Background and Purpose—Although pharmacological treatment of hypertension has important health benefits, it does not capture the benefit of maintenance of ideal health through the prevention or delay of hypertension.

Methods—A total of 26,875 black and white participants aged 45+ years were assessed and followed up for incident stroke events. The association was assessed between incident stroke and: (1) systolic blood pressure (SBP) categorized as normal (<120 mm Hg), prehypertension (120–139 mm Hg), stage 1 hypertension (140–159 mm Hg), and stage 2 hypertension (160 mm Hg+); and (2) number of classes of antihypertensive medications, classified as none, 1, 2, or 3 or more.

Results—During 6.3 years of follow-up, 823 stroke events occurred. Nearly half (46%) of the population were successfully treated (SBP <140 mm Hg) hypertensives. Within blood pressure strata, the risk of stroke increased with each additional class of required antihypertensive medication, with hazard ratio [HR], 1.33; 95% confidence interval, 1.16 to 1.52 for normotensive, HR, 1.15; 95% confidence interval, 1.05 to 1.26 for prehypertension, and HR, 1.22; 95% confidence interval, 1.06 to 1.39 for stage 1 hypertension. A successfully treated (SBP <120 mm Hg) hypertensive person on 3+ antihypertensive medication classes was at marginally higher stroke risk than a person with untreated stage 1 hypertension (HR, 2.48 versus HR=2.19; relative to those with SBP <120 on no antihypertensive medications).

Conclusions—Maintaining the normotensive status solely through pharmacological treatment has a profound impact, as nearly half of this general population cohort were treated to guideline (SBP <140 mm Hg) but failed to return to risk levels similar to normotensive individuals. Even with successful treatment, there is a substantial potential gain by prevention or delay of hypertension. (Stroke. 2015;46:000-000. DOI: 10.1161/STROKEAHA.115.009128.)

Key Words: hypertension ♦ prevention and control ♦ risk factors ♦ stroke
The Framingham Stroke Risk Function to predict 10-year risk of stroke includes terms for both systolic BP (SBP) and antihypertensive medication use, where at any SBP level, use of antihypertensive medication is associated with a 1.39-fold increase in stroke risk for men (with a more complex age-dependent increase in women). The QSTROKE risk function also includes terms for both SBP and antihypertensive medication use, and medication use is associated with a 1.82-fold higher (95% confidence interval [CI], 1.66–2.00) stroke risk after controlling for SBP. The increased stroke risk stroke associated with antihypertensive medication use may seem counterintuitive, but given that a person has a SBP of 160 mm Hg, if a person is on treatment then their pretreatment BP was even higher.

The literature describing risk differences between those taking and not taking antihypertensive therapy in the general population is sparse. Hypertension treatment was not included in the Cardiovascular Health Study risk function, and the Atherosclerosis Risk in Communities Study risk function considered hypertension status, defined as high BP or current medication use, as a single predictor for risk.

Herein, we assessed stroke risk based on SBP strata defined by the Seventh Joint National Committee guidelines, and treatment strata defined by the number of antihypertensive classes of medication used. The goals were to assess whether hypertensive individuals with well-controlled BP have a residual increased risk of stroke, and how the intensiveness of antihypertensive treatment affects this risk.

Methods

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a longitudinal cohort study of 30,239 community-dwelling black and white individuals aged 45+ years from the 48 contiguous states. Participants were recruited by a combination of mail and telephone survey, with a telephone-administered health interview. An in-home assessment that included BP measurement, fasting blood and urine collection, an ECG, and medications inventory was performed ≈2 weeks later. Details of the study methods are provided elsewhere.

Suspected strokes were solicited during telephone interviews conducted at 6-month intervals. Medical records were retrieved for suspected strokes, and stroke end points were physician adjudicated using published methods.

BP measurements were based on the mean of 2 measures taken after the participant was seated for 5 minutes. SBP strata were defined following Seventh Joint National Committee guidelines as normal (<120 mm Hg), prehypertension (120–139 mm Hg), stage 1 hypertension (140–159 mm Hg), and stage 2 hypertension (160 mm Hg+). The number of classes of antihypertensive medications was determined from the medications inventory by summing across the classes: angiotensin-converting enzyme inhibitors, aldosterone antagonists, β-blockers, angiotensin II receptor blockers, β-blockers, calcium channel blockers, central agonists, diuretics, or vasodilators. Participants who reported not taking antihypertensive medications or had no antihypertensive medications in the medications inventory were defined as not taking antihypertensive medication. Because few participants were on ≥4 classes of BP medications, strata were defined as none, 1, 2, or 3 or more.

Diabetes mellitus was defined as fasting glucose of ≥126 mg/dL (or 200 mg/dL or greater for those nonfasting) or self-reported use of antidiabetes medications. Atrial fibrillation was defined by ECG evidence or self-report of a physician diagnosis. Left ventricular hypertrophy was defined by ECG. Coronary heart disease was defined as a self-reported myocardial infarction, ECG evidence of myocardial infarction, or self-reported coronary artery bypass grafting, angioplasty, or stenting.

The incidence of stroke was estimated by strata of SBP and antihypertensive medication classes using proportional hazards analysis, after adjustment for age, race, age-by-race interaction (previously proven to be statistically significant), sex, and the residual SBP deviation. Adjustment for residual SBP deviation was performed to remove potential residual confounding from differences in mean SBP levels within BP strata, and was calculated as the difference between each participant’s SBP and the average for all participants in the BP stratum.

Supplemental analysis assessed further adjustment for other Framingham stroke risk factors (diabetes mellitus, current smoking, atrial fibrillation, and coronary heart disease), with left ventricular hypertrophy omitted as it can reflect a cumulative hypertension burden. A priori, main effects were tested with a 2-sided \(\alpha =0.05\), and with interactions tested at \(\alpha =0.10\).

Results

Of the 30,239 participants, we excluded 59 (0.2%) for data anomalies, 770 (2.5%) without antihypertensive medications data, and 681 (2.3%) reporting antihypertensive use without data in the medication inventory, and 1930 (6.4%) who self-reported a previous stroke at baseline. Collectively, these exclusions reduced the analysis data set to 26,875 participants who were followed for 6.2 years during which 860 participants had a stroke (726 infarctions, 70 intracerebral hemorrhages, 16 subarachnoid hemorrhages, and 48 unclassified strokes).

The combination of 4 SBP strata with the 4 strata of number of medications defined a total of 16 (4×4) strata of participants, with the characteristics of the study population provided in Table 1 (and risk factor prevalence in Table I in the online-only Data Supplement). Within strata defined by the number of medications, individuals in higher SBP strata tended to be older and were more likely black. For each strata defined by SBP, those on more medications also tended to be older and were more likely black.

The associated adjusted hazard ratios (HRs) are provided in Table 2. For those with SBP in the normal range (SBP<120 mm Hg), there was a monotonic increase in stroke risk with increasing medication use, where those on 1, 2, and 3+ antihypertensive medication classes had a 42%, 60%, and 148% increased stroke risk. For each additional class of antihypertensive medication being taken, the stroke risk was estimated to increase 33%.

For those in higher SBP strata (prehypertensive, stage 1 and stage 2 hypertension), stroke risk tended to be higher for those on more classes of antihypertensive medications. Although overall there was no evidence of a difference in the association of stroke risk associated with increasing number of antihypertensive medications across SBP categories (\(P_{interaction}=0.29\)), the increase in stroke risk per category of medication use was numerically smaller for those with prehypertension, stage 1 or stage 2 hypertension. However, the trend for increased stroke risk among those receiving more medications was statistically significant for those with prehypertension (HR, 1.15; 95% CI, 1.05–1.26) and for those with stage 1 hypertension (HR, 1.22; 95% CI, 1.06–1.39).

Adjusting for stroke risk factors did not substantially affect these relationships (Table II in the online-only Data Supplement).

For those not on antihypertensive medication, there was an increase in stroke risk at higher SBP strata, with a HR of 1.44 (95% CI, 1.04–2.01) for those with prehypertension (relative to normotensive individuals), 2.19 (95% CI, 1.45–3.31) for stage 1
hypertension, and 3.35 (95% CI, 1.78–6.28) for stage 2 hypertension. For untreated participants, the increase in stroke risk was 1.49× (95% CI, 1.26–1.76) per each higher SBP stratum.

For those on 1 or 2 antihypertensive medications, there was a suggestion that the increased risk at higher BP levels was smaller than for those on no medications ($P_{\text{interaction}}=0.13$)

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-Race Interaction, Sex, and the Deviation From the Mean SBP Level for the Category

<table>
<thead>
<tr>
<th>Normotensive (&lt;120 mm Hg)</th>
<th>Prehypertension (120 mm Hg–139 mm Hg)</th>
<th>Stage 1 Hypertension (140 mm Hg–159 mm Hg)</th>
<th>Stage 2 Hypertension (160+ mm Hg)</th>
<th>Tests for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antihypertensive medications</td>
<td>1.0 (Ref)</td>
<td>1.44 (1.04–2.01)</td>
<td>2.19 (1.45–3.31)</td>
<td>3.35 (1.78–6.28)</td>
</tr>
<tr>
<td>1 Antihypertensive medication</td>
<td>1.42 (0.94–2.15)</td>
<td>2.00 (1.44–2.77)</td>
<td>1.67 (1.09–2.54)</td>
<td>3.00 (1.71–5.26)</td>
</tr>
<tr>
<td>2 Antihypertensive medications</td>
<td>1.60 (1.06–2.42)</td>
<td>1.88 (1.35–2.62)</td>
<td>2.84 (1.95–4.13)</td>
<td>1.42 (0.67–2.99)</td>
</tr>
<tr>
<td>3+ Antihypertensive medications</td>
<td>2.48 (1.63–3.77)</td>
<td>2.34 (1.66–3.32)</td>
<td>3.35 (2.28–4.92)</td>
<td>4.62 (2.84–7.51)</td>
</tr>
<tr>
<td>Tests for trend</td>
<td>1.33 (1.16–1.52)</td>
<td>1.15 (1.05–1.26)</td>
<td>1.22 (1.06–1.39)</td>
<td>1.10 (0.86–1.40)</td>
</tr>
</tbody>
</table>

Tests for trend represent the estimated increase in the HR per category for number of medications and SBP category (and test for interaction across strata). HR indicates hazard ratio; and SBP, systolic blood pressure.
in primary analysis, and $P_{\text{interaction}}=0.082$ after adjustment for risk factors). Compared with the 49% increase in risk per BP stratum for those on no medications, the increase for those on 1 or 2 medications was only 16% (95% CI, 0.98–1.37) per BP stratum. For those on ≥3 medications, there was an increase in stroke risk at higher SBP strata, and a statistically significant trend for increasing stroke risk with increasing SBP levels (HR, 1.26; 95% CI, 1.07–1.48).

Sensitivity analysis restricted to those with ischemic stroke provided similar results (results not shown). There was little evidence of a differential impact of BP and treatment on the hazard of stroke by race ($P_{\text{interaction}}=0.36$) or sex ($P_{\text{interaction}}=0.63$).

### Discussion

These results suggest that successful pharmacological treatment of hypertension reduces, but does not eliminate, the harmful effects of hypertension. Stroke risk among hypertensive participants receiving 1 class of antihypertensive medication that reduced SBP levels to <120 mmHg was 42% higher than among individuals who were at that same BP level without medications. The risk of stroke was even higher (1.60-fold greater) among hypertensive individuals who were taking 2 classes, and higher yet (2.48-fold greater) for those taking ≥3 classes. Hence, even with normalization of SBP through pharmacological treatment, hypertensive individuals in this study had a residual stroke risk over twice the risk of stroke compared with those who were normotensive without medication.

A similar pattern was observed for those with prehypertension, where participants taking 1 class of antihypertensive medication were at 1.39-fold (2.00/1.44=1.39) the risk of untreated individuals with the same SBP level, and those requiring ≥3 medications to achieve this level of control were at 1.63-fold (2.34/1.44=1.63) risk. The risk was higher among those hypertensive participants whose antihypertensive treatment reduces their BP to below the 140 mmHg guideline than for untreated individuals in the same BP strata, and the risk increases with the intensiveness of treatment required to achieve BP below the guideline. Specifically, there was a 15% (HR, 1.15; 95% CI, 1.05–1.26) incremental increase in the risk of stroke for each additional medication used to treat participants to this BP level. This increase of 15% per additional medication class among those with prehypertension was less than half of the 33% per medication class for those who were normotensive; however, this difference was not statistically significant ($P=0.29$). Among those with stage 1 hypertension (SBP, 140–159 mmHg), there was a 22% (HR, 1.22; 95% CI, 1.06–1.40) increase in stroke risk for every additional class of medication taken compared with those with untreated stage 1 hypertension.

These observations suggest that even with normalization of SBP, there is substantial residual increased stroke risk among those on antihypertensive treatment, and the stroke risk is higher if more aggressive treatment is required to achieve normal SBP. Importantly, compared with individuals who are naturally normotensive, the risk of hypertensive individuals requiring a single medication to achieve a normal SBP level is comparable with the risk among individuals with untreated prehypertension (42% and 44% increased risk, respectively). Likewise, hypertensive persons requiring ≥3 medications to achieve SBP<120 mmHg are at marginally higher risk than individuals with untreated stage 1 hypertension (2.48- and 2.19-fold risk, respectively).

Of the 26,875 participants in the study, 12,327 (46%) were hypertensive and treated to the guideline of <140 mmHg; however, despite successful hypertension management they had a risk between 1.42× and 2.48× greater than normotensive individuals not on treatment. Despite the effectiveness of BP lowering, once hypertension develops there was an increased stroke risk in nearly half the participants, even if SBP is lowered to guideline levels.

Several other reports have compared risk of stroke and other forms of cardiovascular disease between normotensive and treated hypertensive individuals. Data from a longitudinal follow-up study compared stroke risk in 754 treated hypertensive men and 6740 normotensive men. During 25 to 28 years of follow-up 1031 men had a stroke. The relative risk was 1.75-fold (95% CI, 1.50–2.05) comparing the treated hypertensive men to normotensive men.22 However, the results of this previous study are difficult to interpret as (1) treated levels of BP in the hypertensive subjects remained above the levels for the normotensive subjects, and (2) achieved BP levels (either systolic or diastolic) or change in BP from baseline were not associated with stroke risk. More recently, the British Regional Heart Study and the British Women’s Heart and Health study showed that cardiovascular risk among persons with treated and well-controlled BP was 1.47× (95% CI, 1.01–2.15) higher than among normotensive persons.23 Analysis of differences in stroke risk alone was not provided. Furthermore, the study was limited by small numbers of participants and outcomes: only 177 events in 1692 normotensive individuals, compared with 32 events in 215 well-controlled hypertensive individuals.

The rich literature of effective approaches to prevent or delay the development of hypertension was summarized by the National Heart, Lung, and Blood Institute High Blood Pressure Education Program, which concluded that there is randomized clinical trial evidence of 6 approaches with proven efficacy for the prevention of hypertension: engage in moderate physical activity; maintain normal body weight; limit alcohol consumption; reduce sodium intake; maintain adequate intake of potassium; and consume a diet rich in fruits, vegetables, low-fat dairy products and reduced in saturated and total fat.24 The American Heart Association has also issued a scientific statement with strong evidence that dietary interventions can prevent or delay the development of hypertension:25 However, the results of this previous study are difficult to interpret as (1) treated levels of BP in the hypertensive subjects remained above the levels for the normotensive subjects, and (2) achieved BP levels (either systolic or diastolic) or change in BP from baseline were not associated with stroke risk. More recently, the British Regional Heart Study and the British Women’s Heart and Health study showed that cardiovascular risk among persons with treated and well-controlled BP was 1.47× (95% CI, 1.01–2.15) higher than among normotensive persons.23 Analysis of differences in stroke risk alone was not provided. Furthermore, the study was limited by small numbers of participants and outcomes: only 177 events in 1692 normotensive individuals, compared with 32 events in 215 well-controlled hypertensive individuals.

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There are many reasons why hypertensive participants with normal SBP on pharmacological treatment may be at.
higher stroke risk. Their hypertension may not always have been well controlled (including the possibility of a period of undetected hypertension), and that elevated BP earlier in life resulted in vascular damage, including atherosclerosis and accelerated vascular aging, leading to higher stroke risk. In addition, although SBP was well-controlled at the time of the REGARDS in-person evaluation, it is possible that the participants became more adherent with medications in anticipation of the home visit and that their usual SBP levels were higher than those recorded at the REGARDS visit. Finally, hypertension may be secondary to renal arteriolosclerosis and similar small vessel disease may also affect brain parenchyma, predisposing the participant to stroke even when SBP levels are lowered with antihypertensive medications.

This analysis provides data on the effect of SBP differences that are standardized for the intensity of hypertension treatment. The data suggest that the effect of elevated SBP may be greater for those on no medications than for those on 1 or 2 classes of antihypertensive medications ($P_{\text{interaction}}=0.13$ in primary analysis, but $P_{\text{interaction}}=0.082$ in supplemental analysis). Specifically, for every increase in SBP stratum across the spectrum from normotension to stage 2 hypertension, there was a 49% increase in stroke risk for those on no medications, but only a 16% increase in risk for those on 1 or 2 BP medications. This may suggest that antihypertensive medications may have pleiotropic benefits beyond the level of SBP reduction.

This study has several specific strengths and limitations. Strengths include the large sample size and substantial number of stroke events that provide relatively stable estimates of risk after the stratification of participants into 16 strata. However, there are relatively few participants with stage 2 hypertension, raising concern that estimates in these strata may be less stable. A limitation of the study is that the level of BP and medication use was measured only once at a baseline visit. In addition, we characterized the intensity of antihypertensive therapy by the number of classes of medication used. Finally, in this article we did not examine potential differences in stroke prevention between different classes of drugs, an issue we hope to address in subsequent manuscripts.

This study demonstrates that there is an increased residual risk of stroke in hypertensive persons whose SBP is normalized with pharmacological therapy compared with untreated normotensive persons. Forty-six percent of the participants in the study were well-controlled hypertensive individuals, and an approach that waits to treat hypertension after it becomes prevalent places these individuals at a risk of stroke between 1.42x and 2.48x greater than normotensive individuals not on treatment. Therefore, there is a substantial lost opportunity from not focusing prevention efforts on primordial prevention of hypertension—that is, interventions to prevent individuals from developing prehypertension and hypertension. There are well-documented interventions to prevent or delay the development of hypertension, although success in implementing these in the general population is challenging. Additional research on how to successfully implement these population-wide interventions is needed, as is consideration of barriers to policy changes that could have profound population effect on BP.

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References


Is Blood Pressure Control for Stroke Prevention the Correct Goal?: The Lost Opportunity of Preventing Hypertension
George Howard, Maciej Banach, Mary Cushman, David C. Goff, Virginia J. Howard, Daniel T. Lackland, Jim McVay, James F. Meschia, Paul Muntner, Suzanne Oparil, Melanie Rightmyer and Herman A. Taylor

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The Lost Opportunity of Hypertension Prevention

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<th>Diagnoses</th>
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<th>Stage 1 Hypertension (140 mmHg – 159 mmHg)</th>
<th>Stage 2 Hypertension (160+ mmHg)</th>
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</table>

Supplemental Table I: Prevalence of other Framingham stroke risk function variables within strata defined by SBP level and number of antihypertensive medications employed.
Supplemental Table II: Hazard ratio for incident stroke (95% CI) after adjustment for age, race, age-by-race interaction, sex, diabetes, current smoking, atrial fibrillation, and history of heart disease. Tests for trend represent the estimated increase in the hazard ratio per category for number of medications and SBP category (and test for interaction across strata).
뇌졸중 예방을 위한 혈압 조절은 올바른 목표인가?
고혈압 예방의 잃어버린 기회

Is Blood Pressure Control for Stroke Prevention the Correct Goal?
The Lost Opportunity of Preventing Hypertension

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(Stroke. 2015;46:1595-1600.)

Key Words: hypertension ■ prevention and control ■ risk factors ■ stroke

배경과 목적
고혈압의 약물치료는 중요한 건강상의 이득이 있지만, 고혈압 예방 또는 지연을 통한 최적의 건강 유지의 효과는 잘 포착되지 않는다.

방법
총 26875명의 45세 이상 흑인 및 백인 참가자들에서 우발적 뇌졸중 사건에 대하여 평가 및 추적관찰하였다. 우발적 뇌졸중과 (1) 정상(<120 mmHg), 고혈압 전 단계(120–139 mmHg), 1단계 고혈압(140–159 mmHg), 2단계 고혈압(160 mmHg+)으로 분류한 수축기 혈압(systolic blood pressure, SBP)과 (2) 0, 1, 2, 3개 이상으로 분류한 항고혈압제 계열의 개수와의 관련성을 평가하였다.

결과
6.3년의 추적관찰 동안, 823건의 뇌졸중이 발생하였다. 전체 인구집단의 거의 절반(46%)은 성공적으로(SBP<140 mmHg) 고혈압이 치료되었다. 같은 혈압 구간(strata)에서 필요한 항고혈압제 계열이 하나씩 추가될수록 뇌졸중의 위험은 증가하였다. 그 HR은, 정상 혈압군에서 1.33; 95% CI, 1.16–1.52, 고혈압 전 단계에서 HR 1.15; 95% CI 1.05–1.26, 1단계 고혈압에서 HR 1.22; 95% CI, 1.06–1.39였다. 3개 이상 항고혈압제 계열을 사용하여 성공적으로(SBP<120 mmHg) 치료되는 고혈압 환자는 치료되지 않는 1단계 고혈압 환자보다 약간 더 높은 뇌졸중 위험을 가지고 있었다(HR, 2.48 대 HR=2.19; 항고혈압제를 안 먹고도 SBP<120인 사람들과 비교 시).

결론
약물 치료만으로 정상 혈압 상태를 유지하는 것은 정상 혈압인과 유사한 정도의 위험 수준까지 도달하는 데에는 실패했지만 일반 인구집단의 경우, 정상 혈압 상태를 유지하기 위해 고혈압 향상을 시도한 후에 약물을 사용하는 것이 더 안전한 선택이였다. 고혈압의 예방 또는 지연에 의한 상당한 잠재적 이득이 있다.

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-Race Interaction, Sex, and the Deviation From the Mean SBP Level for the Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Normotensive (&lt;120 mm Hg)</th>
<th>Prehypertension (120 mm Hg–139 mm Hg)</th>
<th>Stage 1 Hypertension (140 mm Hg–159 mm Hg)</th>
<th>Stage 2 Hypertension (160+ mm Hg)</th>
<th>Tests for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antihypertensive medications</td>
<td>1.0 (Ref)</td>
<td>1.44 (1.04–2.01)</td>
<td>2.19 (1.45–3.31)</td>
<td>3.35 (1.78–6.28)</td>
<td>1.49 (1.26–1.76)</td>
</tr>
<tr>
<td>1 Antihypertensive medication</td>
<td>1.42 (0.94–2.15)</td>
<td>2.00 (1.44–2.77)</td>
<td>1.67 (1.09–2.54)</td>
<td>3.00 (1.71–5.26)</td>
<td>1.16 (0.98–1.37)</td>
</tr>
<tr>
<td>2 Antihypertensive medications</td>
<td>1.60 (1.06–2.42)</td>
<td>1.88 (1.35–2.62)</td>
<td>2.84 (1.95–4.13)</td>
<td>1.42 (0.67–2.99)</td>
<td>1.16 (0.98–1.37)</td>
</tr>
<tr>
<td>3+ Antihypertensive medications</td>
<td>2.48 (1.63–3.77)</td>
<td>2.34 (1.66–3.32)</td>
<td>3.35 (2.28–4.92)</td>
<td>6.42 (2.84–7.51)</td>
<td>1.26 (1.07–1.48)</td>
</tr>
<tr>
<td>Tests for trend</td>
<td>1.33 (1.16–1.52)</td>
<td>1.15 (1.05–1.26)</td>
<td>1.22 (1.06–1.39)</td>
<td>1.10 (0.86–1.40)</td>
<td></td>
</tr>
</tbody>
</table>

Tests for trend represent the estimated increase in the HR per category for number of medications and SBP category (and test for interaction across strata). HR indicates hazard ratio; and SBP, systolic blood pressure.