

# Extent of Cardiovascular Risk Reduction Associated With Treatment of Isolated Systolic Hypertension

Kim Sutton-Tyrrell, DrPH; Rachel Wildman, PhD; Anne Newman, MD, MPH; Lewis H. Kuller, MD, DrPH

**Background:** The Systolic Hypertension in the Elderly Program (SHEP) demonstrated the benefit of treating isolated systolic hypertension (ISH) in older adults. However, nearly 20% of older adults remain at high risk of heart disease and stroke from untreated ISH.

**Methods:** For the Pittsburgh SHEP cohort, 11- to 14-year death or cardiovascular event rates were compared for active (n=135) and placebo (n=133) arms plus normotensive controls (n=187). Carotid ultrasound and ankle blood pressures were used to identify subclinical atherosclerosis at baseline.

**Results:** Fourteen-year Kaplan-Meier event rate estimates were 58% vs 79% for the active vs placebo groups ( $P=.001$ ). Eleven-year event rates for the control, active, and placebo groups were 35%, 47%, and 65%, respectively. Compared with controls, the relative risk of an event

was 1.6 (95% confidence interval, 1.1-2.4) for the active treatment group and 3.0 (95% confidence interval, 2.1-4.4) for the placebo group. Baseline history of cardiovascular disease was present in 19% of SHEP participants vs 15% of controls ( $P=.32$ ), and subclinical disease (carotid stenosis or low ankle blood pressure) was detected in 33% of SHEP participants vs 10% of controls ( $P<.001$ ). Among those with no clinical or subclinical disease at baseline, the ISH group assigned to active treatment had 10-year event rates similar to those of the control group (29% vs 27%), whereas the placebo rates were much higher (69%).

**Conclusions:** Treatment of ISH in older adults results in reduced event rates in 14 years. Treatment before advanced atherosclerosis develops will likely produce the best long-term outcome.

*Arch Intern Med.* 2003;163:2728-2731

**T**HE PREVALENCE of isolated systolic hypertension (ISH) increases progressively after middle age from 5% among those in their 60s to almost 30% among those in their 80s.<sup>1</sup> Nearly 20% of older adults are at high risk of heart disease and stroke because they have untreated systolic hypertension.<sup>1,2</sup> Systolic hypertension in older adults likely results from progressive arteriosclerotic changes in the media of the aorta and its branches.<sup>3</sup> A loss of elastic fibers and an increase in the amount of collagen eventually leads to arterial stiffening, which causes a rise in systolic blood pressure (BP) without a concomitant rise in diastolic BP.<sup>4</sup> Treating ISH is highly effective. Data from the Systolic Hypertension in the Elderly Program (SHEP)<sup>5</sup> demonstrated a 36% reduction in stroke incidence among participants assigned to active BP treatment, and subsequent studies<sup>6</sup> confirmed a reduction in stroke and cardiovascular disease with ISH treatment.

Despite the clear benefits associated with ISH treatment, many older adults continue to go untreated.<sup>7</sup> Further data demonstrating the magnitude of benefit de-

rived from ISH treatment may help change current practice. This article presents long-term (14-year) outcome data from the Pittsburgh cohort of the SHEP. We also followed an age-similar normotensive comparison population for 11 years. These unique data allow us to compare long-term event rates between normotensive

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older adults and hypertensive adults who were randomized to receive either active treatment or placebo. We use these data to evaluate the degree to which antihypertensive therapy ameliorates the risk associated with ISH and the degree to which the effects of the original SHEP treatment assignment may have persisted.

## METHODS

### PATIENTS

This is a long-term prospective follow-up of the Pittsburgh SHEP cohort and an associated group of control participants recruited dur-

*From the Department of Epidemiology, Graduate School of Public Health (Drs Sutton-Tyrrell, Wildman, and Kuller), and the Division of Geriatrics, Department of Medicine (Dr Newman), University of Pittsburgh, Pittsburgh, Pa. The authors have no relevant financial interest in this article.*

ing the last year of the SHEP using the same methods and criteria. A total of 268 SHEP participants and 187 controls have been followed. All participants were recruited at retirement centers, churches, and other locations where predominantly healthy elderly adults could be found. Qualifications for entry included age 60 years or older and a systolic BP between 160 and 219 mm Hg for SHEP participants and less than 160 mm Hg for controls. Both SHEP and control participants were required to have a diastolic BP less than 90 mm Hg. Exclusions included recent myocardial infarction, stroke with residual paresis, uncontrolled congestive heart failure, peripheral arterial disease with evidence of tissue injury or loss, transient ischemic attacks with associated carotid bruit, and contraindication to study medications. Complete screening techniques and exclusion criteria have been reported previously.<sup>8,9</sup> After study entry, SHEP participants were assigned at random to receive either stepped care BP treatment or matching placebo medication using a double-masked design. Participants initially received chlorthalidone, 12.5 mg/d, or matching placebo. This dosage was doubled for participants who did not achieve their systolic BP goal at follow-up visits. If this maximum dose of chlorthalidone failed to reduce the participant's BP to goal, then 25 mg of atenolol or matching placebo was added. When atenolol was contraindicated, reserpine, 0.05 mg/d, or matching placebo could be substituted.

At the end of the SHEP, participants were counseled on the importance of antihypertensive therapy. Participants assigned to active treatment were given a 4-month supply of medication and were told to visit their primary care physician for continued treatment. Participants assigned to placebo treatment were asked to visit their physician within 4 months so that antihypertensive therapy could be initiated. Participants were interviewed annually after SHEP to determine what type of antihypertensive therapy they were taking, and this information is published in a separate article.<sup>10</sup> Briefly, 1 year after SHEP closeout, 81% of the active group and 55% of the placebo group were undergoing antihypertensive therapy. By 5 years after SHEP closeout, 72% of the active group and 65% of the placebo group were undergoing antihypertensive therapy. The types of antihypertensive agents taken changed during this period, with the use of diuretic monotherapy decreasing and the use of calcium channel blocker monotherapy increasing. The use of diuretics combined with other medications also increased.

Participants in the control group have been followed annually for hypertension development. Of 187 controls, 44 developed hypertension during an 8-year period. The cumulative incidence was 31% (95% confidence interval [CI], 23%-39%), and the average annual incidence was 4.5%. Both SHEP participants and controls have been followed for cardiovascular events via annual telephone contact. Cardiovascular events included stroke, transient ischemic attack, myocardial infarction, hospitalization for unstable angina, coronary revascularization, congestive heart failure, and death. Cause of death was categorized as cardiovascular or other. For SHEP participants and controls, events identified via telephone contact were verified by committee review of hospital records and death certificates according to the SHEP protocol. Total follow-up is now 15 years for SHEP participants and 12 years for controls. During this time, 10 SHEP participants and 3 controls were lost to follow-up.

At the time of control group recruitment, all participants underwent screening for subclinical atherosclerosis, including a duplex scan of the carotid arteries and ankle BPs for the calculation of an ankle-arm index. For this analysis, *subclinical atherosclerosis* was defined as the presence of either an ankle-arm index of 0.90 or less or a carotid stenosis of 40% or greater by pulsed-wave Doppler, without a history of a clinical cardiovascular event. *Clinical atherosclerosis* was defined as a history of a cardiovascular event.

The institutional review board at the University of Pittsburgh approved the SHEP and the ancillary study that covered recruitment of control subjects, subclinical testing, and long-term follow-up. Participants signed separate informed consent forms for SHEP participation, ultrasound evaluation of peripheral atherosclerosis, and long-term follow-up.

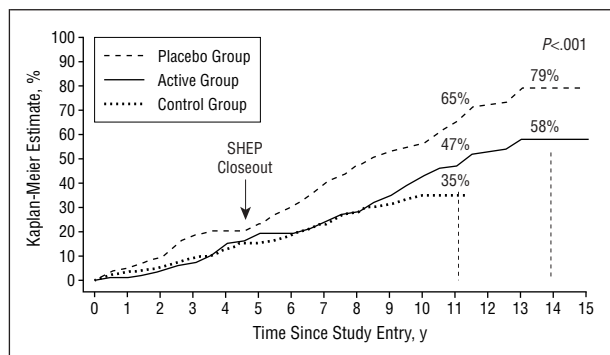
## STATISTICAL METHODS

All statistical analyses were performed using SAS version 6.2 (SAS Institute Inc, Cary, NC). Kaplan-Meier life-table methods were used to estimate mortality and nonfatal cardiovascular event rates for the normotensive, active, and placebo groups. Analysis of mortality included all deaths regardless of the cause. A composite end point was used to evaluate all fatal and nonfatal events. Time zero was SHEP entry for SHEP participants and study entry for the control group. When stratifying the group by the presence or absence of atherosclerotic disease, time zero was changed to the time of subclinical evaluation. The log-rank statistic was used to determine whether the survival curves differed, with  $P < .05$  considered statistically significant. The relationship between hypertensive status (normotensive, active, or placebo) and outcome was adjusted for important baseline cardiovascular risk factors using a Cox proportional hazards model. The Cox model was also used to assess whether important baseline factors modified this relationship via interaction terms between hypertensive status and baseline risk factors. To assess proportionality for all reported Cox models, time-dependent interaction terms of the form  $X \times g(t)$  were used, where  $g(t) = t$ .

## RESULTS

For the 268 SHEP participants (135 receiving active treatment and 133 receiving placebo treatment) and 187 controls, the mean age was 73.5 years. The mean systolic BP was 127 mm Hg for the control group, 171 mm Hg for the SHEP active treatment group, and 171 mm Hg for the SHEP placebo group. We have shown a variety of statistically significant differences between the ISH and control groups. In addition to having higher systolic BPs, those with ISH were older, smoked less often, consumed more alcohol, had higher fasting glucose and total cholesterol levels, and had lower high-density lipoprotein levels.<sup>11</sup> We subsequently showed that participants with ISH had higher homocysteine levels and a higher body mass index.<sup>12</sup> There were no statistically significant baseline differences between the SHEP participants randomized to either active or placebo treatment.

A lower event rate was observed in active SHEP participants compared with placebo participants beginning approximately 1 year after SHEP entry and continuing throughout follow-up (**Figure 1**). By 14 years, the Kaplan-Meier estimates of event rates were 58% (64 events) for the active treatment group and 79% (87 events) for the placebo group ( $P = .001$ ). Using Cox regression, placebo assignment carried a risk of 1.9 (95% CI, 1.3-2.8) for death or a cardiovascular event relative to the active treatment group. When the 2 SHEP groups were compared with controls at 11 years, Kaplan-Meier estimates of event rates were 35% (51 events) for controls, 47% (56 events) for the active treatment group, and 65% (76 events) for the placebo group (Figure 1) ( $P < .001$ ). Using Cox regression, participants with ISH assigned to active treatment were 1.6 times (95% CI, 1.1-2.4 times)



**Figure 1.** Kaplan-Meier estimates of death or nonfatal cardiovascular event rates for normotensive controls (n=187) and Systolic Hypertension in the Elderly Program (SHEP) participants originally assigned to receive active (n=135) or placebo (n=133) treatment.

#### Multivariate Predictors of Time to a Cardiac Event or Death From Any Cause in 387 Participants\*

Variable	Relative Risk (95% CI)	P Value
Male sex	2.8 (2.0-3.9)	<.01
Age (per 5 y)	1.3 (1.0-1.1)	<.01
Apoprotein B level (per 0.25 g/L = 25 mg/dL)	1.4 (1.0-1.0)	<.01
Group		
Control	1.0	
SHEP active	1.4 (0.9-2.1)	.13
SHEP placebo	2.2 (1.5-3.2)	<.01

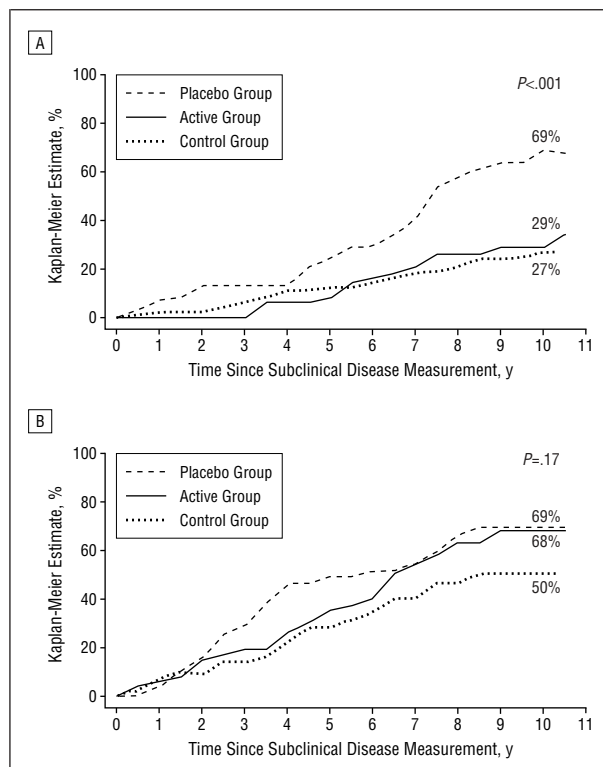
Abbreviations: CI, confidence interval; SHEP, Systolic Hypertension in the Elderly Program.

\*The number of participants with no missing data for the variables in the model.

more likely to experience death or a cardiovascular event than controls, and those assigned to placebo use were 3.0 times (95% CI, 2.1-4.4 times) more likely.

Cox proportional hazards regression was used to model the independent predictors of death or a cardiovascular event (**Table**). When the regression was performed on the 3 groups of participants combined, independent predictors of time to first event were male sex, older age, higher apoprotein B levels, and hypertensive and treatment status. The adjusted relative risk of an event relative to the control group was 1.4 (95% CI, 0.9-2.1) for the treated ISH group ( $P = .13$ ) and 2.2 (95% CI, 1.5-3.2) for the placebo ISH group ( $P < .001$ ). To assess whether the effect of hypertensive and treatment status was mediated by the other covariates in the model, interaction terms between hypertensive and treatment status and each covariate were tested, and none were statistically significant. When the analysis was performed only on the SHEP participants, independent predictors of time to first event were male sex, older age, higher apoprotein B levels, greater body mass index, and placebo treatment assignment ( $P < .05$  for all).

At the time of subclinical testing, the prevalence of atherosclerosis (clinical symptoms or positive subclinical test results) was higher among SHEP participants than controls, and this difference was primarily due to subclinical disease. Clinical disease (history of a cardiovascular event) was pres-



**Figure 2.** Kaplan-Meier estimates of death or nonfatal cardiovascular event rates for individuals without (A) and with (B) clinical or subclinical disease at baseline. Numbers of participants represented in panel A are 123, 52, and 39 for the normotensive control, active, and placebo groups, respectively. Numbers of participants represented in panel B are 43, 48, and 51 for the normotensive control, active, and placebo groups, respectively.

ent in 19% of SHEP participants vs 15% of controls ( $P = .32$ ), and subclinical disease was detected in 33% of SHEP participants vs 10% of controls ( $P < .001$ ). The presence of clinical or subclinical disease was strongly associated with outcome. Compared with individuals with no disease, the relative risk of death or a cardiovascular event was 1.8 (95% CI, 1.2-2.7) for those with subclinical disease and 2.7 (95% CI, 1.8-4.1) for those with clinical disease after controlling for hypertensive status and treatment assignment. We next stratified the analysis based on the presence or absence of atherosclerotic disease at baseline. Among participants who were free of atherosclerosis, those in the active treatment group had similar event rates as those in the control group, and these rates were markedly lower than those in the placebo group (**Figure 2A**). In the group with subclinical or clinical atherosclerosis at baseline, active treatment seemed to delay the onset of events, with the greatest treatment effect at 4 years, when Kaplan-Meier event rates for the placebo, active, and control groups were 46% (31 events), 26% (25 events), and 21% (19 events), respectively. By 10 years, the active and placebo groups had approximately the same event rates (**Figure 2B**).

#### COMMENT

This article presents new data demonstrating the long-term (11- to 14-year) effectiveness of treating ISH in older adults. Among these Pittsburgh participants of the SHEP, placebo treatment assignment was associated with a 90%

greater risk of death or a cardiovascular event during a 14-year period. This extended treatment effect is likely a combination of the SHEP intervention along with the fact that participants assigned to active treatment were more likely to be undergoing antihypertensive therapy in the years after SHEP closeout.

The data presented herein not only underscore the long-term benefits of treatment but also suggest that if treatment is begun before the development of advanced atherosclerosis, the associated risks of ISH are reduced to a level close to the baseline risk experienced by a control group. The prevalence of subclinical atherosclerosis in individuals with ISH is high compared with that of controls, as shown in this study and reported previously.<sup>11</sup> In addition, in this population, active treatment was associated with slower progression of subclinical atherosclerosis compared with placebo treatment.<sup>13</sup> The development of atherosclerosis with ISH likely adds to the acceleration of vascular stiffening, which is the underlying cause of ISH. Thus, early treatment may slow not only the progression of atherosclerosis but the progression of ISH as well. Severe ISH can become difficult to control, requiring multiple medications.

There is a continuing perception in the medical community that ISH, particularly in older individuals, does not need to be treated. At the end of the SHEP, a conscientious attempt was made to educate the participants and their physicians about the need for antihypertensive therapy: seminars were conducted at which the results of the trial were discussed, and literature was distributed to each participant's physician. Despite these efforts, approximately 30% of individuals from the Pittsburgh site either failed to initiate antihypertensive therapy or discontinued treatment.<sup>10</sup> Data from the Third National Health and Nutrition Examination Survey<sup>14</sup> indicate that ISH is the most frequent subtype of uncontrolled hypertension. Of the untreated hypertensive individuals 50 years or older, 82% had an elevated systolic BP, whereas only 17% had an elevated diastolic BP. A separate study<sup>15</sup> of the Third National Health and Nutrition Examination Survey data concluded that uncontrolled hypertension occurs most often among older adults, most of whom have good access to health care and frequent physician contact. Surveys of physician practice in the United Kingdom also indicate less aggressive treatment of systolic BP in older individuals.<sup>7,16</sup> Almost all physicians (97%) reported treating diastolic hypertension, even in patients 80 years and older. However, only 60% reported treating ISH, with only 9% treating patients aged 70 to 79 years.<sup>15,16</sup> Thus, the undertreatment of ISH is pervasive.

The benefits of treating ISH go beyond preventing stroke and cardiovascular events. The SHEP has shown that active treatment improved measures of daily life activity scores.<sup>17</sup> In addition, the Systolic Hypertension in Europe trial<sup>18</sup> found that active treatment significantly reduced the incidence of dementia. Furthermore, the SHEP showed that active treatment exerted a strong protective effect in preventing heart failure.<sup>19</sup> Thus, preventing disability alone is a powerful argument for aggressively treating ISH.

Despite the pervasive undertreatment of ISH in older adults, some progress is being made. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure guidelines now recommend the consideration of both sys-

tolic and diastolic BP in the diagnosis and treatment of hypertension.<sup>20</sup> Continued focus on the benefits of treatment is needed at the patient and physician levels.

In conclusion, the data presented herein underscore the dramatic reduction of death and cardiovascular events associated with treating ISH in older adults. It is likely that early treatment, before advanced atherosclerosis develops, results in the best long-term outcome. In view of the rapidly aging US population and the high prevalence of ISH, a change in practice patterns emphasizing consistent treatment of ISH would likely result in a dramatic decrease in cardiovascular events and associated disability among older adults.

Accepted for publication January 24, 2003.

This work was supported by grant HL50439 from the National Institutes of Health, Bethesda, Md.

Corresponding author: Kim Sutton-Tyrrell, DrPH, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto St, Pittsburgh, PA 15261 (e-mail: Tyrrell@edc.pitt.edu).

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