Association Between Chlorthalidone Treatment of Systolic Hypertension and Long-term Survival

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ANTIHYPERTENSIVE DRUG therapy has been shown to decrease nonfatal and fatal cardiovascular events in controlled clinical trials and meta-analyses.1-7 However, long-term data on gain in life expectancy are not available. In some trials, the benefit of therapy appeared or persisted after the end of the trials when all patients were advised to receive active therapy.8-13 This “legacy effect” has been reported in hypertension, hyperlipidemia, and diabetes.8-13 To examine whether the effect of blood pressure (BP) lowering during a trial was associated with long-term outcomes and extended life expectancy, we obtained long-term mortality data of participants in the Systolic Hypertension in the Elderly Program (SHEP) trial. The SHEP trial was a randomized, placebo-controlled, clinical trial designed to assess the effect of antihypertensive drug treatment in reducing the risk of stroke in patients with isolated systolic hypertension.14 The trial showed that over a mean follow-up of 4.5 years chlorthalidone-based therapy resulted in the prevention of approximately 1 out of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 out of 4 coronary heart disease events.14-16 Although the decreases in cardiovascular events were statistically significant, the effects on all-cause mortality (odds ratio [OR], 0.87; 95% CI, 0.73-1.05) and cardiovascular death (OR, 0.80; 95% CI, 0.60-1.05) were not. At the end of the randomized phase of the SHEP trial, all participants were advised to receive active therapy. The time interval between the beginning of recruitment and the ascertainment of death by National Death Index (December 31, 2006) was approximately 22 years (21 years 10 months).

Main Outcome Measures Cardiovascular death and all-cause mortality.

Results At the 22-year follow-up, life expectancy gain, expressed as the area between the active (n=2365) and placebo (n=2371) survival curves, was 105 days (95% CI, −39 to 242; P=.07) for all-cause mortality and 158 days (95% CI, 36-287; P=.009) for cardiovascular death. Each month of active treatment was therefore associated with approximately 1 day extension in life expectancy. The active treatment group had higher survival free from cardiovascular death vs the placebo group (hazard ratio [HR], 0.89; 95% CI, 0.80-0.99; P=.03) but similar survival for all-cause mortality (HR, 0.97; 95% CI, 0.90-1.04; P=.42). There were 1416 deaths (59.9%) in the active treatment group and 1435 deaths (60.5%) in the placebo group (log-rank P=.38, Wilcoxon P=.24). Cardiovascular death was lower in the active treatment group (669 deaths [28.3%]) vs the placebo group (735 deaths [31.0%]; log-rank P=.03, Wilcoxon P=.02). Time to 70th percentile survival was 0.56 years (95% CI, −0.14 to 1.23) longer in the active treatment group vs the placebo group (11.53 vs 10.98 years; P=.03) for all-cause mortality and 1.41 years (95% CI, 0.34-2.61; 17.81 vs 16.39 years; P=.01) for survival free from cardiovascular death.

Conclusion In the SHEP trial, treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up.

Context In the Systolic Hypertension in the Elderly Program (SHEP) trial, conducted between 1985 and 1990, antihypertensive therapy with chlorthalidone-based stepped-care therapy resulted in a lower rate of cardiovascular events than placebo but effects on mortality were not significant.

Objective To study the gain in life expectancy of participants randomized to active therapy at the 22-year follow-up.

Design, Setting, and Participants A National Death Index ascertainment of death in the long-term follow-up of a randomized, placebo-controlled, clinical trial (SHEP) of patients aged 60 years or older with isolated systolic hypertension. Recruitment was between March 1, 1985, and January 15, 1988. After the end of a 4.5-year randomized phase of the SHEP trial, all participants were advised to receive active therapy. The time interval between the beginning of recruitment and the ascertainment of death by National Death Index (December 31, 2006) was approximately 22 years (21 years 10 months).

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domized phase of the SHEP trial, all participants (both those participants randomized to active therapy and those randomized to placebo) were advised to receive the active therapy.

The goal of our study was to describe cardiovascular death and all-cause mortality of the SHEP trial 22 years after the beginning of randomization.

METHODS
Setting and Participants
Beginning on March 1, 1984, the SHEP trial enrolled men and women aged 60 years or older who had isolated systolic hypertension, defined as systolic blood pressure (SBP) of 160 mm Hg or more and diastolic blood pressure (DBP) of less than 90 mm Hg. The recruitment, inclusion and exclusion criteria, baseline characteristics, and the results of the SHEP trial have been published elsewhere.14,17,18 Participants identified their race on a written form at their initial contact with SHEP personnel. Written informed consent was obtained for the screening phase of the SHEP trial; withdrawal of antihypertensive medications, if applicable; and randomization into the trial from the participants. Also, the participants’ treating physicians were contacted and gave permission during the initial contact. Waiver of consent was obtained from the University of Texas institutional review board for the extension part of the study. The study was approved by the UMDNJ-Robert Wood Johnson Medical School and the University of Texas Health Science Center institutional review boards.

Screening and Eligibility
Both participants who were receiving antihypertensive therapy and participants with hypertension who were not treated with antihypertensive therapy were screened for participation in the clinical trial. In the latter group, participants who were screened who had a first SBP of more than 150 mm Hg and the mean of the last 2 of 3 readings between 160 and 219 mm Hg and a DBP of less than 100 mm Hg were invited for the first of 2 baseline visits. Eligibility of participants receiving antihypertensive therapy was determined at drug evaluation visits during a 2- to 8-week period. The mean of 2 BP measurements at each of the 2 baseline visits was used as the baseline BP.

Participants with baseline BP of between 160 and 219 mm Hg for SBP and less than 90 mm Hg for DBP were randomized if they did not have exclusion criteria, such as history of major cardiovascular disease (cardiac pacemaker, stroke with residuals, myocardial infarction or coronary artery bypass graft surgery within 6 months, uncontrolled heart failure, or atrial fibrillation or flutter), cancer other than nonmelanoma skin cancer, suspected or established renal dysfunction as judged by the investigator, treatment with insulin or anticoagulants, alcoholic liver disease, or medical management problems.

Goal BP was a decrease of SBP to less than 160 mm Hg for participants with baseline SBP of more than 180 mm Hg and an SBP reduction by at least 20 mm Hg for those participants with baseline SBP of between 160 and 179 mm Hg. Initial medication was chlorthalidone (12.5 mg/d) or matching placebo. This medication dose was doubled if SBP goal was not achieved at follow-up visits. If the goal was not reached with 25 mg/d of chlorthalidone, 25 mg/d of atenolol (or 0.05 mg/d of reserpine if atenolol was contraindicated) or matching placebo was administered and, if unsuccessful, the step 2 drug was doubled.

Recruitment took place between March 1, 1985, and January 15, 1988. At the end of the 4.5-year randomized phase, all participants were advised to receive active therapy. Long-term follow-up for mortality and cause of death was obtained by matching personal identifiers of the participants to the National Death Index for deaths through December 31, 2006. Cardiovascular mortality was classified as death due to International Classification of Diseases, Ninth Revision codes 290 to 459 or International Statistical Classification of Diseases, 10th Revision codes 100 to 199. Matching variables used in the probabilistic algorithm included birth date and an acrostic of the initial letters of the last name, first name, and middle initial. The time interval between the beginning of recruitment and the ascertainment of death by National Death Index (December 31, 2006) was approximately 22 years (21 years 10 months).

Statistical Analysis
Time to first stroke using a log-rank test was the primary analysis of the randomized phase of the SHEP trial. Long-term follow-up data were analyzed using R (http://www.r-project.org/). Kaplan-Meier curves for the treatment and placebo groups were generated and compared with each other. The primary prespecified analyses of our study were (1) to estimate the net gain in life expectancy free from cardiovascular death in the active therapy group by calculating the area between the survival curves of the 2 interventions expressed as the mean number of days that the survival of a patient in the active treatment group exceeded that of a patient in the placebo group, and (2) to evaluate the difference in median survival free from cardiovascular death between the active therapy and placebo groups.10-21

These represent 2 complementary measurements of estimating gain in survival. The first (life expectancy) represents the number of days that the participants in the active group lived longer without sustaining cardiovascular death compared with placebo. The second represents the difference in the time it took for half of the participants in each of the randomized groups to sustain cardiovascular death. However, because less than half of the participants (29.5% in the active therapy group) had not sustained cardiovascular death by the end of follow-up to allow estimation of median survival, we analyzed the 70th percentile survival. The 70th percentile was the closest to the median estimable percentile, because at the end of follow-up 70.5% of the participants had not sustained cardiovascular death. The
prespecified level of statistical significance was set at \( P < .05 \).

Similar analyses were performed for all-cause mortality. The precision of the estimators was evaluated by bootstrap confidence intervals. Using bootstrap, the power of the study for cardiovascular death at \( \alpha = .05 \) was 77.2%.

We also performed analyses using traditional statistical methods (log-rank test, Wilcoxon rank sum test, Cox proportional hazards regression model) to compare the 2 interventions.

**RESULTS**

**Randomized Phase of the SHEP Trial**

Of the 4736 participants enrolled in the SHEP trial, 2365 (49.9%) were randomized to active treatment therapy and 2371 (50.1%) were randomized to placebo. The majority of randomized patients (n=3161 [66.7%]) had not been treated for hypertension before screening. Selected baseline characteristics by randomization group are shown in the Table (modified from the final results of the SHEP trial). Mean (SD) age of participants was 71.6 (6.7) years, 56.8% were women, and 13.9% were black.

During follow-up, mean SBP was lower than at baseline by 26 mm Hg in the active treatment group and by 15 mm Hg in the placebo group, and mean DBP was lower than at baseline by 9 mm Hg in the active treatment group and 4 to 5 mm Hg in the placebo group. Goal BP was reached by 65% to 72% in the active treatment group vs 32% to 40% in the placebo group. Mean SBP was lower throughout the trial for the active treatment group by 11 to 14 mm Hg and mean DBP was lower by 3 to 4 mm Hg. The 5-year mean BP was 143/68 mm Hg in the active treatment group vs 155/72 mm Hg in the placebo group.

A significant decrease in the rates of the primary end point of fatal or nonfatal stroke (67 in the active treatment group vs 96 in the placebo group; relative risk [RR], 0.64; 95% CI, 0.50-0.82), myocardial infarction (50 vs 74, respectively; RR, 0.67; 95% CI, 0.47-0.96), and heart failure (55 vs 105, respectively; RR, 0.51; 95% CI, 0.37-0.71) were observed. The effects of cardiovascular death (OR, 0.80; 95% CI, 0.60-1.05) and all-cause mortality (OR, 0.87; 95% CI, 0.73-1.05) were not statistically significant.

**Mortality During the 22-Year Follow-up**

At the end of follow-up, 2851 of the 4736 randomized patients (60.2%) had died (1416/2365 deaths [59.9%] in the active treatment group and 1435/2371 deaths [60.5%] in the placebo group; log-rank \( P = .38 \), Wilcoxon \( P = .24 \)). A total of 294 deaths (12.4%) were related to coronary heart disease and 110 deaths (4.6%) were related to stroke in the active treatment group, and 323 deaths (13.6%) were related to coronary heart disease and 134 deaths (5.6%) were related to stroke in the placebo group. Both life expectancy and 70% survival at the end of follow-up were longer for the SHEP participants who were randomized to the active group compared with those randomized to the placebo group. Life expectancy gain at 22 years was 158 days (95% CI, 36-287; \( P = .009 \)) for cardiovascular death (FIGURE 1) and 105 days (95% CI, −39 to 242; \( P = .07 \)) for all-cause mortality (FIGURE 2).

For participants whose SBP was controlled to the SHEP protocol target, life expectancy free of cardiovascular death was 215.2 days (95% CI, 82.7-351.3) if controlled at the first year, 130.7 days (95% CI, 70.2-257.5) if controlled at the second year, and 215.3 days (95% CI, 70.2-345.7) if controlled at the end of the study. The corresponding results for cardiovascular death with SBP control at the current target of 140 mm Hg were 253.0 days (95% CI, 120.8-385.8), 144.6 days (95% CI, 16.5-272.1), and 306.1 days (95% CI, 174.6-440.8).

For all-cause mortality with control using the SHEP protocol, the corresponding data were 193.6 days (95% CI,
The active treatment group was associated with higher survival free from cardiovascular death compared with the placebo group using traditional statistical methods (669 deaths [28.3%] vs 735 deaths [31.0%], respectively). The

Figure 1. Survival Free of Cardiovascular Death (Noncardiovascular Death Censored) of the SHEP Participants by Randomization Group at 22-Year Follow-up

Figure 2. Survival Probability of All-Cause Mortality of the SHEP Participants by Randomization Group at 22-Year Follow-up

SHEP indicates Systolic Hypertension in the Elderly Program. Active treatment was chlorthalidone-based stepped-care therapy with atenolol as second-line drug and control was stepped-care therapy with matching placebos. The numbers at risk represent the number of participants at risk for every 2 years (given in days) of follow-up for the active treatment and control groups. Survival during follow-up was 516 days (1.41 years; 95% CI, 0.34-2.61) longer for the active treatment group (6501 days) than for the control group (5985 days; \( P = .03 \)) at the 70th survival percentile (horizontal blue dotted line).

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log-rank test and the Wilcoxon rank sum test were statistically significant with $P = .03$ and $P = .02$, respectively. A Cox proportional hazards regression model with the active treatment effect as a covariate yielded a hazard ratio (HR) of 0.89 (95% CI, 0.80–0.99; $P = .03$); however, survival for all-cause mortality was not significant (HR, 0.97; 95% CI, 0.90–1.04; $P = .42$). Cardiovascular death reduction became statistically significant ($P = .02$) 1.5 years after the end of the randomized follow-up.

A total of 134 fatal strokes (9.3% of all deaths) occurred in the placebo group and 110 fatal strokes (7.8% of all deaths) occurred in the active treatment group. Patients in the active treatment group were associated with longer life expectancy free from stroke (59.3 days; 95% CI, −7.4 to 126.2), which was not statistically significant.

Higher resting heart rate was associated with higher cardiovascular death (HR, 1.0013; 95% CI, 1.0003–1.0024; $P = .01$ per 1 beat per minute). However, the HR comparing active treatment vs placebo did not change significantly when adjustment for resting heart rate was included in the Cox proportional hazards regression model (HR, 0.896; 95% CI, 0.806–0.995).

**COMMENT**

Our study of the SHEP trial shows that treating hypertension with chlorthalidone-based therapy for 4.5 years was associated with higher survival and a gain in life expectancy at 22 years of follow-up. The gain in life expectancy free from cardiovascular death corresponds with approximately 1 day (0.89 days; 95% CI, 0.20–1.62) gained for each month of treatment. This gain in life expectancy is important, because it occurred among persons with a mean age of 72 years at baseline. Given competing risks for death, the measured benefit in all-cause mortality, the secondary end point in our analysis, was lower ($P = .07$), with the study treatment associated with approximately 0.59 days (95% CI, −0.22 to 1.37) gain in life expectancy for each month of antihypertensive drug treatment.

Quantitatively, the gain with respect to cardiovascular death is similar to an estimate reported by Kassai et al who modeled data from INDANA (Individual Data Analysis of Antihypertensive drug intervention trials). Assuming a constant treatment effect, the authors projected that for 75-year-old patients treated throughout their life span the gain in life expectancy without a fatal or nonfatal coronary event would be 6.5 months and without a cerebrovascular event the gain would be 15 months. These estimates correspond with a gain of approximately 1 to 2 days per month of treatment. In the SHEP trial, the gain with respect to life expectancy free from cardiovascular death was of the same order of magnitude (approximately 1 day gained per month of treatment).

Our study has several limitations. Most important, treatments beyond the end of the randomized trial were observational and information regarding actual antihypertensive therapy, as well as background interventions such as lipid-lowering therapy, control of diabetes, and surgical and device interventions during the extended follow-up, were not available. However, we have no reason to believe that these interventions were used at different rates in the 2 randomized groups. We also have no data regarding nonfatal clinical events, such as nonfatal myocardial infarction or stroke. The confidence intervals for life expectancy gain at 22 years for cardiovascular death and all-cause mortality are very wide. However, these nonparametric bootstrap confidence intervals use very few assumptions and tend to be wide, because they do rely on normal distribution models. Also, our study pertains only to older patients with isolated systolic hypertension who were treated with chlorthalidone-atenolol stepped-care therapy. However, the prevalence of hypertension increases with age and the majority of older persons have this condition. Also, newer antihypertensive agents may be equally or more effective in decreasing cardiovascular events or may have a better adverse effect profile than the medications used in the SHEP trial.

The strengths of our analysis are that it is based on actual data from a high-quality, randomized, placebo-controlled clinical trial, with long duration of follow-up and with vital status information on 100% of the participants. In addition, our study provides needed long-term mortality data. We are not aware of data sets in hypertension with follow-up exceeding 20 years.

It can be argued that the results of our analysis would be expected because with longer follow-up, reductions in nonfatal cardiovascular events would result in decreased mortality, especially from cardiovascular causes. This has been proposed as one explanation for the legacy effect. Our study demonstrating this association between treatment and long-term benefits supports this hypothesis and provides a quantitative estimate of the mortality benefit. The results mentioned above may underestimate the benefit because of crossover between the active and placebo groups, because some participants randomized to active treatment discontinued therapy, and a significant number of participants in the placebo group were treated and controlled with open-label medication.

Reporting that each month of antihypertensive therapy was associated with 1 day prolongation of life expectancy free from cardiovascular death is a strong message that may result in increased patient adherence to drug therapy and decrease the degree of therapeutic inertia by health care providers. In the NHANES III study, control of hypertension decreased with age from 74% in young individuals to 33% in those patients older than 70 years. In addition, therapeutic inertia is more frequent when physicians take care of older patients. Reviewing data from the NHANES III study, Hyman and Pavlik reported that age 65 years or older accounted for the greatest proportion of attributable risk for the lack of control of hypertension among those pa-
In conclusion, patients in the intervention group of the SHEP trial who were treated with a chlorthalidone-based stepped-care therapy for 4.5 years had significantly lower mortality after 22 years of follow-up. Receiving active therapy each month was associated with an additional day free from risk of cardiovascular death.

Author Contributions: Dr Kostis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kostis, Pressel, Davis.

Acquisition of data: Kostis, Cosgrove, Deng, Pressel, Davis.

Analysis and interpretation of data: Kostis, Cabrera, Cheng, Cosgrove, Davis.

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Critical revision of the manuscript for important intellectual content: Kostis, Cheng, Deng, Pressel, Davis.

Statistical analysis: Cabrera, Cheng, Davis.

Obtained funding: Kostis, Pressel.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kostis reported receiving grant support and travel to meetings from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Aging (NIA). Dr Cabrera reported receiving consulting fees or honorarium from UMDN. Ms Cosgrove reported receiving support for travel to meetings from the NHLBI and the NIA. Ms Pressel reported receiving grant support and travel to meetings from the NHLBI and the NIA. Dr Davis reported receiving grant support and travel to meetings from the NHLBI and the NIA, and being a board member of data monitoring committees of Amgen and Merck. Drs Cheng and Deng reported no disclosures.

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