

Identifying Individuals at Risk for Cardiovascular Events Across the Spectrum of Blood Pressure Levels

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Background—We determined the proportion of atherosclerotic cardiovascular disease (ASCVD) events that occur across the spectrum of systolic blood pressure (SBP) and assessed whether multivariable risk assessment can identify persons who experience ASCVD events at all levels of SBP, including those with goal levels.

Methods and Results—Participants aged 45 to 64 years from the Framingham Offspring and Atherosclerosis Risk in Communities studies were stratified based on treated and untreated SBP levels (<120, 120 to 129, 130 to 139, 140 to 149, 150 to 159, ≥160 mm Hg). We determined the number of excess ASCVD events in each SBP stratum by calculating the difference between observed and expected events (ASCVD event rate in untreated SBP <120 mm Hg was used as the reference). We categorized participants into 10-year ASCVD risk groups using the Pooled Cohort risk equations. There were 18 898 participants (78% white; 22% black) who were followed for 10 years. We estimated 427 excess ASCVD events, of which 56% (109 of 197) and 50% (115 of 230), respectively, occurred among untreated and treated participants with elevated SBP who were not recommended for antihypertensive therapy. Among untreated participants, 10-year ASCVD risk ≥7.5% identified 64% of those who experienced an ASCVD at 10 years and 30% of those who did not. Multivariable risk assessment was less useful in baseline-treated participants.

Conclusions—Half of excess ASCVD events occurred in persons with elevated SBP who were not currently recommended for antihypertensive therapy. Multivariable risk assessment may help identify those likely to benefit from further risk-reducing therapies. These findings support consideration of multivariable risk in guiding prevention across the spectrum of SBP. (*J Am Heart Assoc.* 2015;4:e002126 doi: 10.1161/JAHA.115.002126)

Key Words: epidemiology • hypertension • prevention

Hypertension treatment guidelines in the United States have traditionally prioritized blood pressure thresholds rather than global atherosclerotic cardiovascular disease (ASCVD) risk to guide drug therapy.^{1–3} The 2014 hypertension guidelines, for example, cited specific trial inclusion criteria to define blood pressure treatment thresholds, although opinion was divided regarding treatment thresholds for persons aged ≥60 years, given the limited clinical trial evidence in that

group.^{2,4} Nevertheless, the focus on blood pressure thresholds to define treatment eligibility is inconsistent with the graded and continuous log-linear association between blood pressure and ASCVD risk demonstrated in observational studies, a relationship that continues well below the blood pressure thresholds that define *hypertension*.^{5,6}

Cholesterol treatment guidelines, in contrast, have moved away from single-risk-factor thresholds and instead emphasize absolute risk assessment to guide preventive therapies.^{7–9} The 2013 American College of Cardiology (ACC) and American Heart Association (AHA) cholesterol treatment guidelines use the Pooled Cohort risk equations to estimate 10-year absolute risk for ASCVD in persons without prevalent disease and to identify a 10-year risk threshold of 7.5% to mark the level at which clinical trial data demonstrate the benefits of statin treatment that outweigh the known risks of adverse events.⁹

Although prior analyses have demonstrated the cardiovascular risks of high-normal blood pressure, a strategy for addressing this risk beyond lowering targets for blood pressure treatment has not been proposed.¹⁰ In this study, we analyzed 2 population-based observational cohorts of middle-aged adults to determine the proportion of ASCVD events that occur across the spectrum of systolic blood pressure (SBP) strata and

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An accompanying Table S1 is available at <http://jaha.ahajournals.org/content/4/9/e002126/suppl/DC1>

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whether multivariable risk assessment can identify those who experience ASCVD events at all levels of SBP, including those with goal levels.

Methods

Study Participants

We studied participants from 2 National Heart, Lung, and Blood Institute–funded longitudinal cohort studies based in the United States: the Atherosclerosis Risk in Communities (ARIC) study and the Framingham Offspring study. Study design and entry criteria have been described previously.^{11,12} For the present analysis, we included participants from baseline examination in ARIC and participants who were aged 45 to 64 years at examination 4 in the Framingham Offspring study. This allowed for an assessment of ASCVD risk in a sample of middle-aged adults followed over a contemporaneous time span. Participants with prevalent cardiovascular disease—defined as a history of myocardial infarction (recognized or unrecognized), stroke, congestive heart failure, percutaneous coronary intervention, coronary artery bypass surgery, or atrial fibrillation—were excluded, as were participants with incomplete baseline covariates to predict 10-year ASCVD risk. Participants were followed longitudinally for 10 years for incident ASCVD events to match the time horizon of the Pooled Cohort risk equations.

Risk Factor Measurement

During routine examinations, participants in both cohorts underwent standardized anthropometric measurements to determine height and weight, from which body mass index was calculated. Blood pressure was measured directly as the average of 2 separate readings taken by a physician at least 5 minutes apart. Medication use was determined by self-report. Blood tests were drawn and measured by standardized protocols, as described for each cohort.^{11,12} Diabetes was defined as the use of insulin or hypoglycemic agents, fasting blood glucose of ≥ 126 mg/dL, or random glucose ≥ 200 mg/dL. Current smoking was defined as self-report of active smoking within the last year of the examination.

Case Ascertainment

Protocols and criteria for the ascertainment and diagnosis of events were similar in both cohorts and have been reported previously.^{11,12} The primary outcome for this analysis was incident ASCVD events, defined as a composite of nonfatal myocardial infarction, coronary heart disease death, nonfatal stroke, or fatal stroke.

Statistical Analysis

We stratified participants based on baseline antihypertensive treatment status and then categorized participants into 6 strata based on baseline SBP level: <120 , 120 to 129, 130 to 139, 140 to 149, 150 to 159, and ≥ 160 mm Hg. We determined the distribution of baseline characteristics for each SBP category using general linear models for continuous variables and chi-square tests for categorical variables. Unadjusted incident ASCVD rates were calculated per 1000 person-years of follow-up. We used multivariable Cox proportional hazards models to estimate hazard of an incident ASCVD event over 10 years for each SBP category relative to the reference group of untreated SBP <120 mm Hg, adjusting for demographics and traditional cardiovascular risk factors. We then calculated the number of “excess” ASCVD events attributed to each SBP stratum relative to the unadjusted event rates of the group with untreated SBP <120 mm Hg. For the untreated SBP 140 to 149 mm Hg stratum, for example, we calculated the expected number of events by multiplying the number of participants in the untreated SBP 140 to 149 mm Hg stratum by the ASCVD event rate in the untreated SBP <120 mm Hg stratum. We then took the difference between the observed number of ASCVD events and the expected number of events at 10 years to calculate the number of excess ASCVD events.

We estimated 10-year predicted ASCVD risk at baseline using covariates from the 2013 ACC/AHA Pooled Cohort risk equations.¹³ The Pooled Cohort risk equations are sex- and race-specific prediction models that incorporate age, total and high-density lipoprotein cholesterol levels, SBP, antihypertensive medication use, smoking status, and diabetes status to estimate 10-year absolute risk of ASCVD. Participants were classified into low-risk (10-year ASCVD risk $<5\%$), intermediate-risk (10-year ASCVD risk 5% to 7.5%), and high-risk (10-year ASCVD risk $\geq 7.5\%$) groups.

We performed a sensitivity analysis using diastolic blood pressure strata (<80 , 80 to 89, 90 to 99, ≥ 100 mm Hg). All analyses were performed using SAS 9.2 (SAS Institute). The authors had full access to the data and take responsibility for its integrity.

Both cohorts were approved by the institutional review board from each contributing institution, including Northwestern University. Participants provided informed consent at each examination.

Results

Baseline Characteristics

We analyzed data from 18 898 participants (8710 men, 10 188 women). Over the 10 years of follow-up, 739

Table 1. Baseline Characteristics of ARIC and Framingham Offspring Participants by Baseline SBP Category, Treated and Untreated Participants (n=18 898)

	SBP <120 mm Hg (n=9420)	SBP 120 to 129 mm Hg (n=4125)	SBP 130 to 139 mm Hg (n=2531)	SBP 140 to 149 mm Hg (n=1398)	SBP 150 to 159 mm Hg (n=719)	SBP ≥160 mm Hg (n=705)	P Value
Age, y	51.9 (5.7)	52.9 (6.0)	53.6 (6.3)	54.4 (6.0)	54.9 (6.0)	55.2 (6.0)	<0.001
Female, %	57.7	49.9	48.2	54.4	47.2	53.6	<0.001
Black, %	14.2	20.1	21.1	27.7	37.0	44.8	<0.001
Total cholesterol, mg/dL	210.0 (41.0)	214.9 (42.1)	216.7 (40.7)	221.2 (42.3)	222.1 (43.1)	221.5 (45.0)	<0.001
HDL cholesterol, mg/dL	52.0 (16.6)	50.4 (16.4)	50.0 (16.6)	51.6 (17.6)	51.1 (17.2)	51.8 (18.0)	<0.001
BMI, kg/m ²	26.4 (4.6)	28.1 (5.3)	28.7 (5.7)	29.1 (5.9)	29.2 (6.1)	29.5 (6.0)	<0.001
Current smoker, %	30.4	28.2	29.3	27.5	30.0	36.6	<0.001
Diabetes mellitus, %	5.5	9.2	10.5	12.2	17.4	21.0	<0.001
Treated hypertension, %	12.9	23.7	29.0	36.1	40.3	45.7	<0.001
Treated cholesterol, %	2.5	2.7	3.3	2.4	3.5	1.7	<0.001
10-year estimated ASCVD risk, %	4.3 (4.4)	6.8 (6.0)	8.5 (7.2)	10.1 (7.9)	13.7 (10.3)	19.3 (14.0)	<0.001

Continuous variables are shown as mean (SD). The 10-year ASCVD risk is calculated using the 2013 American College of Cardiology and American Heart Association Pooled Cohort risk equations. ARIC indicates Atherosclerosis Risk in Communities Study; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL, high-density lipoprotein; SBP, systolic blood pressure.

participants experienced an incident ASCVD event. Baseline characteristics for all participants stratified by SBP level are shown in Table 1 (baseline characteristics stratified by SBP treatment status are shown in Table S1). Black participants composed 22% of the total sample and were disproportionately represented in the higher SBP and treated-SBP categories. Notably, the prevalence of traditional cardiovascular risk factors such as body mass index, smoking, total cholesterol, and diabetes mellitus was higher with each progressive SBP category. Treatment rates with lipid-lowering agents were low in all strata ($\approx 3\%$), reflecting the absence of widespread statin treatment during this era of follow-up.

Risk of an ASCVD Event at 10 Years

Among participants with untreated SBP, unadjusted ASCVD incident rates and adjusted relative hazards of ASCVD increased in a stepwise fashion with each successive SBP category compared with those with untreated SBP <120 mm Hg (Table 2). Relative hazards for an ASCVD event at 10 years were lowest in participants with baseline untreated SBP 120 to 129 mm Hg (adjusted hazard ratio 1.56, 95% CI 1.19 to 2.04) and highest in participants with baseline untreated SBP ≥ 160 mm Hg (adjusted hazard ratio 3.27, 95% CI 2.26 to 4.74). Among participants with treated SBP, unadjusted ASCVD incident rates and adjusted relative hazards demonstrated similar stepwise increases. Those who were treated with antihypertensive medications at baseline had a

higher risk of ASCVD at each SBP strata compared with their untreated counterparts. Participants who were treated and controlled to SBP <140 mm Hg had similar relative hazards for an ASCVD event, ranging from 2.28 to 2.71 (Table 2).

Excess ASCVD Events

Using the ASCVD event rate in participants with baseline untreated SBP <120 mm Hg as the reference, we estimated 427 excess ASCVD events during the 10 years of follow-up (Table 3). Among participants who were not treated with antihypertensive medications at baseline, 56% (109 of 197) of excess ASCVD events occurred in those with nonoptimal but not treatment-eligible SBP (SBP ≥ 120 and <140). Among treated participants, 50% (115 of 230) of excess ASCVD events occurred at SBP levels considered at goal (SBP <140) per hypertension treatment guidelines.

Predicted ASCVD Risk

Mean 10-year predicted ASCVD risk calculated using baseline risk factor values was higher in each successively higher SBP category, both for treated and untreated participants (Table 4). Within each SBP stratum, mean 10-year predicted ASCVD risk was higher in participants who subsequently experienced an ASCVD event at 10 years compared with those who did not ($P < 0.001$ for all paired comparisons).

Table 2. Observed ASCVD Incident Rate and Relative Hazards at 10 Years by Baseline SBP Category

Baseline SBP (mm Hg)	Participants (n)	ASCVD Event Rate Per 1000 person-years Follow-up	Adjusted HR (95% CI)
Untreated (n=14 856)			
<120	8205	1.7	1.0 (Ref)
120 to 129	3147	3.8	1.56 (1.19 to 2.04)
130 to 139	1798	4.5	1.71 (1.27 to 2.32)
140 to 149	894	4.5	1.63 (1.11 to 2.40)
150 to 159	429	8.3	2.66 (1.77 to 3.98)
≥160	383	13.2	3.27 (2.26 to 4.74)
		<i>P</i> <0.001	<i>P</i> <0.001
Treated (n=4042)			
<120	1215	5.1	2.28 (1.65 to 3.14)
120 to 129	978	6.6	2.71 (1.96 to 3.75)
130 to 139	733	6.2	2.28 (1.58 to 3.30)
140 to 149	504	8.7	3.74 (2.60 to 5.40)
150 to 159	290	13.1	4.25 (2.87 to 6.29)
≥160	322	21.3	6.94 (4.91 to 9.81)
		<i>P</i> <0.001	<i>P</i> <0.001

An ASCVD event is defined as nonfatal myocardial infarction, coronary heart disease death, nonfatal stroke, and fatal stroke. HRs are adjusted for age, sex, race, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, smoking status, and diabetes history. ASCVD indicates atherosclerotic cardiovascular disease; HR, hazard ratio; SBP, systolic blood pressure.

Excess ASCVD Events

The distribution of observed ASCVD events over 10 years in untreated and treated participants by baseline SBP and baseline 10-year predicted ASCVD risk category is shown in Figure 1. The majority of observed ASCVD events at 10 years occurred at SBP levels <140 mm Hg, reflecting the greater number of participants with these SBPs at baseline. Within each SBP category, the distribution of high-risk participants increased from 14.2% in the group with untreated SBP <120 mm Hg to 90.3% in the group with treated SBP ≥160 mm Hg. The utility of multivariable risk estimation in categorizing participants who experience an ASCVD event at 10 years was seen principally among those who were untreated at baseline (Figure 1A). Among treated participants, 88% had baseline 10-year ASCVD risk ≥7.5%. The distribution of participants without ASCVD events at 10 years in untreated and treated participants by baseline SBP and baseline 10-year predicted ASCVD risk category is shown in Figure 2.

Among all participants, 73% (540 of 739) of those who experienced an ASCVD event at 10 years and 32% (5962 of

Table 3. Excess* ASCVD Events at 10 Years by Baseline SBP Category

Baseline SBP (mm Hg)	ASCVD Events (n)	Expected ASCVD Events (n)	Excess ASCVD Events (n)	Excess ASCVD Events (%)
Untreated (n=14 856)				
<120	135	—	—	—
120 to 129	114	52	62	31.6
130 to 139	77	30	47	24.1
140 to 149	38	15	23	11.8
150 to 159	33	7	26	13.2
≥160	45	6	39	19.6
Total	442	110	197	100.0
Treated (n=4042)				
<120	59	20	39	16.9
120 to 129	61	16	45	19.5
130 to 139	43	12	31	13.4
140 to 149	41	8	33	14.2
150 to 159	35	5	30	13.1
≥160	58	5	53	22.9
Total	297	67	230	100.0

An ASCVD event was defined as nonfatal myocardial infarction, coronary heart disease death, nonfatal stroke, or fatal stroke. ASCVD indicates atherosclerotic cardiovascular disease; SBP, systolic blood pressure.

*Excess ASCVD events were calculated as the difference between observed and expected ASCVD events, using the ASCVD event rate in the group with untreated SBP <120 mm Hg as the reference (expected in stratum: number in stratum × event rate in untreated SBP <120 mm Hg; excess: observed in stratum—expected in stratum).

18 898) of those who did not experience an ASCVD event had 10-year predicted ASCVD risk ≥7.5% at baseline. These findings were primarily driven by untreated participants, who made up the majority of our sample. Among untreated participants with nonoptimal but not treatment-eligible SBP (ie, untreated SBP 120 to 139 mm Hg), 64% (123 of 191) of those who experienced an ASCVD event at 10 years and 30% (1446 of 4754) of those who did not experience an ASCVD event had 10-year predicted ASCVD risk ≥7.5% at baseline. Consequently, a threshold of ≥7.5% 10-year ASCVD risk identified untreated participants with nonoptimal but not treatment-eligible SBP with sensitivity of 64% and specificity of 70% for potential risk-reducing therapy. Test characteristics comparing thresholds based on SBP level and risk among untreated participants are shown in Table 5.

Sensitivity analysis using diastolic blood pressure categories confirmed that the majority of excess ASCVD events occurred among participants with nonoptimal but not treatment-eligible diastolic blood pressure. We elected to present only information on SBP categories, given the

Table 4. Mean Estimated 10-Year ASCVD Risk at Baseline Stratified by Blood Pressure Treatment Status

	Mean Predicted 10-Year ASCVD Risk (%)		
	Total (95% CI)	ASCVD Event at 10 Years (95% CI)	No ASCVD Event at 10 Years (95% CI)
No Blood Pressure Treatment at Baseline			
Number of events	14 856	442	14 414
Baseline SBP (mm Hg)			
<120	3.8 (3.7 to 3.9)	8.9 (7.5 to 10.4)	3.7 (3.6 to 3.8)
120 to 129	5.9 (5.7 to 6.1)	10.9 (9.3 to 12.4)	5.7 (5.6 to 5.9)
130 to 139	7.1 (6.9 to 7.3)	11.8 (9.9 to 13.7)	6.9 (6.7 to 7.1)
140 to 149	8.3 (8.0 to 8.6)	13.3 (10.6 to 16.0)	8.1 (7.7 to 8.4)
150 to 159	10.8 (10.3 to 11.2)	16.5 (13.6 to 19.4)	10.3 (9.8 to 10.8)
≥160	15.2 (14.7 to 15.7)	20.6 (18.1 to 23.1)	14.5 (14.0 to 15.0)
Blood Pressure Treatment at Baseline			
Number of events	4042	297	3745
Baseline SBP (mm Hg)			
<120	7.3 (6.8 to 7.8)	12.0 (8.9 to 15.0)	7.1 (6.6 to 7.6)
120 to 129	9.4 (8.9 to 10.0)	14.5 (11.6 to 17.5)	9.1 (8.6 to 9.6)
130 to 139	12.1 (11.5 to 12.7)	18.7 (15.2 to 22.3)	11.7 (11.1 to 12.3)
140 to 149	13.3 (12.5 to 14.1)	20.9 (17.3 to 24.5)	12.6 (11.9 to 13.4)
150 to 159	18.1 (17.0 to 19.1)	27.5 (23.6 to 31.4)	16.8 (15.7 to 17.8)
≥160	24.2 (23.2 to 25.2)	32.9 (29.9 to 36.0)	22.3 (21.3 to 23.3)

An ASCVD event was defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Ten-year ASCVD risk was calculated using the 2013 American College of Cardiology and American Heart Association Pooled Cohort risk equations. ASCVD indicates atherosclerotic cardiovascular disease; SBP, systolic blood pressure.

stronger association of SBP with ASCVD in middle-aged adults.⁵

Discussion

In this analysis of a population-based sample of middle-aged US adults, we confirmed the continuous log-linear association between SBP and ASCVD risk, a relationship known to continue well below the SBP threshold of ≥140 mm Hg used to define treatment eligibility and treatment goals in blood pressure-based hypertension guidelines.^{5,6} We also demonstrated the implications of this relationship by indicating that half of excess ASCVD events attributable to nonoptimal SBP occurred at levels not currently eligible for antihypertensive therapy. Furthermore, we demonstrated that among participants with nonoptimal but not treatment-eligible SBP, a 10-year predicted ASCVD risk threshold ≥7.5% had superior sensitivity and specificity compared with SBP thresholds, particularly for participants who were not treated with antihypertensive medications at baseline.

Several key observations stand out in our analyses. First, there was no SBP threshold at which ASCVD risk ceased to exist, highlighting the arbitrary dichotomization of elevated

SBP into hypertension and normotension. Second, treatment of elevated SBP did not reduce ASCVD risk to rates seen among untreated participants, underscoring the importance of primordial prevention. Third, blood pressure-based guidelines that advocate single-risk-factor management leave significant ASCVD risk unaddressed, particularly among those who are not on antihypertensive medications at baseline, a group that comprises the majority of the population. Fourth, multivariable risk estimation may help identify, with reasonable sensitivity and specificity, persons who are likely to benefit from risk-reducing therapies across the spectrum of SBP, particularly among those who are not already treated with antihypertensive medications.

ASCVD risk patterns across the spectrum of blood pressure have been previously demonstrated in observational studies.^{5,10,14} Analyses of the ≈347 000 Multiple Risk Factor Intervention Trial (MRFIT) screenees aged 35 to 57 years demonstrated that nearly two-thirds of excess coronary heart disease-related deaths occurred in men with “mild” hypertension, defined as SBP 130 to 159 mm Hg; of those, 20.7% of excess coronary heart disease deaths were in men with SBP 130 to 139 mm Hg.^{6,15} Data from the Global Burden of Disease similarly demonstrated that only half of the burden of

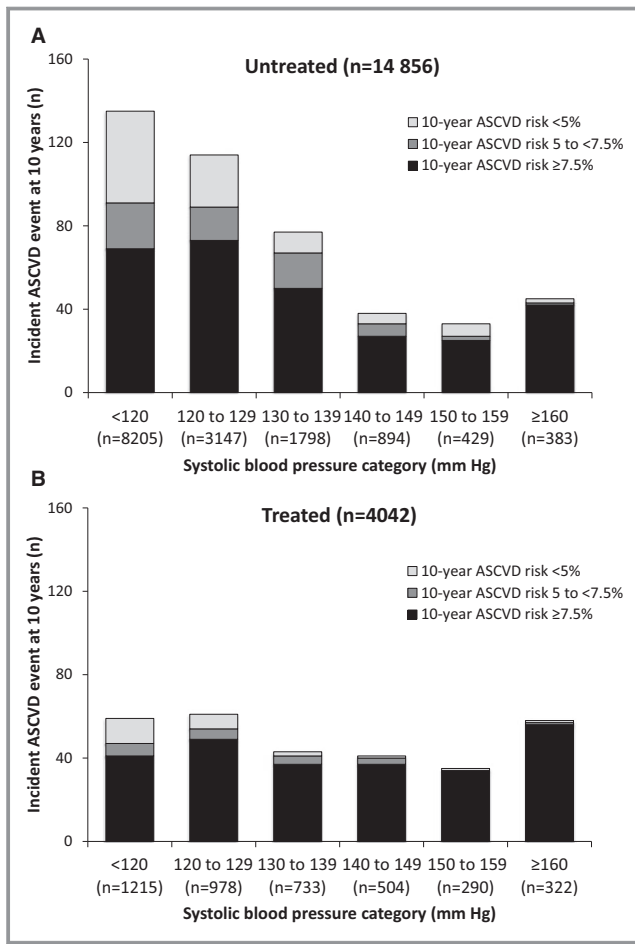


Figure 1. Incident atherosclerotic cardiovascular disease (ASCVD) events at 10 years by baseline systolic blood pressure group for participants who were untreated (A) and treated (B) for hypertension at baseline. ASCVD events at each systolic blood pressure group are categorized by 10-year predicted ASCVD risk at baseline.

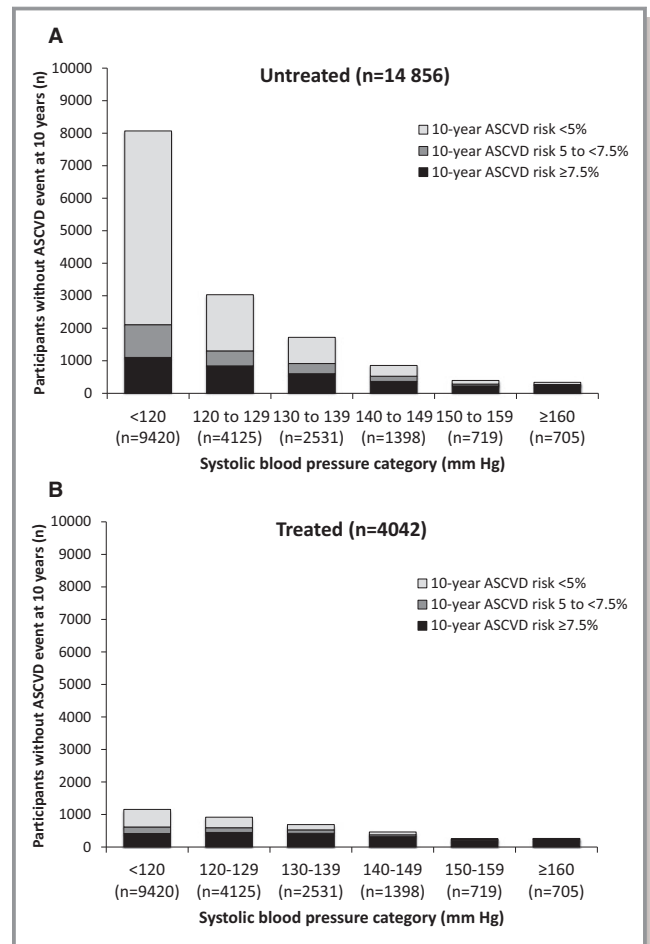


Figure 2. Participants *without* atherosclerotic cardiovascular disease (ASCVD) events at 10 years by baseline systolic blood pressure group for participants who were untreated (A) and treated (B) for hypertension at baseline. Participants without an ASCVD event at each systolic blood pressure group are categorized by 10-year predicted ASCVD risk at baseline.

stroke and ischemic heart disease was attributable to people with hypertension (defined as SBP ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or blood pressure treatment), with the other half attributable to those with lesser degrees of high blood pressure.¹⁶ Our results confirmed these findings in a contemporary, US-based cohort. The principal novel finding of our analysis is the use of multivariable risk to identify those persons potentially destined for an ASCVD event.

The importance of multifactorial management, beyond antihypertensive therapy, to reduce cardiovascular risk in hypertensive persons has been demonstrated in studies like the Hypertension Optimal Treatment (HOT) study, in which the addition of low-dose aspirin resulted in a 22% reduction in the incidence of major cardiovascular events compared with placebo.¹⁷ In addition, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 19 342 hypertensive persons with at

least another cardiovascular risk factor and elevated fasting total cholesterol (>260 mg/dL) who were randomized to atorvastatin 10 mg and 1 of 2 antihypertensive regimens had a 36% reduction in the primary end point of nonfatal myocardial infarction and coronary heart disease death as well as reductions in the secondary end points of stroke and total cardiovascular events at 3.3 years.¹⁸ International prevention guidelines have recognized the importance of a multifactorial strategy to treat elevated blood pressure and the role of cardiovascular risk assessment in guiding that clinical decision making.^{7,8,19}

The incorporation of global cardiovascular risk assessment in prevention efforts also raises the notion of abandoning blood pressure targets altogether and instead using multivariable risk to guide use of antihypertensive medications.^{20–22} Decision analysis modeling using expected benefits of

Table 5. Test Characteristics of SBP-Based Thresholds Versus Risk-Based Thresholds in Participants Who Were Not Treated With Antihypertensive Medications at Baseline

	All Untreated		Untreated SBP ≥120 and <140	
	Blood Pressure Threshold*	10-Year ASCVD Risk ≥7.5%	Blood Pressure Threshold†	10-Year ASCVD Risk ≥7.5%
Sensitivity	26%	65%	40%	64%
Specificity	89%	77%	64%	70%
Positive predictive value	7%	8%	4%	8%
Negative predictive value	98%	99%	96%	98%
Positive likelihood ratio	2.38	2.76	1.11	2.12
Negative likelihood ratio	0.83	0.46	0.94	0.51

ASCVD indicates atherosclerotic cardiovascular disease; SBP, systolic blood pressure.
 *Using an SBP threshold ≥140 mm Hg.
 †Using an SBP threshold ≥130 mm Hg.

treatment have suggested that risk-based blood pressure treatment strategies have the potential to prevent more events while treating fewer patients compared with traditional blood pressure-based treatment.^{23,24} A recent meta-analysis of individual participant trial data from the Blood Pressure Lowering Treatment Trialists’ Collaboration provided further empirical support for such an approach by demonstrating that the relative risk reduction from blood pressure-lowering therapy was similar across risk strata and thus that the absolute risk reductions were greatest in those at the highest pretreatment risk.²⁵

Trials such as the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and the International Verapamil SR/Trandolapril Study (INVEST) provide indirect evidence for the added benefit of lowering SBP in high-risk persons²⁶; however, clinical trial data are limited among high-risk, nondiabetic persons with SBP <140 mm Hg in need of primary prevention. Ongoing trials like the National Institutes of Health-sponsored Systolic Blood Pressure Intervention Trial (SPRINT) will be particularly informative about the merits of more- versus less-intensive SBP reduction in this patient population.²⁷

Nevertheless, the present findings support the adoption of an alternative strategy to treat elevated SBP. With the decline in SBP within the population,²⁸ greater numbers of people now have modest elevations in SBP requiring a more holistic treatment strategy that pivots from correction of significantly

elevated SBP levels in isolation to assessment of multiple cardiovascular risk factors, in addition to SBP, that influence the likelihood of an ASCVD event. Our results suggest that multivariable risk assessment with a clinical prediction tool may provide a strategy to guide clinical decision making by integrating multiple cardiovascular risk factors, estimating risk and potential benefit from treatment, and enhancing clinician–patient discussions to individualize recommendations surrounding the use of antihypertensive medications, much as the cholesterol guidelines recommend statin use.⁹

Although the sensitivity and specificity of risk-based categories are modest, the test characteristics compare favorably with SBP-based thresholds, particularly among untreated participants with nonoptimal but not treatment-eligible SBP, in whom the majority of excess ASCVD events occur. Critically, the use of a high-risk strategy to guide pharmacological preventive therapy must be combined with population-based strategies to reduce the overall prevalence of nonoptimal blood pressure and primordial prevention to prevent the development of elevated blood pressure in the first place.

Two features of our analysis warrant further discussion. First, in our primary analyses, we did not adjust for potential confounders in describing excess ASCVD rates by SBP stratum. Therefore, excess ASCVD events at each SBP stratum reflect not only the effects associated with elevated SBP but also the unfavorable ASCVD risk factors that are correlated with elevated SBP. We chose to use the unadjusted ASCVD rates for our analyses to reflect the unadjusted SBP levels encountered in routine clinical practice. Second, we recognize that our choice of a 10-year risk threshold of 7.5% for these analyses was arbitrary. This choice had the virtue of being consistent with the evidence-based threshold recommended to identify patients for consideration of a statin for primary prevention of ASCVD.⁹ If risk estimation is to be incorporated into guidelines for blood pressure management, it would be preferable to determine an evidence-based risk threshold for blood pressure treatment using an approach that balances treatment benefits and risks in a manner similar to the approach used in cholesterol guidelines.⁹

Limitations

Several important limitations must be acknowledged in our analyses. First, the cohorts are not nationally representative population samples; however, the detailed baseline examinations and comprehensive longitudinal surveillance with adjudication of ASCVD events within these cohorts more than mitigate this potential limitation. Second, the study was not designed to analyze the effect of transitions, so we do not know the relationship of changes in SBP and cardiovascular outcomes. Third, follow-up in both cohort studies occurred in

an era before widespread statin use, so the effects of intensive lipid lowering on the relationship of SBP and ASCVD events is unclear. Last, the mere identification of higher risk persons does not necessarily lead to improvement in outcomes, highlighting the importance of testing a strategy of risk-based prevention prospectively.

Conclusions

In summary, a hypertension treatment strategy focused solely on blood pressure thresholds leaves substantial ASCVD risk unaddressed. Multivariable risk estimation may help identify the types of persons who are likely to benefit from risk-reducing therapies across the spectrum of SBP. Clinical trials that stratify participants by pretreatment absolute risk and blood pressure and then randomize the groups with discordant treatment recommendations to antihypertensive medications and other risk-reducing therapies versus placebo are needed to confirm the merits of absolute risk assessment in guiding primary prevention therapies.

Addendum

On September 11, 2015, the National Institutes of Health (NIH) announced the early termination of the Systolic Blood Pressure Intervention Trial (SPRINT) due to significant benefit from more intensive treatment to a target of <120 mm Hg systolic compared to a target of <140 mm Hg systolic. Preliminary results released by the NIH report that treatment to a systolic blood pressure of <120 mm Hg reduced rates of heart attack, heart failure, and stroke by nearly one third, and death by nearly one-quarter compared to treatment to <140 mm Hg.²⁹ The trial, which included adults age 50 years and older without diabetes but with at least one additional cardiovascular risk factor, provides important evidence supporting more intensive blood pressure management in high-risk individuals. Our findings suggest that multivariable risk assessment may provide a framework to identify these high-risk individuals who benefitted from more intensive blood pressure management.

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Disclosures

None.

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