

Residual Cardiovascular Risk in Individuals on Blood Pressure–Lowering Treatment

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Background—Hypertensive individuals on blood pressure (BP)–lowering treatment with BP in the normal or high-normal range have higher cardiovascular risk than untreated persons with usual BP in the same range. This residual risk (relative and absolute) is not well quantified and may be attributable in part to the higher burden of subclinical disease in treated individuals.

Methods and Results—We assigned 3024 Framingham Offspring Cohort participants to 5 categories based on systolic BP (SBP) and diastolic BP (DBP) and use of BP-lowering treatment: (1) untreated SBP/DBP <120/80 mm Hg; (2) untreated SBP/DBP ≥120/80 to <140/90 mm Hg; (3) treated SBP/DBP <140/90 mm Hg; (4) untreated SBP/DBP ≥140/90 mm Hg; and (5) treated SBP/DBP ≥140/90 mm Hg. A composite subclinical disease score was constructed, including information on left ventricular hypertrophy, systolic dysfunction, carotid ultrasound abnormality, peripheral artery disease, and microalbuminuria. The prevalence of subclinical disease rose across BP groups, as did the event rates for incident cardiovascular disease (449 events, median follow-up of 11 years; group 1, 0.65 event per 100 person-years; group 5, 3.20 events per 100 person-years; $P < 0.0001$ for trend). On multivariable adjustment, treated hypertensives in groups 3 and 5 had 50% (95% CI 13% to 99%) and 28% (95% CI –6% to 73%) higher hazards, respectively, of developing cardiovascular disease compared with their untreated counterparts with similar levels of BP (groups 1 and 2 and group 4, respectively). The increased risk of cardiovascular disease in treated hypertensives was attributable in part to greater subclinical disease burden.

Conclusions—Treated hypertensives have higher subclinical cardiovascular disease burden, which partly explains their higher cardiovascular disease risk compared with untreated persons with similar BP levels. (*J Am Heart Assoc.* 2015;4:e002155 doi: 10.1161/JAHA.115.002155)

Key Words: blood pressure • cardiovascular disease • subclinical disease

High blood pressure (BP) is a major cardiovascular disease (CVD) risk factor.¹ Observational studies established a graded positive relation between BP levels and CVD risk,^{1,2} and randomized controlled trials demonstrated that reductions in BP levels through antihypertensive treatment were paralleled by reductions in CVD events.^{3,4} Ample evidence indicates that

antihypertensive treatment also reduces the burden of subclinical CVD, including regression of left ventricular (LV) mass, carotid intima-media thickness, and urinary albumin excretion, during short-term follow-up.^{5–8} Most of the latter analyses, however, focused on selected parameters of subclinical disease and were performed in clinical trials with limited durations of follow-up^{6,8} or in clinical samples of modest size.^{5,7}

In some population-based and clinical samples, higher CVD risk has been reported in persons on antihypertensive treatment^{9–11}; however, the residual cardiovascular risk and particularly the subclinical disease burden in people on antihypertensive treatment in the community has not been adequately quantified. Those on antihypertensive treatment in the community have both greater duration of hypertension and higher levels of BP, both of which may drive the higher burden of subclinical disease in these people.

It is unclear whether BP reduction to normal or high-normal levels by BP-lowering medications “normalizes” CVD risk and subclinical disease burden. We aimed to quantify the burden of subclinical CVD and the risk of incident CVD associated with different levels of BP in the community, focusing on comparing treated versus untreated persons in the

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Accompanying Data S1, Tables S1 through S3 and Figures S1 and S2 are available at <http://jaha.ahajournals.org/content/4/11/e002155/suppl/DC1>

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community with similar BP levels. We hypothesized that at similar BP levels, treated hypertensives have higher subclinical CVD burden and greater risk of overt CVD than persons with similar BP who are not on treatment. In addition, we postulated that the greater residual CVD risk in treated hypertensives is attributable in part to the greater subclinical disease burden in these individuals.

Methods

Study Sample

The present investigation was performed using data from attendees of the sixth examination cycle (conducted between 1995 and 1998) of the Framingham Offspring Cohort.¹² Participants were comprehensively characterized with respect to CVD risk factors and subclinical disease.¹³ Participants with prevalent CVD (n=412) and missing BP levels (n=3) were excluded from the analyses. An additional 8 participants with missing follow-up information were excluded, yielding a sample size of 3024 for analyses of incident CVD. In a subsample of 1915 participants, several measures of subclinical CVD burden were available. All participants provided written informed consent, and the study protocol was approved by the institutional review board at Boston University Medical Center.

Measurement of BP and Subclinical CVD

A more detailed description of the subclinical disease assessment is provided in Data S1.

At the sixth examination cycle, BP levels were measured twice on the participant's left arm using a mercury column sphygmomanometer after the participant had been seated for ≥ 5 minutes. To determine the ankle brachial index, BP was measured twice on both the arms and at both the ankles using an 8-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Park Medical Electronics Inc), as described elsewhere.¹⁴ Participants also underwent transthoracic echocardiography, and M-mode images were used to determine measurements of LV structure. LV mass was calculated as described by Devereux et al.¹⁵ The sex-specific 80th percentile of LV mass was used as a cut point for echocardiographic evidence of LV hypertrophy, consistent with prior publications (Table S1).^{13,16} LV fractional shortening and visually assessed ejection fraction served as measures of LV systolic function. In addition, a 12-lead electrocardiogram was obtained with participants in supine position. Sex-specific Cornell voltage criteria were used to assess electrocardiographic evidence of LV hypertrophy.^{13,17} Ultrasound of the carotid arteries was performed, as described previously.¹⁸ Images of the common carotid artery and the internal carotid artery were obtained using a 7.5-MHz transducer and a 5.0-MHz transducer, respectively.¹⁸

These images were used to calculate near- and far-wall intima-media thickness. Stenoses of the carotid arteries were likewise assessed, with $\geq 25\%$ stenoses indicating significant narrowing of the carotid artery. Intima-media thickness values that met or exceeded the sex-specific 80th percentile were defined as increased carotid artery intima-media thickness (Table S1).¹³ Urinary albumin and creatinine were measured in a morning spot urine sample. Urine albumin was assayed using an immunoturbidimetric test (Tina-quant albumin assay; Roche Diagnostics), and urinary creatinine was determined with a modified Jaffe method. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.¹⁹

Subclinical Disease Score

We quantified the cumulative subclinical disease burden by generating a subclinical disease score, as reported previously.¹³ A detailed description of the score is provided in Table S1. In essence, this score is the sum of 5 dichotomized indices of subclinical atherosclerosis and target organ damage: LV hypertrophy (by electro- or echocardiography), LV systolic dysfunction (by echocardiography), abnormal ultrasound of the carotid arteries (increased intima-media thickness or carotid artery stenosis), peripheral artery disease (abnormal ankle brachial index), and glomerular endothelial dysfunction (indicated by microalbuminuria).¹³ The score ranged from 0 (none of the above abnormal) to 5 (all abnormal). In addition to this score, we evaluated the 5 individual components of the score. We also modeled subclinical disease as a binary variable (yes/no). The complete score and its components were available for 1915 participants.

Assessment of Incident CVD

Participants were under surveillance for incident CVD events. Cardiovascular events were adjudicated by a panel of 3 physicians, and strokes were adjudicated by a panel of 3 neurologists, using standardized criteria. Our primary outcome of interest was a first CVD event over 11.1 years (median) of follow-up; events were defined as fatal and nonfatal myocardial infarction, angina, coronary insufficiency (acute coronary syndrome), peripheral vascular disease (intermittent claudication), cerebrovascular events (stroke or transient ischemic attack), and heart failure.²⁰

Statistical Methods

Based on BP levels and the intake of antihypertensive medication at examination cycle 6, participants were categorized into 5 BP groups: (1) usual (untreated) systolic BP (SBP)/diastolic BP (DBP) $< 120/80$ mm Hg, (2) usual (untreated) SBP/DBP $\geq 120/80$ to $< 140/90$ mm Hg, (3) SBP/DBP

<140/90 mm Hg on antihypertensive medication, (4) usual (untreated) SBP/DBP \geq 140/90 mm Hg, and (5) SBP/DBP \geq 140/90 mm Hg on antihypertensive medication.

If the SBP and DBP values of a participant belonged to different BP groups, the participant was assigned to the higher BP group using the higher of the SBP or DBP value; for example, an untreated participant with BP of 130/70 mm Hg would belong to group 2.

Association of BP Group With Measures of Subclinical Disease

We estimated the multivariable-adjusted mean subclinical disease score for each BP group and tested for differences between BP groups using generalized linear models. We adjusted these models for age, sex, total and high-density lipoprotein cholesterol, lipid-lowering medication, smoking, diabetes, estimated glomerular filtration rate, and aspirin use. Furthermore, for each BP group, we estimated multivariable-adjusted odd ratios for the presence of subclinical disease (defined as a score \geq 1) and for each of the 5 components of the score, using multiple logistic regression analysis with the first BP group (SBP/DBP <120/80 mm Hg) as the referent. Because subclinical disease was relatively common in some BP groups (Table S2), we also estimated relative risks for the presence of subclinical disease using Poisson regression with robust error variance.²¹ In additional analyses, we specifically compared group 5 with group 4 and compared group 3 with groups 1 and 2 groups 1 and 2 combined with respect to the cumulative subclinical disease score using a general linear model to compare treated hypertensives with untreated participants with comparable levels of BP.

Association of BP Group With Incident CVD

We assessed the absolute risk of CVD (event rates per 100 person-years) according to BP group (as defined) over a median follow-up period of 11.1 years. Furthermore, we graphically displayed the association between BP group at examination cycle 6 and incident CVD after examination cycle 6 using Kaplan–Meier curves. To adjust for potential confounders, including age, sex, total and high-density lipoprotein cholesterol, lipid-lowering medication, smoking, diabetes, estimated glomerular filtration rate, and aspirin use, we estimated Cox proportional hazard models using the BP group as an exposure variable after verifying that the assumption of proportionality of hazards was met. We performed 2 main analyses. In the first analysis, we estimated hazard ratios (HRs) for incident CVD for each BP group using BP group 1 (untreated SBP/DBP <120/80 mm Hg) as the referent category. In additional analyses, we specifically compared treated hypertensives with participants with similar BP who were not

on BP-lowering treatment; to this end, multivariable-adjusted HRs were calculated for incident CVD in group 5 (treated BP \geq 140/90 mm Hg), with group 4 (usual BP \geq 140/90 mm Hg) as the referent category, and for group 3 (treated BP <140/90 mm Hg), with groups 1 and 2 combined (usual BP <140/90 mm Hg) as the referent category, using the full sample and contrasting the respective subgroups. In secondary analyses, we calculated a propensity score using multivariable logistic regression analysis (outcome was BP group membership) including the following covariates: age, male sex, SBP and DBP, body mass index, smoking, diabetes, total and high-density lipoprotein cholesterol, and lipid-lowering treatment. We then adjusted the above-mentioned analyses additionally for the propensity score. Finally, we adjusted the statistical models relating BP group to incident CVD for the duration of hypertension and the duration of BP-lowering treatment.

Impact of Subclinical Disease Burden on CVD Risk

To assess the extent to which the increased CVD risk in treated hypertensives was explained by their greater subclinical disease burden, we performed 2 sets of analyses. First, we calculated multivariable-adjusted HRs for incident CVD in a subsample restricted to those participants on whom information regarding subclinical disease was available ($n=1915$). We then additionally adjusted our statistical model for the subclinical disease score (modeled as a continuous trait) and evaluated how much the HR for incident CVD was attenuated on such adjustment. In an alternative model, we adjusted for the presence of subclinical disease (defined as a subclinical disease score \geq 1). Second, we calculated the absolute disease risk for incident CVD in each BP group, stratifying by presence versus absence of subclinical disease within each BP group; thus, at a given level of BP, we compared the absolute risks for incident CVD in those with versus without subclinical disease.

Results

Baseline characteristics stratified by BP group are displayed in Table 1. Mean SBP and DBP were lower in group 3 (treated hypertensives) compared with group 2 (untreated persons) (Table 1). In group 5 (treated hypertensives), participants had slightly higher levels of SBP but slightly lower levels of DBP, as in group 4 (untreated persons) (Table 1). Baseline characteristics of the subclinical disease samples are provided in Table S2. The average duration of hypertension in groups 4 and 5 were 6.9 years (SD 6.7) and 15.5 years (SD 7.8), respectively. The average duration of treatment for hypertension was 6.3 years (SD 6.3) and 8.4 years (SD 7.4) in groups 3 and 5, respectively.

Table 1. Baseline Characteristics in the Overall Sample (n=3024), Stratified by Blood Pressure Group

Characteristics	Overall Sample (N=3024)					<i>P</i> _{trend}
	Group 1, <120/80 mm Hg, No Treatment (n=909)	Group 2, ≥120/80 to <140/90 mm Hg, No Treatment (n=970)	Group 3, <140/90 mm Hg, On Treatment (n=393)	Group 4, ≥140/90 mm Hg, No Treatment (n=413)	Group 5, ≥140/90 mm Hg, On Treatment (n=339)	
Clinical and biochemical features						
Age, y, mean±SD	53.7±8.8	57.9±9.1	61.0±8.5	61.4±9.1	65.7±8.1	<0.0001
Women, n (%)	582 (64.0)	503 (51.9)	201 (51.2)	211 (51.1)	178 (52.5)	<0.0001
SBP, mm Hg, mean±SD	109±7	127±7	125±10	152±13	154±14	<0.0001
DBP, mm Hg; mean±SD	68±6	77±7	75±8	84±10	82±10	<0.0001
Hypertension treatment, n (%)	0 (0.0)	0 (0.0)	393 (100.0)	0 (0)	339 (100.0)	<0.0001
BMI, kg/m ²	26.1±4.4	27.9±5.0	29.8±5.8	28.4±5.4	29.3±5.3	<0.0001
Smoking, n (%)	165 (18.2)	139 (14.3)	39 (9.9)	65 (15.8)	32 (9.4)	0.0004
Diabetes, n (%)	21 (2.3)	52 (5.4)	62 (15.8)	32 (7.8)	61 (18.0)	<0.0001
Total cholesterol, mg/dL, mean±SD	200±37	209±38	203±34	214±39	207±36	<0.0001
HDL cholesterol, mg/dL, mean±SD	54±16	52±16	49±16	52±17	50±16	<0.0001

DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Association of BP Group With Subclinical Disease Burden

The subclinical disease score and the prevalence of subclinical disease (subclinical disease score ≥1) were higher in persons with increasing BP level (Table S2), a trend that persisted on multivariable adjustment (Figure 1A and 1B). At comparable levels of BP, treated hypertensives (groups 5 and 3) had significantly higher subclinical disease scores (Figure 1A) and greater odds (Figure 1B) and relative risks (Figure S1) of subclinical disease compared with untreated participants with similar (usual) BP levels (group 4 and groups 1 and 2 combined). Similar trends were observed for the individual components of the score, including LV hypertrophy, LV systolic dysfunction, carotid ultrasound abnormality, peripheral artery disease, and microalbuminuria (Figure S2), with generally higher odd ratios by the higher BP groups and with greater subclinical disease burden in treated hypertensives (groups 3 and 5) compared with their untreated counterparts with comparable levels of BP (groups 1 and 2 combined and group 4) (Figure S2).

Association of BP Group With Incident CVD

During a median follow-up of 11.1 years (range 0.005 to 14.4 years), 449 (201 women) of 3024 participants developed an incident CVD event. The Kaplan–Meier curves by BP group are displayed in Figure 2 and show unadjusted survival free of CVD. As expected, treated hypertensives (group 5, yellow line, and group 3, red line) had shorter cumulative survival free of CVD compared with their untreated counterparts with similar BP levels (group 4, blue line, and group 2, green line). The crude event rate was lowest (0.65 event per 100 person-years) (Table 2) in group 1 (usual BP <120/80 mm Hg), rose with increasing BP, and was highest in group 5 (treated BP ≥140/90 mm Hg) (Table 2). At comparable levels of BP, treated hypertensives had higher event rates compared with their untreated counterparts (comparison of group 5 versus group 4 and of group 3 versus groups 1 and 2) (Table 2). Even after multivariable adjustment, participants in group 3 (on BP-lowering treatment) had 50% (95% CI 13% to 99%;

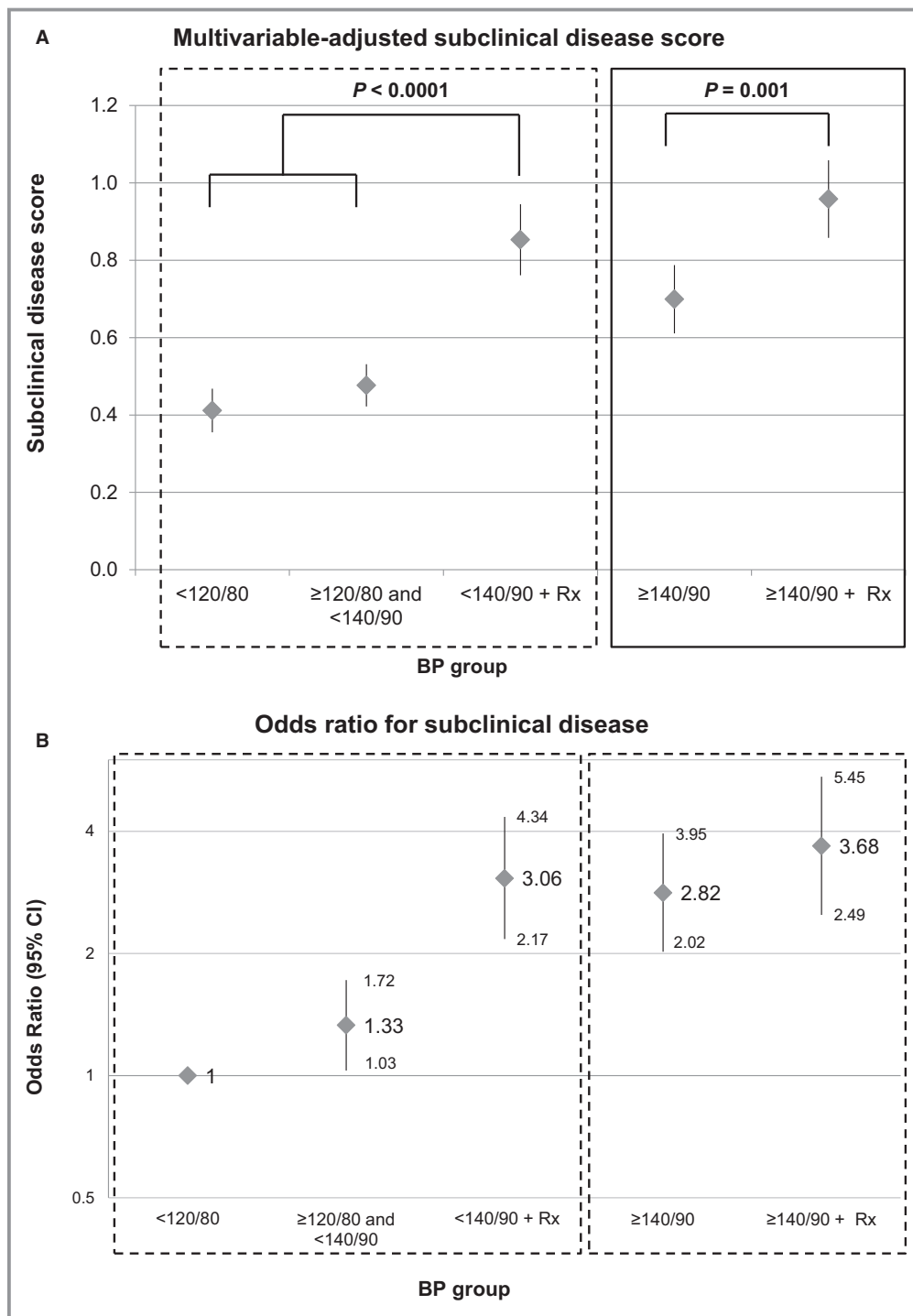


Figure 1. Multivariable-adjusted subclinical disease score (A) and odds ratio for presence of subclinical disease (score ≥ 1) (B) by BP group. BP indicates blood pressure; hr, blood-pressure lowering medication.

$P=0.005$) higher hazard of developing incident CVD compared with the untreated participants in groups 1 and 2 with similar BP levels (Table S3). On a similar note, participants in group 5 (on BP-lowering treatment) tended to have greater hazards for incident CVD compared with (untreated) participants in group 4 (HR 1.28; 95% CI 0.94 to 1.73; $P=0.12$). Additional adjustment for a propensity

score did not alter these results (Table S3); however, adjustment for the duration of hypertension and the duration of hypertension treatment attenuated the HR for incident CVD in groups 3 and 5 (Table 2, right column) and rendered the differences between treated and untreated participants with similar levels of BP statistically nonsignificant (Table S3, right column).

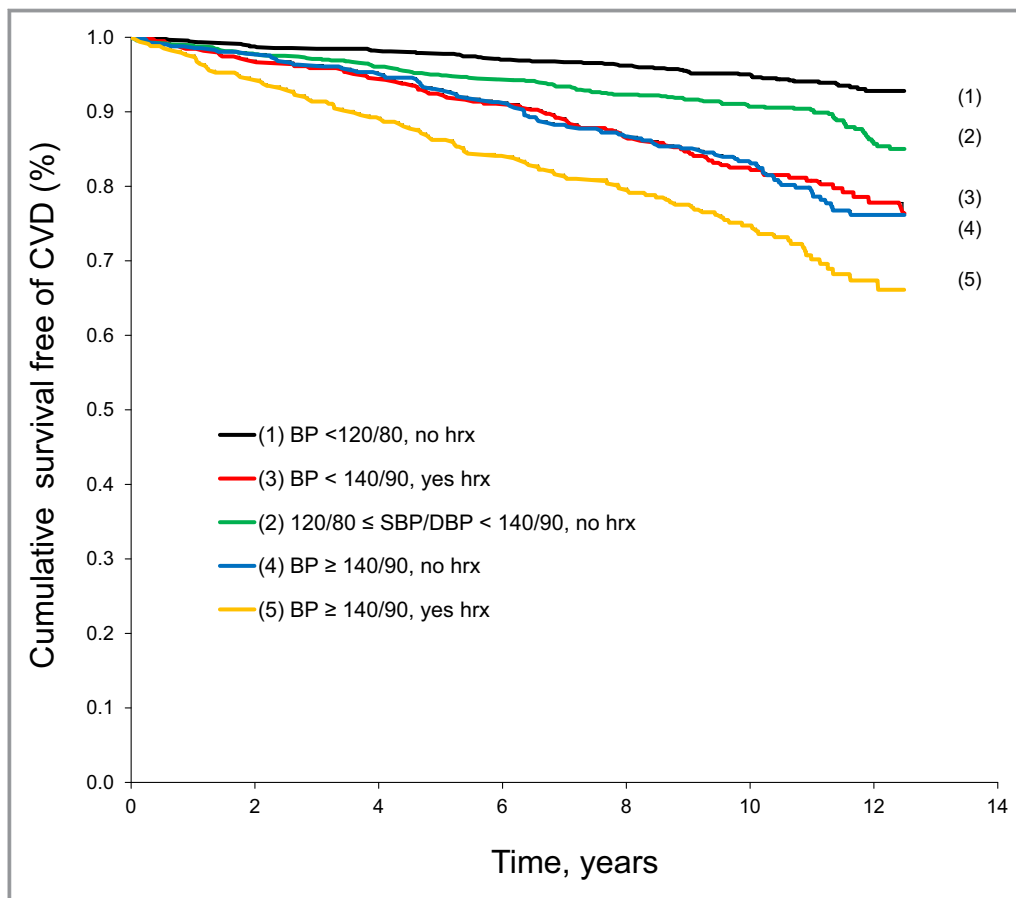


Figure 2. Unadjusted survival free of CVD by BP group (log-rank $P < 0.0001$). BP indicates blood pressure; CVD, cardiovascular disease; hr, blood pressure–lowering medication.

Impact of Subclinical Disease Burden on CVD Risk

Table 3 displays the multivariable-adjusted HRs for incident CVD in those participants in whom all subclinical disease measures were available ($n=1915$). In essence, the association pattern in this subgroup ($n=1915$) was comparable to the results in the overall sample (Table 2). On additional adjustment for subclinical disease, the HRs for incident CVD were attenuated by 3.4% to 20.5% (Table 3). The attenuation was stronger with increasing BP levels and was greater in treated hypertensives compared with untreated participants with similar BP (Table 3).

The absolute disease risk in each BP group, stratified by the presence versus absence of subclinical disease, is shown in Table 4. Across all levels of BP, participants with subclinical disease had a greater absolute risk of incident CVD compared with participants without subclinical disease.

Discussion

Hypertension is a silent killer because people are often not aware of having high BP levels; even if they are aware of their

high BP, often they are not treated. Furthermore, many treated patients are not well controlled.²²

In a large sample from the general population, we compared the absolute and relative disease risks for incident CVD and the subclinical CVD burden according to different BP levels, with a specific focus on comparing treated and untreated participants with similar levels of BP. By doing so, we wanted to explore whether reduction of BP to normal or high-normal levels through antihypertensive medication was paralleled by normalization of CVD risk to a level comparable to the risk experienced by untreated persons with similar levels of BP. Our main findings are summarized as follows. First, higher levels of BP were associated with higher burden of subclinical disease and with greater hazards for incident CVD prospectively. Second, at similar levels of BP, treated hypertensives had a more substantial burden of subclinical CVD and were at higher risk of incident CVD compared with untreated participants. Third, this increased CVD risk was partly related to the greater burden of subclinical disease in treated hypertensives and to the duration of hypertension and hypertension treatment.

Table 2. Association of BP Group With Incident Cardiovascular Disease in Different Multivariable-Adjusted Models in the Overall Sample (n=3024)

	BP Group, mm Hg	BP Treatment	No. Events/No. at Risk	Person-Years	Crude Event Rates (95% CI)*	HR (95% CI) [†]	P Value	HR (95% CI) [‡]	P Value
1	<120/80	No	65/909	9997	0.65 (0.51–0.83)	1		1	
2	≥120/80 to <140/90	No	116/970	10 170	1.14 (0.95–1.37)	1.35 (1.00–1.84)	0.054	1.36 (1.00–1.85)	0.053
3	<140/90	Yes	80/393	3842	2.08 (1.67–2.59)	1.92 (1.36–2.71)	0.0002	1.60 (1.08–2.38)	0.020
4	≥140/90	No	88/413	4091	2.15 (1.75–2.64)	1.94 (1.39–2.71)	0.0001	1.97 (1.39–2.79)	0.0001
5	≥140/90	Yes	100/339	3125	3.20 (2.64–3.88)	2.44 (1.74–3.43)	<0.0001	1.96 (1.30–2.98)	0.0015
	Total		449/3024	31 225	1.44 (1.31–1.58)				

BP indicates blood pressure; HDL, high-density lipoprotein; HR, hazard ratio.

*Events per 100 person-years.

[†]HRs are adjusted for age, sex, total and HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, and estimated glomerular filtration rate.

[‡]HRs are adjusted for age, sex, total and HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, estimated glomerular filtration rate, duration of hypertension, and duration of hypertension treatment.

In the Context of the Published Literature

Association of BP and BP treatment with clinical and subclinical CVD

Observational studies have established a positive and graded relation between BP levels and CVD risk.^{1,2} Even slightly elevated BP levels (>120/80 mm Hg) are associated with higher risk of BP progression toward hypertension²³ and with greater hazards for incident CVD events prospectively compared with participants with BP levels <120/80 mm Hg.¹ Furthermore, BP is a key correlate of cardiovascular remodeling traits, including LV mass,^{24,25} intima-media thickness,²⁶ and albuminuria.²⁷ Randomized controlled trials consistently demonstrated that lowering high BP through pharmacological interventions was associated with reduced risks for CVD events.⁴ Consistent with the latter observations, measures of subclinical cardiac and vascular disease also improved in parallel to the reduction in BP on antihypertensive medication. In the LIFE study, the prevalence of LV hypertrophy decreased from 70% at baseline to 23% over 5 years of antihypertensive treatment, and such regression in LV mass was associated with reduced relative risks of CVD events.²⁸ In other clinical trials, antihypertensive treatment was associated with benign structural remodeling of the common carotid artery.^{29,30} Higher BP values were also associated with indices of early kidney damage.^{27,31} Nevertheless, data regarding the residual CVD risk of treated hypertensives in the general population are limited.

Consistent with the above-mentioned reports, in our large community-based sample, we observed that higher BP values were associated with greater cumulative subclinical disease burden, including higher prevalence of LV hypertrophy and systolic dysfunction, carotid artery abnormalities, peripheral artery disease, and microalbuminuria. Furthermore, we estimated the absolute disease risks for incident CVD associated with different levels of BP in the community and demonstrated that treated hypertensives had a greater risk of incident CVD compared with untreated participants with similar BP. These observations are in line with the results from population-based analyses from Japan and Sweden reporting greater risks of cardiovascular mortality and stroke in treated versus untreated persons.^{9–11} Finally, we report that the increased hazard for CVD is attenuated by ≈3% to 20% on adjustment for the greater subclinical disease burden in treated hypertensives, consistent with the concept that part of the increased CVD risk is related to the greater subclinical disease burden. Adjustment for the duration of hypertension and hypertension treatment also attenuated the increased CVD risk in persons with hypertension, underscoring that the cumulative exposure to high BP throughout the life course affects CVD risk. Alternative reasons for residual cardiovascular risk in treated hypertensives include noncompliance with medication intake and dietary recommendations.

Table 3. Impact of Subclinical Disease Burden on the HR for Incident Cardiovascular Disease in the Subsample With Available Subclinical Disease Measures (n=1915)

	BP Group, mm Hg	BP Treatment	HR (95% CI)*	HR (95% CI) †	Change in HR (%)‡	HR (95% CI)§	Change in HR (%)‡
1	<120/80	No	1	1		1	
2	≥120/80 to <140/90	No	1.48 (0.99–2.20)	1.43 (0.96–2.13)	3.37% decrease	1.43 (0.96–2.13)	3.37% decrease
3	<140/90	Yes	2.46 (1.57–3.85)	2.07 (1.31–3.27)	15.85% decrease	2.14 (1.36–3.37)	13.01% decrease
4	≥140/90	No	2.15 (1.39–3.35)	1.93 (1.24–3.01)	10.23% decrease	1.87 (1.20–2.93)	13.02% decrease
5	≥140/90	Yes	2.39 (1.52–3.78)	1.90 (1.18–3.03)	20.50% decrease	2.05 (1.29–3.25)	14.23% decrease

BP indicates blood pressure; HDL, high-density lipoprotein; HR, hazard ratio.

*Multivariable-adjusted model with adjustment for age, sex, total and HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, and estimated glomerular filtration rate.

†Multivariable model additionally adjusted for subclinical disease score, modeled as a continuous trait.

‡Change in HR on additional adjustment for the subclinical disease score or for the presence of subclinical disease, respectively, compared with the HR adjusted for age, sex, total and HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, and estimated glomerular filtration rate only.

§Multivariable model additionally adjusted for the presence vs absence of subclinical disease (defined as a subclinical disease score ≥1).

Table 4. Absolute Disease Risk by BP Group and Within Each BP Group Further Stratified by the Presence or Absence of Subclinical Disease (Defined as a Subclinical Disease Score ≥1)

	BP Group, mm Hg	BP Treatment	Subclinical Disease (Score ≥1)	No. Events/No. at Risk	No. Events/No. at Risk	Person-Years	Crude Event Rates (95% CI)*
1. A.	<120/80	No	Absent	22/474	41/640	5294	0.42 (0.27–0.63)
1. B.	<120/80	No	Present	19/166		1799	1.06 (0.67–1.65)
2. A.	≥120/80 to <140/90	No	Absent	31/386	66/608	4192	0.74 (0.52–1.05)
2. B.	≥120/80 to <140/90	No	Present	35/222		2216	1.58 (1.13–2.19)
3. A.	<140/90	Yes	Absent	6/87	44/223	915	0.66 (0.30–1.46)
3. B.	<140/90	Yes	Present	38/136		1255	3.03 (2.21–4.14)
4. A.	≥140/90	No	Absent	16/98	48/243	994	1.61 (0.99–2.62)
4. B.	≥140/90	No	Present	32/145		1440	2.22 (1.58–3.13)
5. A.	≥140/90	Yes	Absent	7/56	53/201	569	1.23 (0.59–2.57)
5. B.	≥140/90	Yes	Present	46/145		1335	3.44 (2.59–4.58)
	Total				252/1915	20 008	1.26 (1.11–1.42)

BP indicates blood pressure.

*Events per 100 person-years.

Our results agree well with risk prediction models in the primary prevention setting. Multivariable-adjusted statistical models that predict absolute disease risks for a first cardiovascular event in initially healthy persons revealed that the intake of antihypertensive medication is an independent adverse predictor in such models for various forms of CVD, even after accounting for measured BP levels.^{32,33} In large clinical trial cohorts, prediction models have estimated the impact of antihypertensive treatment on the 5-year risk for CVD.³⁴ On a similar note, antihypertensive treatment was independently associated with the progression of important subclinical disease traits, including LV mass and mean aortic root diameter over the short term (4 years) and over the life course, above and beyond measured BP levels.^{24,35}

Clinical Implications

Our observations of increased CVD risk and subclinical disease burden in treated hypertensives (compared with untreated participants with similar BP) support the concept that the intake of antihypertensive medication is a marker for the chronicity and severity of elevated BP and for greater subclinical disease burden. It is conceivable that physicians treat patients with antihypertensive medication if patients have higher BP levels more frequently and over a longer period of time. Consequently, even though antihypertensive medications significantly lower BP and improve clinical outcome, treated individuals are still at higher CVD risk compared with untreated persons with similar usual BP levels. These observations suggest that those on

BP-lowering medication should be monitored closely for target organ damage and potential symptoms of overt CVD, even if their BP levels reach normal or high-normal values. Given the well-documented burden of hypertension with significant deficits in the awareness, treatment, and control of hypertension in the United States,²² these data underscore the need for better screening strategies for hypertension in the community to improve the rates of early detection and subsequent treatment and control of hypertension. Finally, our analyses emphasize the importance of primary prevention of hypertension because the CVD risk cannot be entirely eliminated by medications once hypertension has developed.

Strengths and Limitations

The large sample size, the community-based design, the careful assessment of BP and clinical covariates, the broad panel of subclinical disease traits, and the prospective design with up to 14 years of follow-up for incident CVD strengthen our investigation. Some limitations merit consideration. We focused our BP group classification on the mean of 2 BP measurements at 1 examination cycle (examination cycle 6). This examination cycle was chosen because it offered the broadest and most comprehensive spectrum of subclinical disease measures and because using it as the baseline examination ensured a sufficiently long follow-up period for incident CVD analyses (follow-up of up to 14 years, 449 events). Nevertheless, classification based on BP measurement and treatment information from a single examination cycle might have led to some nondifferential misclassification, biasing us toward the null hypothesis of no association between higher BP group and disease outcome. Our sample was middle-aged and of European American descent. It is unknown whether our results are applicable to nonwhite ethnicities and other age groups.

It is well established that, compared with white persons, black women and men have a greater burden of hypertension³⁶ (eg, age-adjusted prevalences of 44.9% and 46.1% for men and women, respectively),³⁶ earlier onset of hypertension,³⁶ greater burden of subclinical disease (eg, higher prevalence of LV hypertrophy^{37,38} and peripheral artery disease^{36,39}), and greater relative risk increases for CVD events (eg, stroke) for similar increments in SBP.^{36,40} Consequently, similar analyses of the residual cardiovascular risk associated with BP-lowering medication in black persons and other ethnic groups are warranted.

We cannot entirely rule out that the observed differences in CVD risk and subclinical disease burden between treated and untreated participants with similar BP values could be partially due to the fact that clinicians identified individuals at higher risk for CVD and prescribed them antihypertensive drugs (confounding by indication).

In conclusion, we determined subclinical disease burden and risk for incident CVD according to different levels of BP in the community, with a specific focus on comparing treated and untreated persons with similar BP levels. At comparable levels of BP, treated hypertensives had higher subclinical disease burden and greater risk of incident CVD compared with their untreated counterparts. This risk was partly attributable to the greater burden of subclinical disease. These observations support the concept that treated hypertensives should be monitored closely for target organ damage and potential symptoms of CVD, even if their BP levels reach normal or high-normal levels. Furthermore, these data highlight the need for early detection, treatment, and appropriate follow-up of patients with hypertension.

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Disclosures

None.

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