The Role of Diastolic Blood Pressure When Treating Isolated Systolic Hypertension

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Objective: To assess the role of treated diastolic blood pressure (DBP) level in stroke, coronary heart disease (CHD), and cardiovascular disease (CVD) in patients with isolated systolic hypertension (ISH).

Design: An analysis of the 4736 participants in the Systolic Hypertension in the Elderly Program (SHEP) was undertaken. The SHEP was a randomized multicenter double-blind outpatient clinical trial of the impact of treating ISH in men and women aged 60 years and older.

Main Outcome Measures: Cox proportional hazards regression analysis, with DBP and systolic blood pressure (SBP) as time-dependent covariates.

Results: After adjustment for the baseline risk factors of race (black vs other), sex, use of antihypertensive medication before the study, a composite variable (diabetes, previous heart attack, or stroke), age, and smoking history (ever vs never) and adjustment for the SBP as a time-dependent variable, we found, for the active treatment group only, that a decrease of 5 mm Hg in DBP increased the risk for stroke (relative risk, [RR], 1.14; 95% confidence interval [CI], 1.05-1.22), for CHD (RR, 1.08; 95% CI, 1.00-1.16), and for CVD (RR, 1.11; 95% CI, 1.05-1.16).

Conclusions: Some patients with ISH may be treated to a level that uncovers subclinical disease, and some may be overtreated. Further studies need to determine whether excessively low DBP can be prevented by more careful titration of antihypertensive therapy while maintaining SBP control. It is reassuring that patients receiving treatment for ISH never perform worse than patients receiving placebo in terms of CVD events.

METHODOLOGY

DESIGN AND PARTICIPANTS

The SHEP was a randomized double-blind placebo-controlled clinical trial jointly funded by the National Heart, Lung, and Blood Institute, Bethesda, Md, and the National Institute on Aging, Bethesda. The methods of the SHEP have been described in detail elsewhere.24 The primary end point of the trial was the combined incidence of fatal and nonfatal stroke during a 5-year period. Secondary end points were myocardial infarction, fatal coronary disease, and major cardiovascular morbidity and mortality. The events were adjudicated independently by members of an end point adjudication committee who used predetermined standardized criteria and were blind to treatment and BP status. Beginning in 1985, 447,921 persons aged 60 years and older were screened in 16 clinical centers; 4736 participants with ISH were recruited. Medical history, electrocardiogram, and a physical examination were assessed at baseline. Seated BP was measured by trained technicians according to a standardized protocol. The BP inclusion criteria were systolic BP (SBP) of 160 to 219 mm Hg and DBP less than 90 mm Hg; both were assessed as the average of 2 measurements at each of the 2 baseline visits. Exclusion criteria were SBP of 220 mm Hg or higher; recent myocardial infarction or stroke; or presence of a major illness, such as cancer, alcoholic liver disease, renal failure, insulin-treated diabetes, or depression. Participants who were receiving antihypertensive treatment were considered potentially eligible if they had SBP greater than 130 mm Hg and less than 219 mm Hg and DBP less than 85 mm Hg and were free of major illnesses. They were asked to obtain permission from their physician to participate in the study and were asked to give informed consent for drug withdrawal. They were monitored for 2 to 8 weeks after withdrawal from current antihypertensive therapy to determine BP eligibility according to the criteria listed above.

This article reports primarily on the first occurring major CVD event, which included stroke, transient ischemic attack, myocardial infarction, heart failure, coronary artery bypass surgery, angioplasty, aneurysm, endarterectomy, sudden death, or rapid cardiac death (within 1-24 hours of the onset of severe cardiac symptoms that were unrelated to any other known cause). In addition, the incidences of fatal and nonfatal stroke (stroke) and fatal and nonfatal coronary heart disease (CHD) were reported.

INTERVENTION

The participants were randomized to receive active treatment or placebo. A stepped-care treatment approach was used. The treatment goal was SBP less than 160 mm Hg or a drop in SBP of at least 20 mm Hg, whichever was lower. In the active treatment group, the first step was the administration of chlorthalidone treatment at 12.5 mg/d. The dosage was doubled if the BP goal was not achieved. If the goal was not reached at the first step, treatment with atenolol, 25 mg/d, was added (second step). If atenolol treatment was not tolerated, treatment with reserpine, 0.05 mg/d, could be substituted. The dosage of the second-step drugs could be doubled if the BP goal was not reached. No active antihypertensive agent was given to the participants who were randomized to receive placebo. An open-label potassium supplement was given to the participants in both treatment arms who had serum potassium concentrations below 3.5 mmol/L.

FOLLOW-UP

All participants were evaluated monthly until the BP goal or maximum drug step was reached; patients were evaluated quarterly thereafter until the end of follow-up. Blood samples were drawn routinely at baseline and at each annual clinic follow-up visit. The blood samples were centrifuged and sent by overnight mail to a central laboratory for analysis (MetPath, Teterboro, NJ). Serum creatinine, uric acid, urea nitrogen, sodium, and potassium levels were determined as part of the blood test battery.

ANALYSES

In the original article, the Cox proportional hazards model was used to demonstrate treatment effect. In one model, baseline SBP was included as a covariate. Our major analytic strategy was also to use Cox proportional hazards regression analysis but to include time-dependent covariates, including SBP, DBP, and, in one model, creatinine level. The proportionality assumption for the Cox model was tested and satisfied. Since the number of subjects and timing of follow-up visits were variable and since there were a large number of events, we were forced to create consistent follow-up time points in order to do the analysis. The time-dependent values for a given subject for DBP, for example, were the baseline value and the mean values from baseline through 40 days, from 40 through 75 days, from 75 through 110 days, and for every 90 days from 110 to 2180 days. In most situations, beyond the first few values, the mean quarterly value (every 90 days) was just one value. When an event occurred, the time-dependent value was one of the above (then current) values.

Statistics describing the sample that was studied and results demonstrating a treatment effect have been given in detail elsewhere.24 Briefly, 4736 subjects were randomized, with a mean age of 72 years (57% women and 14% black). The mean SBP at baseline was 170.3 mm Hg and the mean DBP was 76.6 mm Hg. A proportional hazards regression analysis published previously indicated a significant treatment effect for stroke (relative risk [RR], 0.63), CHD (RR, 0.75), and CVD (RR, 0.68).

We first assessed the effect of the time-dependent covariates SBP and DBP on these cardiovascular events (after adjustment for treatment) to determine if the effect was different by treatment (interaction of SBP and DBP by treatment). The inclusion of SBP and DBP in the
same model does not give rise to multicollinearity problems in this population of subjects with ISH. Analyses with either SBP or DBP in the model gave virtually identical results to those described below. We found that a higher SBP was significantly associated with stroke, CHD, and CVD. A lower DBP was significantly associated with stroke and CVD. There was also a significant DBP-by-treatment interaction for stroke and CVD. Given the significant interaction, we decided to look at the effect of SBP and DBP on the outcomes in the placebo and active treatment groups separately.

The Table shows the effects of SBP and DBP on stroke, CHD, and CVD by treatment assignment (active vs placebo). Other risk factors included in the model were race (black vs other), sex, the use of hypertension medication before the study, a composite variable (diabetes, previous heart attack, or stroke), age, and smoking history (ever vs never). There were 2358 subjects in the active treatment group and 2364 in the placebo group. As demonstrated in the Table, those already at increased risk based on the composite variable had approximately a 2-fold greater risk (RR, 1.56-2.50) of having an event regardless of event type or treatment group. There was usually an effect of sex (CHD, CVD) and occasionally an age effect (stroke and CVD in the placebo group). There was never an effect of smoking history, use of previous medication, or race. After adjustment for these other factors, a decrease of 5 mm Hg in SBP decreased the risk of stroke in the active treatment group (RR, 0.90; 95% confidence interval [CI], 0.85-0.95), the risk of CHD in the placebo group (RR, 0.95; 95% CI, 0.91-1.00), and the risk of CVD in both the active treatment (RR, 0.94; 95% CI, 0.91-0.97) and placebo (RR, 0.95; 95% CI, 0.93-0.98) groups. A decrease of 5 mm Hg in DBP decreased the risk of stroke only in the placebo group (RR, 0.92; 95% CI, 0.85-1.00). Somewhat surprisingly, for the active treatment group only, a decrease of 5 mm Hg in DBP increased the risk for stroke (RR, 1.14; 95% CI, 1.05-1.22), for CHD (RR, 1.08; 95% CI, 1.00-1.16), and for CVD (RR, 1.11; 95% CI, 1.05-1.16).

As CVD encompasses the other outcomes, the remainder of this section will concentrate only on CVD.

Figure 1 and Figure 2 demonstrate the comparisons made with a Cox model. Figure 1 shows the mean SBP at specific time points for patients who did or did not experience a CVD event. Patients who did not have an event are essentially the same patients over time, while those who did have an event are a different set of patients for each period. As seen in Figure 1, participants in the placebo group who experienced a CVD event tended to have significantly higher SBP than those who did not experience an event. The same was true in the active treatment group. Figure 2 shows the mean DBP at specific time points for patients who did or did not have a CVD event. In the placebo group, participants who had a CVD event did not differ significantly from those who did not experience an event. In the active treatment group, the DBP of those who experienced an event was significantly lower than that of those who did not experience an event. These results reflect those listed in the Table; in both the placebo and active treatment groups, SBP discriminated between patients with and without CVD events. Likewise, as reflected in the Table, the effect of DBP on the incidence of CVD events was significant for the active treatment group only.

To check that low DBP was not the result of a generalized medical condition, we included creatinine level as a time-dependent covariable in the model for CVD. The basic associations described above were not altered. To check whether the results were specific to a certain group of subjects and to investigate possible alternative explanations for the results, we looked at the effect of SBP and DBP on CVD by treatment group and by various baseline characteristics after adjustment for the other risk factors given in the Table. We looked at the results stratified by age, sex, and previous hypertension medication status. We divided our previous composite variable into 3 categories. Clinical disease (n = 709) includes patients with a previous stroke, myocardial infarction, or diabetes at baseline, and those without these conditions are subdivided into subclinical risk (n = 2935) or no risk (n = 1092) categories. Subclinical risk includes electrocardiogram abnormality, baseline cholesterol level above 6.21 mmol/L (240 mg/dL), baseline high-

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*CHD indicates coronary heart disease; CVD, cardiovascular disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
†For 5-mm Hg decrease; values are relative risk (95% confidence interval).
‡For 5-mm Hg decrease; values are relative risk (95% confidence interval).
density lipoprotein level below 0.90 mmol/L (35 mg/dL), baseline creatinine level greater than or equal to 115 µmol/L (1.3 mg/dL) (90th percentile), fasting blood glucose level greater than or equal to 7.0 mmol/L (126 mg/dL), or a random nonfasting glucose level greater than or equal to 11.1 mmol/L (200 mg/dL). Finally, we divided baseline PP into tertiles (<88, 88-97, and >97 mm Hg) and ran the same model. A change in the significance of DBP within a treatment group for these last 2 variables (baseline disease status and baseline PP) might explain the results shown in Figures 1 and 2.

Figure 3 gives the RR estimate and 95% CI for the effect of a decrease of 5 mm Hg in DBP on CVD in the active treatment group. A lower DBP is almost always a risk for CVD. The small numbers of treated subjects older than 80 years and those taking hypertension medication at baseline compromised the statistical significance of the effect of DBP on a CVD event for these treated subjects. Except for these 2 subgroups, the differing baseline characteristics, baseline clinical disease status, and baseline PP did not affect the results observed in the Table or the effect of DBP on CVD in subjects who received active treatment.

In order to further demonstrate the effect of SBP and DBP on CVD, we dichotomized all values of SBP and DBP for all subjects. As described in the “Methods” section, subjects were assigned an SBP goal. We dichotomized all values of SBP for each subject as either falling below or greater than or equal to their SBP goal. We likewise dichotomized all values of DBP as either falling below or greater than or equal to 12 different cutoff values for DBP; these were 25 through 80 mm Hg. Figure 4 gives the estimated RR and 95% CI for the effect of DBP on CVD in the active treatment subjects. These risk estimates were calculated after adjustment for the other potential risk factors described above and for subjects achieving their
SBP goals. It appears that there is a dose-response relationship; a lower DBP is associated with an increased risk of CVD, and the lower the achieved DBP, the greater the risk of CVD. The RR becomes significant for DBP below 70 mm Hg and starts to approach a 2-fold increase in risk for DBP below 55 mm Hg.

As a check on the specificity of this model, we changed the outcome to all non-CVD deaths and then to cancer deaths. With the same model (using 55 mm Hg as the cutoff, since this value discriminated the best), the time-dependent variable of DBP above or below 55 mm Hg did not predict non-CVD deaths or cancer deaths after adjustment for other variables in the model.

Finally, in order to determine if receiving treatment and having a DBP below 55 mm Hg (n=814) was worse than not receiving treatment, we compared these 2 groups using the same Cox proportional hazards model, while also including treatment in the model. For this comparison, patients who received active treatment were included if they ever had a DBP below 55 mm Hg, while the comparisons shown in Figure 4 are for the most recent DBP below 55 mm Hg. This comparison showed no treatment effect; patients who received active treatment whose DBP fell below 55 mm Hg did not do worse than patients who received placebo. For completeness, we also compared patients who received placebo with those who received active treatment and never had a DBP below 55 mm Hg. This comparison did show there was a treatment effect; patients who received treatment whose DBP never fell below 55 mm Hg did significantly better than patients receiving placebo.

**COMMENT**

The purpose of this article was to assess the effect of SBP and DBP on CVD events in older patients with ISH who received active treatment or placebo. This population lends itself to such an investigation since low DBP is correlated with carotid stenosis in patients with ISH. By definition, ISH is associated with a high PP (≈70 mm Hg at baseline for SHEP participants) and thus with increased arterial stiffness.

In the SHEP study, we found that a low DBP in subjects who received active treatment was associated with increased stroke, CHD, and CVD, while in subjects receiving no treatment this was not the case. These associations were determined after adjustment for sex, use of previous hypertension medication, smoking history, age, race, and previous clinical disease (stroke, myocardial infarction, or diabetes). Concentrating on the CVD outcome only, we also found that the association between a low DBP and a CVD event was consistent across all demographic and risk-based strata only for subjects receiving active treatment. Furthermore, we observed a strong dose-response effect: lower DBP was associated with increased CVD, with significant effects observed first at 70 mm Hg and then more strongly at 60 mm Hg or below. Finally, the effect was specific—we did not observe increases in non-CVD events or cancer associated with low values of DBP in persons randomized to the active treatment group.

In an attempt to include some alternative explanations, we did 3 more analyses. First, we ran the same models as in the Table but also included creatinine level as a time-dependent variable. An increase in serum creatinine level is one type of comorbid condition, and advanced renal disease is associated with an increase in both SBP and DBP. Inclusion of this variable did not significantly alter any of the observed relationships discussed above. Second, we stratified patients into risk categories of clinical disease, subclinical disease, or low risk. As seen in Figure 3, the relationship of low DBP and CVD events held for all 3 strata. Finally, as discussed by Arnett et al,25 arterial stiffness is associated with CVD. Even within a group of patients who had ISH there is a range of PP. We stratified baseline PP into tertiles and found that low DBP was associated with CVD events within each stratum for the subjects who received active treatment. Therefore, our finding of an association of low DBP with increased CVD in patients who received active treatment cannot be attributed solely to an age-related increase in arterial stiffness.

As with all studies using available data, there are limitations. Clearly, this study was not designed to look at the effect of in-trial SBP or DBP on CVD outcome. This might discount post hoc analyses if previous studies had not shown a possible J-shaped curve for the relationship of DBP and CVD events.7-17 As our study was restricted to patients with ISH, we found the relationship of DBP to CVD events to be negatively linear in the active treatment group but not in the placebo group.

In the HOT trial, patients who were randomized to a lower DBP goal had a risk of CVD events similar to that of those who were randomized to a higher DBP goal.22 The HOT trial showed that aiming at a lower DBP goal (80 or 85 vs 90 mm Hg) does not improve outcomes. Despite the numerous treatment options to lower DBP in the HOT trial, there were only minimal differences in achieved DBP (2.3 mm Hg instead of 5 mm Hg) between the targeted DBP goals (≤90 vs ≤85 mm Hg and ≥85 vs ≥80 mm Hg). In all 3 randomized groups, a proportion of patients reached a DBP of less than 70 mm Hg. These data suggest that, despite the treatment effort of attaining a determined DBP goal, other, uncontrolled factors contributed to the achieved DBP level. Additional analyses of observational data in the HOT trial showed that, independent of the randomized assignments, there were no significant differences in risk of CVD events across achieved DBP levels ranging from 70 to 105 mm Hg.

The present study complements and extends the findings of the HOT trial, which excluded patients with ISH, such as those enrolled in the SHEP, and failed to report CVD outcome data for those patients who reached a DBP of less than 70 mm Hg. We show that in older patients who were treated for ISH, a DBP of less than 70 mm Hg (and especially below 60 mm Hg) identifies a high-risk group that deserves special monitoring and even more aggressive treatment for other risk factors. It is possible that some of these participants may be treated to a level that uncovers subclinical disease or that they may be overtreated. Further studies are needed to determine whether such an excess drop in DBP and the associated excess risk of CVD events could be prevented by a more careful titration of antihypertensive therapy while maintaining SBP.
control. It is reassuring that patients who received active treatment never performed worse than patients who received placebo in terms of CVD events.

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