

Rapid Decreases in Blood Pressure from Antihypertensive Treatment were Associated with Increased Cancer Mortality in the Systolic Hypertension in the Elderly Program

Joel N. Swerdel^{1,2}, Teresa M. Janevic², Javier Cabrera^{1,3}, Nora M. Cosgrove¹, Jeanine E. Sedjro¹, Sara L. Pressel⁴, Barry R. Davis⁴, and John B. Kostis¹

Abstract

Background: Research on the association between antihypertensive drug treatment (HTDT) and cancer is equivocal. We tested the hypothesis that large, rapid decreases in blood pressure following HTDT are associated with higher cancer mortality.

Methods: Data from the Systolic Hypertension in the Elderly Program (SHEP) with 15-year cause-specific follow-up for mortality were used. We used changes from baseline in seated and standing systolic blood pressure (SBP) measurements at 3, 6, 9, and 12 months after the initiation of HTDT. Hazard ratios adjusted for demographics, comorbidities, and competing risk of non-cancer-related deaths were estimated to determine the association between SBP change, as a continuous or time-dependent measure, and cancer-related death.

Results: SHEP participants taking antihypertensive medication who exhibited a decrease in seated SBP of 29 mm Hg or more (50th percentile and above) at 3 months were at a 58% greater risk of cancer-related death during a 15-year follow-up compared with those with no decrease in SBP ($P = 0.007$, 42% increased risk $P = 0.02$ for standing SBP). Those participants whose maximal seated SBP change occurred in the first 3 months of treatment had 2.6-times greater risk of cancer mortality compared with those whose maximal seated SBP change occurred at 12 months ($P = 0.004$).

Conclusions: Large SBP decreases early in HTDT were associated with an increased risk of cancer-related death during a 15-year follow-up. Further studies are needed to confirm and explore the potential mechanisms for this association.

Impact: Rapid decreases in blood pressure following HTDT may be a risk factor for cancer. *Cancer Epidemiol Biomarkers Prev*; 23(8); 1589–97. ©2014 AACR.

Introduction

Researchers have examined the association between hypertension, antihypertensive drug treatment (HTDT), and cancer for several decades. The results are equivocal with a number of studies demonstrating an increased risk of cancer after HTDT and others finding either no effect or a protective effect (1–7). Angiogenesis may be a factor underlying the relationship between cancer and HTDT. Patients with hypertension have been shown to undergo vascular rarefaction, a reduction, both functionally and structurally, in arteriolar and capillary density (8, 9).

Reversing rarefaction has been proposed as a mechanism of antihypertensive agents (9). Rarefaction occurs in conjunction with increased vascular wall thickness due to an increase in the number of smooth muscle cells in the vessel wall. Noon and colleagues found that patients with a family history of hypertension or with existing hypertension have lower capillary density compared with nonhypertensive controls (10). Regardless of etiology, rarefaction may, along with reduction of vessel lumen diameter from vessel wall encroachment, increase total peripheral vascular resistance (TPR), which is likely responsible for chronic hypertension (11). Patients with controlled hypertension have higher plasma levels of vascular endothelial growth factor (VEGF), a potent angiogenic promoter, compared with non-hypertension controls (12). Elevated VEGF and subsequent new vessel growth may account, in part, for the lowering of blood pressure (BP) through decreasing TPR. Folkman and colleagues established the role of angiogenesis in tumor growth (13). Antiangiogenic agents are frequently used in treating cancer. One side effect of this therapy is hypertension (14). This effect may be similar to the effect shown in preeclampsia in which plasma levels of

Authors' Affiliations: ¹The Cardiovascular Institute at Rutgers Robert Wood Johnson Medical School, New Brunswick; ²Department of Epidemiology, Rutgers University School of Public Health; ³Department of Statistics, Rutgers University, Piscataway, New Jersey; and ⁴University of Texas Health Science Center, Houston, Texas

Corresponding Author: Joel N. Swerdel, The Cardiovascular Institute at Rutgers Robert Wood Johnson Medical School, 125 Paterson Street, Suite 5200, New Brunswick, NJ 08901. Phone: 732-235-2146; Fax: 732-235-6550; E-mail: joel.swerdel@rutgers.edu

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fms-like tyrosine kinase 1 (sFlt1), an antagonist of VEGF, are elevated (15).

Isolated systolic hypertension (ISH) is an important health concern in the United States and worldwide. On the basis of an analysis of the National Health and Nutrition Examination Survey III (1988–1991), ISH occurs in 65% of those over the age of 60 where it accounts for 87% of all hypertension in that age group (16). Systolic blood pressure (SBP) increases monotonically with aging, whereas after about the age of 50 to 60 diastolic blood pressure (DBP) decreases, leading to increased pulse pressure and the development of ISH. ISH is associated with a marked increase in the risk of developing coronary heart disease, stroke, and heart failure as well as renal and central nervous system dysfunction. Treatment of ISH results in lower rate of the mortal and morbid effects associated with hypertension mentioned above.

Previous studies examining the link between HTDT and cancer have compared participants on HTDT to participants not on HTDT. However, the pattern of the patient's response to HTDT has not been examined in relation to cancer risk. The mixed results observed in previous studies may be due to differing BP responses to HTDT among each study population leading to different outcomes. If an association between hypertension, HTDT, and cancer does exist, it may be more likely to occur in HTDT participants with a greater propensity for concomitant angiogenesis. Patients with a greater propensity for angiogenesis should show a more rapid decrease in BP following HTDT as reversing rarefaction occurs through both new vessel growth as well as through a reduction in vessel wall thickness through apoptosis. The objective of this study was to test the hypothesis that large, rapid decreases in SBP following HTDT are associated with higher cancer mortality in the Systolic Hypertension in the Elderly Program (SHEP).

Materials and Methods

SHEP background and prior data collection

Beginning on March 1, 1984, the SHEP trial enrolled men and women of ages 60 years or older who had ISH, defined as SBP of 160 mm Hg or greater and DBP of less than 90 mm Hg. Individuals with a prior history of cancer other than non-melanoma skin cancer were excluded from SHEP. There were 4,736 participants in SHEP. The patient recruitment and consent process, inclusion and exclusion criteria, methods, baseline characteristics, and the results of the SHEP trial have been published elsewhere (17). Participants, who were alive at the end of SHEP, were matched by the National Death Index for death and cause of death until December 31, 2006. Deaths were categorized as due to cardiovascular causes [*International Classification of Diseases*, 9th Revision (ICD-9), 390–459], cancer causes (ICD-9, 140–239), or other causes (18). Participant outcomes were categorized as alive or by cause of death at follow-up. Outcomes were classified as cardiovascular death (CVD), cancer death

(CaD), or "Other Deaths." Death from any cause was classified as "All-Cause" death.

Initial medication used was chlorthalidone 12.5 mg once a day or matching placebo. This medication dose was doubled if significant SBP reduction was not achieved at follow-up visits. Significant SBP reduction was defined in SHEP as a decrease to below 160 mm Hg for those with a baseline SBP above 180 mm Hg and a reduction of at least 20 mm Hg for those with a baseline SBP between 160 and 179 mm Hg. Atenolol (25 mg/day or 0.05 mg once a day of reserpine if atenolol was contraindicated) or matching placebo was added if significant SBP reduction was still not achieved. If a participant was above the goal at two consecutive monthly visits on the same drug step and dose, he or she was stepped up to an increased dose or the next step drug until the maximum steps and dose were reached.

During the first year of the trial, participants visited the clinic for BP and other measurements before the start of the drug treatment (baseline), and at a minimum of 1, 2, 3, 6, 9, and 12 months after the start of treatment. Four BP measurements were performed during each patient visit. Two seated BP measurements were taken first followed by two standing BP measurements, one at 1 minute after standing, and the other at 3 minutes after standing.

Present analysis

The current study was approved by the Robert Wood Johnson Medical School and the University of Texas Health Science Center Institutional Review Boards. We excluded 86 participants due to a small number of BP measurements and 19 participants who were more than 90 years old at the start of the study resulting in a sample size of 4,631 for this analysis. We categorized participants by whether they received antihypertensive drugs or placebo.

We used the four SBP measurements taken at each visit to determine our exposure at 3, 6, 9, and 12 months.

The change in seated SBP at 3 months was calculated as:

$$\text{Change seated SBP}_{3 \text{ mo}} = \frac{(\text{first seated SBP measurement at 3 mo} + \text{second seated SBP measurement at 3 mo})}{2} - \frac{(\text{first seated SBP measurement at baseline} + \text{second seated SBP measurement at baseline})}{2}$$

The change in standing SBP at 3 months was calculated as:

$$\text{Change standing SBP}_{3 \text{ mo}} = \frac{(1 \text{ min standing SBP measurement at 3 mo} + 3 \text{ min standing SBP measurement at 3 mo})}{2} - \frac{(1 \text{ min standing SBP measurement at baseline} + 3 \text{ min standing SBP measurement at baseline})}{2}$$

The changes in seated and standing SBP at 6, 9, and 12 months were calculated similarly using the 6, 9, or 12 month SBP measurements in place of the 3-month SBP measurements. For one analysis, SBP changes, used as a continuous measurement, at the 3 and 12 month time points were considered the main exposures.

We also conducted an analysis using data from participants on active treatment who met, at a minimum, the

goal of at least a 20 mm Hg decrease in seated SBP within 12 months of treatment. The participants were divided approximately into quartiles depending on the magnitude of seated SBP change at 3, 6, 9, and 12 months. Quartiles were extended to include all participants with the nadir SBP for that quartile. The first quartile included participants whose seated SBP decrease was at least 40 mm Hg within 3 months. The second quartile included remaining participants whose seated SBP decrease at 6 months was at least 34 mm Hg. The third quartile included remaining participants whose seated SBP decrease at 9 months was at least 30 mm Hg. The final quartile included the remaining participants whose seated SBP decrease was at least 20 mm Hg at 12 months.

We used a follow-up period of 15 years after the start of their treatment or until the age of 90, whichever came first. The participants alive at 15 years after study start or reaching the age of 90 before death were considered alive for all demographic and statistical calculations.

Statistical analysis

For categorical variables, differences in proportions were determined using χ^2 analyses. For continuous variables, differences in means were determined by ANOVA or Student *t* tests. Cox regression models were developed to determine the hazard ratio (HR) between the exposure measures and the outcomes. We calculated cumulative incidence functions and HR with direct adjustment for competing risk using SAS V9.3 (SAS Corporation) macros developed by Zhang and Zhang (19) and based on the methodology of Fine and Gray (20). Fine and Gray proposed a methodology using a weighted score equation based on the inverse probability of censoring weight technique to adjust for right censoring and estimate model coefficients. In these models, a cause-specific death of interest was designated, e.g., cancer, the other cause-specific deaths, e.g., cardiovascular and other death, were combined and included as competing risks, and those alive at the end of follow-up were censored. Although no model can completely adjust for counterfactual outcomes, this methodology has been used in other studies involving competing risk (21–23). Regression models were developed to compare exposures within a treatment category (i.e., active or placebo). The proportional hazards assumption was tested both through visual inspections of Kaplan–Meier curves and through the inclusion of time-dependent variables, if necessary. Both the Wald and likelihood ratio tests were used to test for the violation of the proportional hazards assumption.

The main exposures in the regression models were seated SBP change and standing SBP change as described above. For the first analysis, each of the main exposures was tested at 3 and 12 months after the start of treatment and was included in the model as a continuous measure. The second analysis incorporated the exposures into the model as categorical variables as described above. All covariates were assessed at the time of randomization and were selected for this analysis based on previous

literature. We used the following covariates in all regression models: gender, race (White/Black/other), smoking status (never/former/current), smoking dosage in pack-years [(number of cigarettes smoked per day \times number of years smoked)/20], body mass index (BMI; underweight, ≤ 18.5 BMI units; normal weight, >18.5 and ≤ 25 BMI units; overweight, >25 and ≤ 30 BMI units; and obese, >30 BMI units), diabetes status (yes/no), alcohol consumption status (some/none), and age (≤ 65 years old; >65 and ≤ 71 years old; >71 and ≤ 76 years old; and >76 years old). Categorization of age was based on quartiles.

The level for statistical significance for all tests was set at $P < 0.05$.

Results

The baseline characteristics of the participants in this study for the two main exposures in the first analysis, 3- and 12-month SBP decrease in both treatment categories, active and placebo, may be found in Table 1. Patients are further categorized by their outcome at the end of the follow-up period, either as alive, CVD, CaD, or Other death. For CaD, the types of cancer were lung (23.2%), gastrointestinal (21.6%), prostate (14.4%), breast (8.8%), and other/unspecified sites (21.6%). Baseline measures and 3- and 12-month SBP changes for both active and placebo groups are shown in Table 2.

Results for the regression models are shown in Tables 3 and 4. HRs for the association between SBP decreases and CaD were significantly higher for both the seated and standing SBP measures ($P = 0.007$ and $P = 0.02$, respectively) at 3 months. The risk of cancer-related death was about 17% higher per 10 mm Hg seated SBP decrease at 3 months after adjusting for competing risk and all covariates. Interpolating from the model, those participants above the median seated SBP decrease (29 mm Hg decrease from baseline) exhibited an increased risk of CaD of about 59% compared with those with no seated SBP decrease. Those participants in the 75th percentile and above for seated SBP decrease (42 mm Hg decrease from baseline) exhibited a 94% increased risk of CaD compared with those with no seated SBP decrease. We found similar results in the association between standing SBP decrease and increased risk of CaD. The opposite effect was seen in standing SBP change in association with risk of CVD. With each 10 mm Hg decrease in standing SBP, the risk of CVD decreased by 7% reduced risk; those in the 50th percentile or higher in seated SBP decrease had a 15% reduced risk of CVD compared with those with no change in seated SBP ($P = 0.02$). There was no significant difference between the SBP change and either CaD or CVD in the placebo group for either of the measures used.

The effect of SBP change on cancer mortality was not evident at the 12-month exposure (Table 4). Neither measure was associated with a significant increase or decrease in CaD risk. However, the risk for CVD was significantly associated with the standing SBP measure. Those active

Table 1. Baseline patient characteristics

15-year outcome	All-cause death	CaD	CVD	Other death ^a	Alive
Active					
<i>N</i>	787	125	364	298	1,455
Age at start (SD), y	72.3 (5.8)	71.6 (5.7)	72.0 (5.6)	73.1 (6.0)	71.1 (6.9)
Age at death (SD) y	81.0 (6.0)	81.3 (5.8)	80.9 (6.0)	81.1 (6.1)	NA
Years follow-up (Med)	8.6	8.7	9.0	7.5	15.0
Female (%)	54.5	47.2	58.8	52.4	57.3
Race					
White (%)	80.3	82.4	81.3	78.2	78.5
Black	16.5	15.2	15.1	18.8	12.6
Other	3.2	2.4	3.6	3.02	8.9
BMI					
Normal (%)	24.4	20.8	22.5	28.2	23.5
Underweight	1.4	0.0	0.8	2.7	0.3
Overweight	39.6	47.2	40.7	35.2	44.6
Obese	34.6	32.0	36.0	33.9	31.6
Smoking					
Never (%)	45.5	37.6	48.9	44.6	53.5
Former (%)	37.3	44.0	34.8	37.6	36.5
Current (%)	17.2	18.4	16.2	17.8	10.0
Pack-years (SD) ^b	18.6 (25.7)	21.1 (26.5)	17.8 (25.8)	18.4 (25.3)	13.4 (21.7)
Diabetic (%)	13.0	6.4	14.8	13.4	8.3
Alcohol use (%)	27.1	34.4	23.9	27.9	32.0
Placebo					
<i>N</i>	914	144	463	307	1,475
Age at start (SD), y	71.8 (5.8)	70.7 (5.4)	71.7 (5.7)	72.6 (6.0)	71.2 (7.0)
Age at death (SD), y	80.5 (6.1)	80.2 (5.5)	80.6 (6.0)	80.5 (6.5)	NA
Years follow-up (med)	8.6	9.2	8.8	7.2	15.0
Female (%)	55.0	56.3	55.7	53.4	58.0
Race					
White (%)	82.9	84.0	84.7	79.8	77.4
Black	14.4	13.2	12.5	17.9	13.0
Other	2.6	2.8	2.8	2.3	9.7
BMI					
Normal (%)	24.0	22.2	23.5	25.4	24.9
Underweight	0.4	0.0	0.0	1.3	0.5
Overweight	42.6	45.1	42.6	41.4	44.3
Obese	33.0	32.6	33.9	31.9	30.4
Smoking					
Never (%)	44.3	39.2	46.2	43.8	52.4
Former (%)	38.8	42.0	37.7	38.9	37.1
Current (%)	17.0	18.8	16.1	17.3	10.5
Pack-years (SD)	19.0 (26.0)	25.5 (30.0)	17.4 (24.7)	18.3 (25.7)	13.1 (21.4)
Diabetic (%)	14.0	10.4	15.1	14.0	7.8
Alcohol use (%)	29.7	37.5	28.7	27.4	29.6

Abbreviations: CaD, cancer death; CVD, cardiovascular death; Med, median.

^aDeath due to causes other than cardiovascular disease and cancer.

^bIncludes 0 pack-years for never smokers.

participants in the 50th percentile for seated SBP change and above (29 mm Hg decrease from baseline) showed a 20% reduced risk of CVD compared with those with no response to HTDT; those in the 75th percentile (39 mm Hg

decrease from baseline) showed a 26% reduced risk ($P = 0.04$). Those in the placebo group showed no significant increase or decrease in the risk of CaD in either of the measures.

Table 2. Mean SBP changes at baseline, 3, and 12 months for active and placebo groups and cause-specific deaths

15-year outcome	All-cause death	CaD	CVD	Other death ^a	Alive	P ^b	P ^c
Active							
N	787	125	364	298	1,455		
Baseline							
Seated SBP (SD)	171.2 (12.4)	172.2 (12.5)	171.1 (12.6)	170.9 (12.3)	169.6 (11.5)	0.02	0.40
Standing SBP (SD)	165.9 (15.7)	166.0 (15.1)	165.8 (15.4)	166.1 (16.3)	164.1 (14.4)	0.06	0.89
3 mo							
dSeated SBP (SD)	26.9 (16.4)	30.8 (16.5)	25.7 (16.0)	26.6 (16.7)	27.3 (15.9)	0.02	0.002
dStanding SBP (SD)	23.4 (18.1)	26.8 (17.5)	21.4 (17.7)	24.4 (18.5)	23.3 (16.9)	0.01	0.003
12 mo							
dSeated SBP (SD)	27.9 (17.3)	29.5 (16.8)	26.3 (18.2)	29.0 (16.3)	28.6 (15.7)	0.07	0.09
dStanding SBP (SD)	25.3 (18.5)	27.1 (17.3)	23.8 (17.8)	26.2 (19.6)	25.0 (16.5)	0.19	0.08
Placebo							
N	914	144	463	307	1,475		
Baseline							
Seated SBP (SD)	170.3 (12.0)	168.7 (11.4)	170.4 (11.9)	170.8 (12.3)	168.7 (11.0)	0.003	0.12
Standing SBP (SD)	165.2 (15.0)	162.9 (15.2)	166.8 (14.0)	163.8 (16.0)	163.2 (14.3)	0.0001	0.05
3 mo							
dSeated SBP (SD)	11.5 (17.2)	13.1 (13.9)	10.9 (16.9)	12.4 (18.8)	12.7 (16.6)	0.24	0.16
dStanding SBP (SD)	7.8 (17.9)	8.7 (15.4)	7.9 (18.1)	7.3 (18.8)	8.2 (17.3)	0.82	0.60
12 mo							
dSeated SBP (SD)	13.0 (18.4)	12.0 (16.1)	12.4 (19.1)	14.5 (18.4)	13.0 (17.3)	0.40	0.79
dStanding SBP (SD)	9.2 (20.0)	8.2 (17.0)	9.7 (20.9)	8.9 (20.0)	9.6 (18.7)	0.81	0.45

NOTE: The prefix "d" indicates the change (delta) in a measurement.

Abbreviations: CaD, cancer death; CVD, cardiovascular death; SBP, systolic blood pressure.

^aDeath due to causes other than cardiovascular disease and cancer.

^bANOVA for differences in means between alive, cancer, CVD, and other death.

^cStudent *t* test for differences in means of cancer versus CVD.

Results for the categorical analysis, in which participants were placed in quartiles based on the magnitude of seated SBP change at 3, 6, 9, and 12 months, are shown in Fig. 1. Participants in the first quartile with a seated SBP decrease of at least 40 mm Hg in the first 3 months of treatment had 160% greater risk of CaD compared with those participants in the fourth quartile with a seated SBP that met the treatment goal within the first 12 months of treatment ($P = 0.003$). The risk of CaD for those in the second (6-month maximal decline of 34 mm Hg or more in seated SBP) and third (9-month maximal decline of 30 mm Hg or more in seated SBP) quartiles was 60% higher compared with the fourth quartile but was not statistically significant ($P = 0.2$).

Several sensitivity analyses were performed. In the current study, participants were included in either the "active" or "placebo" group based on adherence to protocol as described above. In an analysis including only SHEP participants randomized to the active group, we found similar results for the association between SBP decrease and cancer mortality risk as in the main analysis. We analyzed the SHEP data throughout the 22-year follow-

up with and without age cutoff and found a significant increased risk of cancer mortality with a large, rapid response to HTDT. We analyzed the data excluding lung cancer-related deaths and found no significant change in the HR per mm Hg decrease in those treated with HTDT. Finally, we analyzed the data including only those who claimed to have "never smoked" and also found no change in the HR per mm Hg decrease in the HTDT group.

Discussion

We found in SHEP participants that large SBP decreases early in HTDT were associated with an increased risk of cancer-related death. Our study is the first to our knowledge to examine the association between the pattern of BP response to HTDT and cancer-related death.

Our results are in accordance with our *a priori* hypothesis that a link between hypertension, HTDT, and cancer may be through a mechanism involving angiogenesis. Chronic HTDT is associated with decreased systemic vascular resistance (11). We hypothesized that a large, rapid SBP response to HTDT may be an indication that the

Table 3. Three-month adjusted^a HRs for the association between SBP change and cause-specific death at 15-year follow-up in SHEP

	Active			Placebo		
	CaD	CVD	All-cause death	CaD	CVD	All-cause death
dSeated SBP	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
10 mm Hg	1.17 (1.04–1.31)	0.94 (0.88–1.01)	0.97 (0.93–1.02)	1.02 (0.94–1.11)	0.95 (0.89–1.01)	0.98 (0.94–1.02)
GE 50th percentile ^b	1.58 (1.13–2.21)	0.86 (0.72–1.02)	0.93 (0.82–1.06)	1.02 (0.95–1.09)	0.95 (0.89–1.01)	0.93 (0.84–1.05)
GE 75th percentile ^b	1.94 (1.20–3.14)	0.81 (0.64–1.03)	0.90 (0.75–1.09)	1.04 (0.89–1.21)	0.89 (0.79–1.02)	0.91 (0.77–1.07)
<i>P</i> ^c	0.007	0.08	0.3	0.6	0.09	0.2
dStanding SBP	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
10 mm Hg	1.13 (1.02–1.26)	0.93 (0.87–0.99)	0.99 (0.95–1.03)	1.02 (0.93–1.12)	0.99 (0.94–1.04)	0.99 (0.95–1.03)
GE 50th percentile ^b	1.42 (1.06–1.91)	0.85 (0.74–0.98)	0.98 (0.87–1.10)	1.03 (0.96–1.10)	0.99 (0.95–1.04)	0.97 (0.88–1.08)
GE 75th percentile ^b	1.59 (1.08–2.35)	0.79 (0.64–0.97)	0.97 (0.83–1.13)	1.07 (0.91–1.25)	0.98 (0.89–1.09)	0.96 (0.84–1.11)
<i>P</i>	0.02	0.02	0.7	0.6	0.7	0.6

NOTE: The prefix "d" indicates the change (delta) in a measurement.

Abbreviations: CaD, cancer death; CVD, cardiovascular death; GE, greater than or equal to; HR, hazard ratio; SBP, systolic blood pressure.

^aAdjusted for gender, race, smoking status, BMI, diabetes status, alcohol consumption status, and age.

^bHRs for "GE 50th percentile" and "GE 75th percentile" are extrapolated from the regression model based on 29 and 42 mm Hg SBP decreases respectively, compared with 0 mm Hg SBP change.

^c*P* value for the level of statistical significance for the change in hazard per unit decrease in SBP.

individual has a greater propensity for lowering TPR through vasodilatory mechanisms and increased angiogenesis. These mechanisms would act to reverse rarefaction that may have occurred during the development of hypertension. Lowered BP initiates the proangiogenic

signaling cascade similar to that seen in occlusive disorders (24). Evidence for angiogenesis following HTDT was shown by Debbabi and colleagues, who demonstrated that patients undergoing HTDT have capillary densities similar to normotensive subjects and greater than

Table 4. Twelve-month adjusted^a HRs for the association between SBP change and cause-specific death at 15-year follow-up in SHEP

	Active			Placebo		
	CaD	CVD	All-cause death	CaD	CVD	All-cause death
dSeated SBP	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
10 mm Hg	0.94 (0.81–1.08)	0.92 (0.85–1.00)	0.97 (0.93–1.01)	0.98 (0.90–1.07)	0.98 (0.93–1.04)	1.01 (0.97–1.05)
GE 50th percentile ^b	0.82 (0.55–1.24)	0.80 (0.65–0.99)	0.92 (0.81–1.04)	0.97 (0.87–1.09)	0.97 (0.90–1.05)	1.03 (0.92–1.15)
GE 75th percentile ^b	0.75 (0.42–1.37)	0.74 (0.55–0.99)	0.88 (0.74–1.06)	0.95 (0.78–1.17)	0.95 (0.82–1.10)	1.04 (0.89–1.22)
<i>P</i> ^c	0.4	0.04	0.2	0.6	0.5	0.6
dStanding SBP	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
10 mm Hg	0.97 (0.85–1.10)	0.92 (0.85–1.00)	0.98 (0.94–1.02)	1.01 (0.93–1.10)	1.01 (0.96–1.07)	1.01 (0.97–1.04)
GE 50th percentile ^b	0.91 (0.63–1.30)	0.84 (0.71–1.00)	0.95 (0.84–1.06)	1.01 (0.94–1.08)	1.01 (0.96–1.07)	1.02 (0.92–1.12)
GE 75th percentile ^b	0.88 (0.54–1.42)	0.77 (0.59–1.01)	0.93 (0.80–1.08)	1.02 (0.86–1.20)	1.03 (0.91–1.16)	1.03 (0.90–1.17)
<i>P</i>	0.6	0.06	0.4	0.8	0.7	0.7

NOTE: The prefix "d" indicates the change (delta) in a measurement.

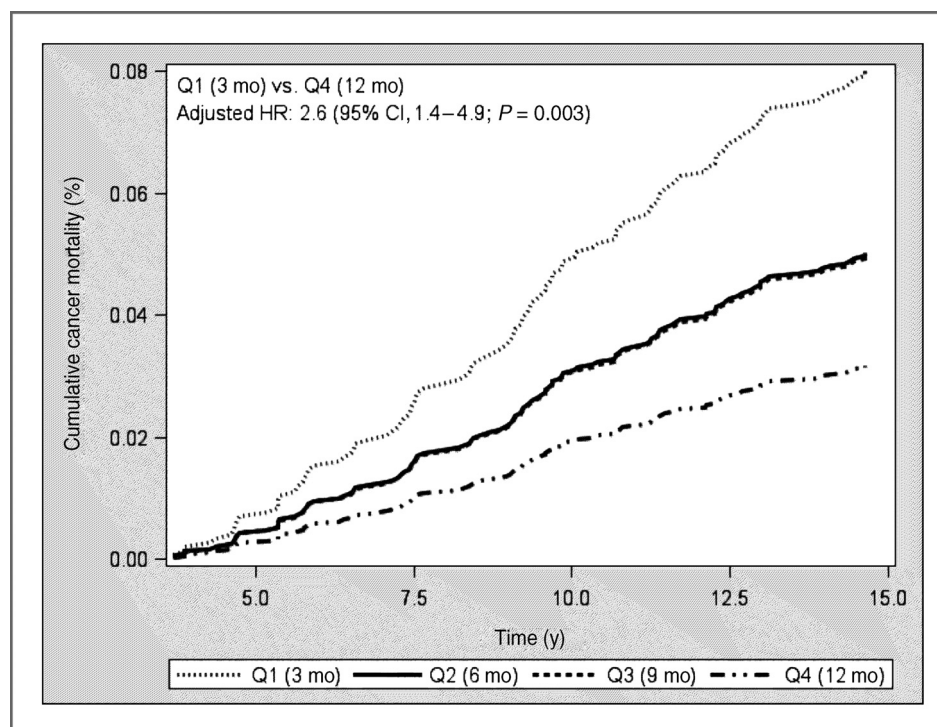
Abbreviations: CaD, cancer death; CVD, cardiovascular death; GE, greater than or equal to; HR, hazard ratio; SBP, systolic blood pressure.

^aAdjusted for gender, race, smoking status, BMI, diabetes status, alcohol consumption status, and age.

^bHRs for GE 50th percentile and GE 75th percentile are extrapolated from the regression model based on 29 and 39 mm Hg SBP decreases respectively, compared with 0 mm Hg SBP change.

^c*P* value for the level of statistical significance for the change in hazard per unit decrease in SBP.

Figure 1. Comparison of 15-year cancer mortality between active participants categorized by time and magnitude of seated SBP change after adjusting for competing risk of CV and Other Death ($N = 1,855$). Q1 (3 mo), participants in active treatment with SBP decrease greater than or equal to 40 mm Hg at 3 months ($N = 479$). Q2 (6 mo), participants in active treatment with SBP decrease less than 40 mm Hg at 3 months and greater than or equal to 34 mm Hg at 6 months ($N = 483$). Q3 (9 mo), participants in active treatment with SBP decrease less than 34 mm Hg at 6 months and greater than or equal to 30 mm Hg at 9 months ($N = 457$). Note that the "Q3 (9 mo)" cumulative cancer mortality curve is superimposed on the "Q2 (6 mo)" curve. Q4 (12 mo), participants in active treatment with SBP decrease less than 29 mm Hg at 9 months and greater than or equal to 20 mm Hg at 12 months ($N = 436$); 95% CI, 95% confidence interval.



untreated hypertension patients (25). It is this increase in capillary density that may play a role in the growth of cancerous tumors following HTDT. In the present study, participants who exhibited a large decrease in SBP in response to 3 months of HTDT were at higher risk of cancer-related death. It is possible that this response included using angiogenic mechanisms. Participants who were more resistant to HTDT, requiring up to 12 months of treatment and higher doses and/or secondary medications to achieve the same SBP decrease, may have been less capable of using angiogenic mechanisms. If the resistance to HTDT was due to a lower propensity for an angiogenic response, it may have accounted for the reduced risk of cancer-related death.

Tumors cannot grow beyond 1 to 2 mm in diameter without new vessel growth (26). Inhibiting angiogenesis has been an important tool of antitumor drug treatment for a number of years. The promotion of new vessels following HTDT may act as a facilitator of tumor growth. This may occur in areas where small tumors have remained relatively dormant due to lack of new vessel growth and may persist for years.

We hypothesize that the variability in the 3 month response to HTDT and the association of that response to cancer mortality may be due to differences related to angiogenesis. It has been shown that there are population differences in regard to single-nucleotide polymorphisms (SNP) involving angiogenic factors such as VEGF (27). For example, it was demonstrated that certain polymorphisms in the *VEGF* gene may be associated with more aggressive tumors (28). It may be likely that different genetic profiles make one more or less prone to an angiogenic response to

the ischemic stimuli following decreased BP. If that is the case, those with lower angiogenic propensity would have an attenuated response to HTDT and may be more prone to cardiovascular disease and death, and those with a higher angiogenic propensity would have a greater response to HTDT and may be more prone to cancer.

The increase in cancer mortality in the "active" treatment group with large, rapid SBP decreases may be also due to competing risk. The same participants who were, according to our results, at higher risk for CaD were also at lower risk for CVD. The increased risk of cancer-related death may be due to more participants surviving (i.e., not dying from CVD) and gaining the added years to allow for cancer-related death. Our Cox models, which accounted for competing risk of non-cancer-related death, indicated that this may not be a significant factor in the increase in cancer mortality risk in those with a greater response to HTDT. In fact, on the basis of our models, the opposite effect seems to have occurred with somewhat greater risk for CaD after accounting for competing risk of non-cancer-related death. Nonetheless, we cannot rule out that competing risk could, at least in part, explain our findings.

There are, of course, other possible explanations for the effect seen in this study other than angiogenesis. While those with a rapid decrease in SBP used diuretics, it is possible that after some time these individuals may have added beta-blockers to their drug regimen as the efficacy of the diuretics diminished or side effects, such as hypokalemia, increased. There is evidence that long-term use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and calcium-channel blockers are positively associated with cancer mortality

risk (29–31). The rapid decrease in SBP following HTDT may have also been caused by some unmeasured confounder, for instance an environmental toxin, which may have also promoted cancer many years later. Some household molds have been thought to have these properties (32). Considering the relatively small number of cancer-related deaths in the study, about 6% of the study population, it is also possible that our results were found by the play of chance.

There were several limitations to our study. This study included only participants that were at least 60 years old at the time of randomization and our results may not be generalizable to younger patients undergoing HTDT. The SHEP study exclusively enrolled participants with ISH, which is determined primarily by low large vessel compliance. Results may be different in patients with both systolic and diastolic hypertension. The number of cancer-related deaths was small in comparison with CVD and other causes of death. Because of low frequencies, we were unable to analyze site-specific cancer differences. As lung cancer may play a significant role in this age cohort, this is a limitation. We were able to perform a sensitivity analysis excluding lung cancer mortality and found no differences in our results. Our outcome measures, CaD and CVD, were based on administrative mortality records and some misclassification may have occurred. However, at least one study has demonstrated that CVD is overestimated by as much as 25% to 50% as a cause of death especially in the elderly (33). If that were the case in this study, misclassification in cause of death would have biased the reported associations toward the null. The vast majority of the data in our study is based on participants who received diuretics. Our results may not apply to other types of HTDT such as angiotensin receptor blockers or angiotensin-converting enzyme inhibitors. As SHEP included only participants of more than age 60, long-term environmental exposures may play a significant role in cancer mortality. These were not measured as part of SHEP. It is also possible that an individual's lifetime diet and exercise habits may have played a role in cancer mortality. In addition, those participants who achieved successful lowering of SBP within the first 3 months of treatment may have altered their lifestyle less than those with a slower response to HTDT. Neither possible confounder, pre- nor posttreatment lifestyle habits, were measured as part of SHEP.

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Our study has a number of strengths. It is based on a well-conducted clinical trial in which BP measurement was a primary focus resulting in accurate measurement of, our primary exposure, SBP response at 3 and 12 months after HTDT. Our study was also able to compare results between the SHEP active and placebo participants. Although the placebo participants showed no significant association between SBP response and cancer mortality, the effect was in the same direction as the active treated participants. Finally, our hypothesis was generated *a priori*. In a study with a large number of results, this is critical.

Our study found an apparent association between a rapid decrease in SBP following HTDT and cancer mortality. If this association is also shown in future studies, large BP changes early in HTDT may be used as a marker for future cancer risk. This response would be included along with other risk factors such as familial history and age. Also, the present data provide additional support to physicians who "Start low, go slow" in using HTDT in certain patient subgroups such as the elderly. Future research in this area should focus on the mechanism of action involved to determine whether angiogenic propensity is the link between the response to HTDT and cancer mortality.

Disclosure of Potential Conflicts of Interest

J.B. Kostis has received commercial research grants from Sanofi and Novartis; has received speakers' bureau honoraria from Bristol-Myers Squibb/Pfizer, Merck, and Sanofi; and is a consultant/advisory board member for St. Jude Medical and White and Case LLC. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.N. Swerdel, J.B. Kostis
Development of methodology: J.N. Swerdel
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.L. Pressel, B.R. Davis, J.B. Kostis
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.N. Swerdel, J. Cabrera, J.E. Sedjro, B.R. Davis
Writing, review, and/or revision of the manuscript: J.N. Swerdel, T.M. Janevic, N.M. Cosgrove, J.E. Sedjro, B.R. Davis, J.B. Kostis
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.N. Swerdel, S.L. Pressel, J.B. Kostis
Study supervision: S.L. Pressel

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