBP of 153 mm Hg, were 1.31 (95% CI, 1.04-1.66) and 0.95 (95% CI, 0.72-1.25). In subjects without treated hypertension, the

HRs, below and above SBP of 153 mm Hg, were 1.55 (95% CI, 1.31-1.84) and 0.94 (95% CI, 0.70-1.28). Table 7 also includes the spline analysis for the association between SBP and total mortality. Although the HR for the upper quartile was slightly higher than the HR for the other 4 quartiles (1.20 vs 1.07), the spline model did not significantly improve the model fit ( $\chi^2 = 1.1$ ,  $P = .29$ ).

In sensitivity analyses, changing the cut point from 153 to 146 mm Hg (approximately the 60th percentile) had little effect on the improved fit of the spline model for describing the association between level of SBP and the risk of myocardial infarction ( $\chi^2 = 6.7$ ,  $P = .01$ ). In analyses stratified on median age, sex, diabetes, and cardiovascular disease, the associations between level of blood pressure and risk were generally similar between groups. Of 40 interactions examined, only 2 (as expected by chance alone) were significant. Models adjusting for carotid intimal medial thickness or race were generally similar to models that omitted these covariates. In additional analyses using the Doppler brachial SBP rather than the seated sphygmomanometric SBP, the association with risk of myocardial infarction still appeared to be flat at high levels of SBP.

#### COMMENT

In this population-based study, all 3 blood pressure measures alone—SBP, DBP, and pulse pressure—were directly associated with the risk of incident myocardial infarction and stroke. Systolic blood pressure or DBP, but not pulse pressure, was associated with total mortality in adjusted models. Importantly, SBP was a better predictor of cardiovascular events than either DBP or pulse pressure. For myocardial infarction, neither pulse pressure nor DBP improved the prediction provided by SBP alone. For stroke, while SBP was the best predictor, either DBP or pulse pressure did improve the model fit significantly. The association between blood pressure level and cardiovascular disease risk was generally linear. Specifically, there was no evidence of a J-shaped relationship, either for SBP and the risk of stroke or for DBP and the risk of coronary events among the treated hypertensive participants; however, for SBP and myocardial in-

**Table 5. Risk of Stroke by Blood Pressure Level and Quintiles of Blood Pressure in All 4902 Subjects\***

	BP Range	Unadjusted Model			Adjusted Model†		
		HR (95% CI)	$\chi^2$	P	HR (95% CI)	$\chi^2$	P
<b>Linear term</b>							
1. Systolic BP	SD = 21.4	1.52 (1.39-1.67)	76.8	<.001	1.34 (1.21-1.47)	33.8	<.001
2. Diastolic BP	SD = 11.2	1.25 (1.13-1.38)	18.5	<.001	1.29 (1.17-1.42)	25.2	<.001
3. Pulse pressure	SD = 18.5	1.43 (1.31-1.57)	57.2	<.001	1.21 (1.10-1.34)	14.1	<.001
<b>2-Term models</b>							
4a. Systolic BP	SD = 21.4	1.53 (1.38-1.70)	76.9	<.001	1.25 (1.11-1.40)	39.0	<.001
4b. Diastolic BP	SD = 11.2	1.00 (0.89-1.11)			1.14 (1.02-1.28)		
5a. Systolic BP	SD = 21.4	1.51 (1.26-1.82)	76.9	<.001	1.61 (1.34-1.94)	39.0	<.001
5b. Pulse pressure	SD = 18.5	1.01 (0.84-1.21)			0.80 (0.66-0.97)		
6a. Diastolic BP	SD = 11.2	1.24 (1.13-1.37)	76.9	<.001	1.28 (1.16-1.42)	39.0	<.001
6b. Pulse pressure	SD = 18.5	1.44 (1.32-1.58)			1.21 (1.10-1.33)		
<b>Quintiles</b>							
<b>7. Systolic BP</b>							
1	≤125	1.00 Reference	76.3	<.001	1.00 Reference	36.4	<.001
2	>125 to ≤135	1.47 (1.05-2.05)			1.28 (0.92-1.80)		
3	>135 to ≤147	1.81 (1.32-2.48)			1.48 (1.08-2.03)		
4	>147 to ≤160	2.78 (2.03-3.81)			2.16 (1.57-2.97)		
5	>160	3.39 (2.49-4.62)			2.29 (1.66-3.14)		
<b>8. Diastolic BP</b>							
1	≤62	1.00 Reference	22.5	<.001	1.00 Reference	27.4	<.001
2	>62 to ≤69	0.98 (0.71-1.35)			1.03 (0.75-1.42)		
3	>69 to ≤75	1.10 (0.80-1.52)			1.20 (0.87-1.66)		
4	>75 to ≤82	1.25 (0.91-1.73)			1.40 (1.01-1.94)		
5	>82	1.90 (1.39-2.59)			2.10 (1.54-2.88)		
<b>9. Pulse pressure</b>							
1	≤56	1.00 Reference	59.0	<.001	1.00 Reference	17.1	.002
2	>56 to ≤65	1.17 (0.84-1.63)			0.97 (0.70-1.35)		
3	>65 to ≤73	1.68 (1.23-2.31)			1.32 (0.96-1.83)		
4	>73 to ≤86	2.29 (1.71-3.07)			1.60 (1.19-2.17)		
5	>86	2.75 (2.03-3.73)			1.62 (1.17-2.24)		

\*There were 385 events. BP indicates blood pressure; HR, hazard ratio; and CI, confidence interval.

†Adjusted for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery.

fraction risk, the 2-slope spline model improved the model fit over the simple linear model. In treated hypertensive participants, the HRs for the association of SBP with the risks for myocardial infarction and stroke were less pronounced than in participants without treated hypertension.

This population-based study included a more representative sample than is recruited to clinical trials, measurements were done in a standardized fashion, and events follow-up was complete. Since the primary effort was to describe associations and to test previously reported findings in CHS, we made no adjustment for multiple testing.

Findings from the CHS are similar to those reported by some other cohort studies of older adults. In a study from Italy,<sup>8</sup> SBP but not DBP was associated with both cardiovascular and total mortality, and there was no evidence of a J-shaped curve for either SBP or DBP. In a report from the Established Populations for Epidemiologic Studies of the Elderly,<sup>13</sup> pulse pressure was a slightly better predictor mortality than SBP or DBP in age- and sex-adjusted models. In nontreated subjects in the Rotterdam Study, both SBP and DBP were directly related to the risk of stroke, but in treated subjects, the association appeared to be J-shaped, significantly so for DBP.<sup>9</sup>

Previous studies have reported a J-shaped association between treated level of DBP and the risk of coronary events.<sup>30</sup> Many<sup>30-32</sup> but not all<sup>33</sup> of these studies

included subjects with prevalent heart disease. One hypothesized source of the J-shaped association may be the possibility of an adverse effect of overtreatment, or alternatively, a wide pulse pressure may simply be a reflection of underlying vascular disease.<sup>34</sup> The CHS analysis excluded subjects who had had a previous myocardial infarction, stroke, or heart failure at entry into the study and focused only on the association with incident events. Adjustment for potential confounders included not only traditional risk factors but also carotid intimal medial thickness, which is strongly associated with coronary events.<sup>29,35</sup>

Port and colleagues<sup>15</sup> recently used Framingham 18-year data to examine the association between level of SBP and total mortality. Although there was little association with total mortality for the lower 4 quintiles of SBP, mortality risk was strongly associated with level of SBP for levels in the upper quintile. In their analysis, the spline model significantly improved the fit. In the CHS, the spline model used by Port and colleagues did not improve prediction of total mortality.

In CHS, the spline model (Figure 2), compared with either the linear or the quadratic models, did improve the fit for assessing the association between level of SBP and the risk of myocardial infarction. Analyses using the Doppler brachial blood pressure, which is more accurate than the standard seated blood pressure measure-

**Table 6. Risk of Death by Blood Pressure Level in All 4902 Subjects\***

	BP Range	Unadjusted Model			Adjusted Model†		
		HR (95% CI)	χ <sup>2</sup>	P	HR (95% CI)	χ <sup>2</sup>	P
Linear term							
1. Systolic BP	SD = 21.4	1.24 (1.17-1.32)	43.6	<.001	1.08 (1.01-1.16)	5.6	.02
2. Diastolic BP	SD = 11.2	1.03 (0.96-1.10)	0.7	.40	1.07 (1.00-1.14)	3.9	.048
3. Pulse pressure	SD = 18.5	1.26 (1.18-1.34)	49.9	<.001	1.05 (0.99-1.13)	2.4	.13
2-Term models							
4a. Systolic BP	SD = 21.4	1.30 (1.21-1.40)	51.2	<.001	1.06 (0.98-1.15)	6.3	.04
4b. Diastolic BP	SD = 11.2	0.90 (0.84-0.97)			1.04 (0.96-1.12)		
5a. Systolic BP	SD = 21.4	1.07 (0.95-1.21)	51.2	<.001	1.13 (1.00-1.28)	6.3	.04
5b. Pulse pressure	SD = 18.5	1.18 (1.05-1.34)			0.95 (0.83-1.07)		
6a. Diastolic BP	SD = 11.2	1.04 (0.97-1.11)	51.2	<.001	1.07 (1.00-1.14)	6.3	.04
6b. Pulse pressure	SD = 18.5	1.26 (1.18-1.34)			1.05 (0.99-1.13)		
Quintiles							
7. Systolic BP							
1	≤125	1.00 Reference	43.0	<.001	1.00 Reference	10.8	.03
2	>125 to ≤135	1.05 (0.86-1.28)			0.92 (0.75-1.12)		
3	>135 to ≤147	1.12 (0.93-1.36)			0.91 (0.75-1.11)		
4	>147 to ≤160	1.49 (1.22-1.83)			1.16 (0.95-1.43)		
5	>160	1.81 (1.48-2.20)			1.21 (0.99-1.48)		
8. Diastolic BP							
1	≤62	1.00 Reference	2.3	.67	1.00 Reference	4.6	.33
2	>62 to ≤69	0.94 (0.77-1.14)			1.03 (0.85-1.25)		
3	>69 to ≤75	0.96 (0.78-1.17)			1.07 (0.87-1.30)		
4	>75 to ≤82	1.07 (0.87-1.31)			1.22 (1.00-1.50)		
5	>82	1.05 (0.85-1.31)			1.14 (0.92-1.42)		
9. Pulse pressure							
1	≤56	1.00 Reference	50.7	<.001	1.00 Reference	7.5	.11
2	>56 to ≤65	1.03 (0.84-1.25)			0.84 (0.69-1.02)		
3	>65 to ≤73	1.19 (0.97-1.46)			0.92 (0.75-1.14)		
4	>73 to ≤86	1.48 (1.22-1.79)			1.02 (0.84-1.25)		
5	>86	1.92 (1.58-2.33)			1.12 (0.91-1.38)		

\*There were 896 deaths. BP indicates blood pressure; HR, hazard ratio; and CI, confidence interval.

†Adjusted for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery.

**Table 7. Spline Models for Assessing the Association Between Systolic Blood Pressure (SBP) and the Risk of Myocardial Infarction and Total Mortality**

Outcome	Model*	Adjusted	χ <sup>2</sup>	df	P	Hazard Ratio (95% Confidence Interval)	
						SBP <153 mm Hg	SBP ≥153 mm Hg
Myocardial infarction	1	Age, sex	41.8	1	<.001	1.30 (1.20-1.41)	1.30 (1.20-1.41)
	2	Age, sex	52.6	2	<.001	1.55 (1.36-1.78)	0.98 (0.80-1.19)
Myocardial infarction	1	Full†	28.3	1	<.001	1.25 (1.15-1.35)	1.25 (1.15-1.35)
	2	Full†	39.0	2	<.001	1.49 (1.30-1.71)	0.93 (0.76-1.14)
Total mortality	1	Age, sex	10.8	1	.001	1.12 (1.05-1.19)	1.12 (1.05-1.19)
	2	Age, sex	11.9	2	.003	1.07 (0.97-1.18)	1.20 (1.03-1.40)

\*Model 1 = linear (1 slope across the entire range of SBP); model 2 = spline (piecewise linear, 2 slopes possible, 1 on each side of cut point).

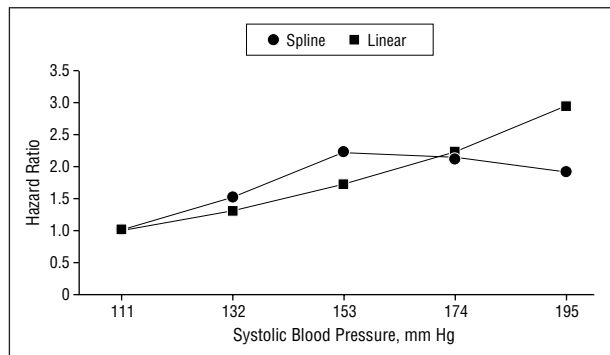
†Adjusted for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery.

ment, yielded similar results, so measurement error at high levels of SBP is an unlikely explanation for these non-linear findings. While it is possible that subsequent treatment reduced the risk at high levels of SBP, the spline models improved the fit for those with and without treated hypertension at baseline. These findings need to be examined and, if possible, replicated in other settings.

There appeared to be differences in blood pressure associations between subjects with and without treated hypertension. The HRs for the association of SBP with myocardial infarction and stroke incidence were less pro-

nounced for participants with than without treated hypertension. The treatment of blood pressure to low levels did not return the incidence of myocardial infarction and stroke to the levels of persons with those levels in the absence of treatment (Figure 1). This gap may be related to the inability of treated blood pressure level to serve as a valid surrogate for the effects of pharmacologic treatment on risk reduction.<sup>36,37</sup>

A number of recent studies, including a subset of the Framingham population,<sup>12</sup> have emphasized the importance of pulse pressure. Most of the reports focus on



**Figure 2.** Adjusted association between level of systolic blood pressure and risk of myocardial infarction, linear and spline models.

older adults who participated in clinical trials of isolated systolic hypertension.<sup>10,11,14</sup> In an analysis of data from the Systolic Hypertension in the Elderly Project (SHEP), pulse pressure was a strong predictor of stroke and total mortality.<sup>11</sup> In a recent meta-analysis, Staessen and colleagues<sup>10</sup> report that among 15 693 patients with isolated systolic hypertension, SBP is strongly and directly associated with a number of cardiovascular events, but DBP was inversely associated with the same end points. In another analysis of data from 3 of these trials, the authors reported that pulse pressure not mean pressure determined cardiovascular risk in older hypertensive patients.<sup>14</sup>

For the CHS, both the findings and the population are different. In CHS, SBP rather than pulse pressure was the best predictor of coronary events, cerebrovascular events, and total mortality. The CHS was a population-based sample of older adults recruited regardless of their level of blood pressure. In contrast, the clinical trial participants included in many of these recent reports were selected on the basis of having had a large pulse pressure, and it is not surprising that extremes of the selection criteria may be related to risk. To randomize 4736 participants, moreover, the SHEP investigators had to screen 447 921 persons. Although isolated systolic hypertension is the most common form of high blood pressure in older adults, the observational findings from the clinical trials are properly generalized to other persons who would have met entry criteria for the trial. The findings of the CHS are more readily generalizable to the population of older adults as a whole.

In this population-based study of older adults, although all measures of blood pressure were strongly and directly related to the risk of coronary and cerebrovascular events, SBP and not pulse pressure was the best predictor of cardiovascular events. For myocardial infarction, pulse pressure did not improve the fit of the model including SBP alone. For stroke, although a 2-blood pressure model was the best, any 2 of the 3 blood pressure measures provide the same information (models 4 to 6 in Tables 3, 5, and 6). The third measure is redundant, always a linear combination of the other 2. Physicians already think in terms of SBP and DBP. Pulse pressure is not now used clinically. To become useful clinically or to form part of future guidelines for the definition or treatment of high blood pressure, pulse pressure would have

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to be clearly superior to the traditional measures of SBP or DBP. Data from this population-based cohort study suggest that it is not superior and that there is no need to revise clinical or guideline approaches to the definition of hypertension in older adults.

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