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Is blood pressure control for stroke prevention the correct goal? The lost opportunity of preventing hypertension

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Abstract

Background and Purpose—While pharmacologic 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—26,875 black and white participants aged 45+, were assessed and followed for incident stroke events. The association was assessed between incident stroke and: 1) systolic blood pressure categorized as normal (< 120 mmHg), prehypertension (120–139 mmHg), stage-1 hypertension (140–159 mmHg) and stage-2 hypertension (160 mmHg+), 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 mmHg) 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%CI: 1.16–1.52 for normotensive, HR=1.15; 95%CI: 1.05–1.26 for prehypertension, and HR=1.22; 95%CI: 1.06–1.39 for stage 1 hypertension. A

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successfully treated (SBP<120 mmHg) 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 pharmacologic treatment has a profound impact, as nearly half of this general population cohort were treated to guideline (SBP<140 mmHg) 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.

Keywords

Hypertension; risk factors; prevention; antihypertensive therapy; stroke

Introduction

Global efforts are being directed to prevention of development of cardiovascular risk factors, also known as primordial prevention.[–] There is an increasing emphasis on prevention as a central pillar of the Affordable Care Act in the United States, and regulatory efforts for sodium reduction in the United Kingdom. The American Heart Association (AHA) has initiatives for obesity prevention and to improve diet and physical activity in the young to help to maintain ideal health (i.e., prevent the development of risk factors, including hypertension). In addition, the AHA is funding a Strategically Focused Prevention Research Network with a focus on preventing the development of risk factors.

However, this stands in contrast to the focus of the literature and clinical focus on primary stroke prevention, where hypertension is recognized as a pivotal risk factor, but the focus is overwhelmingly on blood pressure control of individuals with established hypertension.[–] This focus on hypertension control could be attributable to the remarkable success of randomized clinical trials that have shown the use of antihypertensive medications in the hypertensive population profoundly reduce the risk of stroke, and because improvement in blood pressure (BP) control is one of the major contributors to the temporal decline in stroke mortality. However, even “optimal” treatment for established hypertension may not return individuals to the risk level of normotensive individuals.

The Framingham Stroke Risk Function (FSRF) to predict 10-year risk of stroke includes terms for both 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% CI: 1.66 – 2.00) stroke risk after controlling for SBP. The increased stroke risk associated with antihypertensive medication use may seem counterintuitive, but given that a person has a SBP of 160 mmHg, if a person is on treatment then their pre-treatment blood pressure 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 (JNC 7) 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 SBP have a residual increased risk of stroke, and how the intensiveness of anti-hypertensive 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 electrocardiogram, and medications inventory was performed approximately 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 endpoints 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 JNC-7 guidelines as normal (< 120 mmHg), prehypertension (120 – 139 mmHg), stage 1 hypertension (140 – 159 mmHg) and stage 2 hypertension (160 mmHg+). The number of classes of antihypertensive medications was determined from the medications inventory by summing across the classes: angiotensin converting enzyme inhibitors, aldosterone antagonists, alpha blockers, angiotensin II receptor blockers, beta 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 or more classes of BP medications, strata were defined as none, 1, 2, or 3 or more.

Diabetes was defined as fasting glucose of 126 mg/dL or greater (or 200 mg/dL or greater for those non-fasting) or self-reported use of antidiabetes medications. Atrial fibrillation was defined by ECG evidence or self-report of a physician diagnosis. Left ventricular hypertrophy (LVH) was defined by ECG. Coronary heart disease (CHD) was defined as a self-reported myocardial infarction, electrocardiogram 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, 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 two-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 1,930 (6.4%) who self-reported a prior 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 suffered a stroke (726 infarctions, 70 ICH, 16 SAH and 48 unclassified strokes).

The combination of 4 SBP strata with the 4 strata of number of medications defined a total of 16 (4 x 4) strata of participants, with the characteristics of the study population provided in Table 1 (and risk factor prevalence in Table I). 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 are provided in Table 2. For those with SBP in the normal range (SBP < 120 mmHg), 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 (pre-hypertensive, stage 1 and stage 2 hypertension), stroke risk tended to be higher for those on more classes of antihypertensive medications. While 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 (see Supplemental Table II).

For those not on antihypertensive medication, there was an increase in stroke risk at higher SBP strata, with a hazard ratio 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-times (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 ($p_{interaction}$ = 0.13 in primary analysis, and $p_{interaction}$ = 0.082 after adjustment for risk factors). Compared to 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 to 1.37) per BP stratum. For those on 3 or more 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 ($p_{interaction}$ = 0.36) or sex ($p_{interaction}$ = 0.63).

Discussion

These results suggest that successful pharmacologic treatment of hypertension reduces, but does not eliminate, the harmful effects of hypertension. Stroke risk among hypertensive participants receiving one 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 or more classes. Hence, even with normalization of SBP through pharmacologic 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 or more 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 to 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 to individuals who are naturally normotensive, the risk of hypertensive individuals

requiring a single medication to achieve a normal SBP level is comparable to the risk among individuals with untreated prehypertension (42% and 44% increased risk, respectively). Likewise, hypertensive persons requiring 3 or more medications to achieve SBP below 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 times 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 6,740 normotensive men. Over 25-to-28 years of follow-up 1,031 men suffered a stroke. The relative risk was 1.75-fold (95% CI: 1.50 – 2.05) comparing the treated hypertensive men to normotensive men. However, the results of this prior 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) times higher than among normotensive persons. Analysis of differences in stroke risk alone was not provided. Further, the study was limited by small numbers of participants and outcomes: only 177 events in 1,692 normotensive individuals, compared to 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 NHLBI High Blood Pressure Education Program, which concluded 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.*" The American Heart Association has also issued a scientific statement with strong evidence that dietary interventions can prevent or delay the development of hypertension. Thus, there are known and established pathways by which hypertension can be prevented, thereby avoiding the issue of the residual risk associated with medically treated hypertension. While there is randomized trial evidence for effective interventions to prevent (or delay) incident hypertension, there is less evidence that the prevention of hypertension will subsequently reduce stroke risk. In addition, the challenges of implementing these life-style changes should not be understated. Much work on the science of implementing and disseminating behavior change, including potential policy changes that might nurture environments supportive of these behavior changes, is needed to effectively delay the development of hypertension at the population level.

There are a number of reasons why hypertensive participants with normal SBP on pharmacologic 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, while 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 ($p_{interaction}$ = 0.13 in primary analysis, but $p_{interaction}$ =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 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 paper we did not examine potential differences in stroke prevention between different classes of drugs, an issue we hope to address in subsequent manuscripts.

The current study demonstrates that there is an increased residual risk of stroke in hypertensive persons whose SBP is normalized with pharmacologic therapy compared to 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 1.42 and 2.48 times 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 pre-hypertension 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of study population. Within each cell the rows show: 1) the number of REGARDS participants, 2) the mean and standard deviation of the age, 3) the proportion black, 4) the proportion male, 5) the mean and standard deviation of SBP, and 6) the number and percent of participants with stroke events.

Number **Age (mean ± SD)** **Black (%)** **Male (%)** **SBP (mean ± SD)** **Events (N/%)**	**Normotensive (< 120 mmHg)**	**Prehypertension (120 mmHg – 139 mmHg)**	**Stage 1 Hypertension (140 mmHg – 159 mmHg)**	**Stage 2 Hypertension (160+ mmHg)**
No antihypertensive medications	4,521 60.2 ± 8.8 25.0% 37.7% 109.5 ± 7.7 (55/1.2%)	4,662 63.0 ± 9.2 32.2% 50.2% 127.4 ± 5.9 (100/2.2%)	1,060 65.3 ± 9.2 37.8% 55.6% 145.8 ± 5.5 (39/3.7%)	215 65.5 ± 9.8 56.3% 50.0% 171.8 ± 14.6 (12/5.6%)
1 antihypertensive medication	1,757 64.2 ± 9.3 33.0% 40.3% 111.1 ± 7.0 (39/2.2%)	3,223 65.8 ± 9.2 43.0% 45.2% 128.4 ± 5.8 (144/3.5%)	1,166 67.3 ± 9.4 47.4% 46.5% 146.0 ± 5.5 (37/3.2%)	287 67.7 ± 9.8 58.2% 45.6% 170.3 ± 11.2 (16/5.6%)
2 antihypertensive medications	1,436 65.6 ± 9.7 42.6% 40.7% 111.2 ± 6.9 (42/2.9%)	3,096 66.3 ± 9.0 47.8% 42.6% 128.6 ± 5.9 (104/3.4%)	1,150 67.2 ± 8.7 54.6% 45.2% 146.3 ± 5.7 (58/5.0%)	305 68.2 ± 9.2 61.3% 44.9% 170.1 ± 11.2 (8/2.6%)
3 + antihypertensive medication	868 65.7.3 ± 8.8 45.9% 44.4% 111.0 ± 7.1 (39/4.5%)	1,947 67.4 ± 8.8 52.2% 45.6% 129.1 ± 6.0 (83/4.3%)	899 67.7 ± 8.5 60.7% 48.3% 147.0 ± 5.8 (53/5.9%)	283 68.8 ± 9.0 65.4% 43.5% 170.5 ± 11.6 (24/8.5%)

Table 2

Hazard ratio for incident stroke (95% CI) after adjustment for age, race, age-by-race interaction, sex and the deviation from the mean SBP level for the category. 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).

	Normotensive (< 120 mmHg)	**Prehypertension (120 mmHg – 139 mmHg)**	**Stage 1 Hypertension (140 mmHg – 159 mmHg)**	**Stage 2 Hypertension (160+ mmHg)**	**Tests for Trend**	
No Meds	1.0 (ref)	1.44 (1.04 – 2.01)	2.19 (1.45 – 3.31)	3.35 (1.78 – 6.28)	1.49 (1.26 – 1.76)	$p_{interaction} = 0.13$
1 Med	1.42 (0.94 – 2.15)	2.00 (1.44 – 2.77)	1.67 (1.09 – 2.54)	3.00 (1.71 – 5.26)	1.16 (0.98 – 1.37)	
2 Meds	1.60 (1.06 – 2.42)	1.88 (1.35 – 2.62)	2.84 (1.95 – 4.13)	1.42 (0.67 – 2.99)	1.16 (0.98 – 1.37)	
3+ Meds	2.48 (1.63 – 3.77)	2.34 (1.66 – 3.32)	3.35 (2.28 – 4.92)	4.62 (2.84 – 7.51)	1.26 (1.07 – 1.48)	
Tests for Trend	1.33 (1.16 – 1.52)	1.15 (1.05 – 1.26)	1.22 (1.06 – 1.39)	1.10 (0.86 – 1.40)		
	$p_{interaction} = 0.29$					