Treatment of Isolated Systolic Hypertension Is Most Effective in Older Patients With High-Risk Profile

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Background—Although present guidelines suggest that treatment of hypertension is more effective in patients with multiple risk factors and higher risk of cardiovascular events, this hypothesis was never verified in older patients with systolic hypertension.

Methods and Results—Using data from the Systolic Hypertension in the Elderly Program, we calculated the global cardiovascular risk score according to the American Heart Association Multiple Risk Factor Assessment Equation in 4,189 participants free of cardiovascular disease (CVD) and in 264 participants with CVD at baseline. In the placebo group, rates of cardiovascular events over 4.5 years were progressively higher according to higher quartiles of CVD risk. The protection conferred by treatment was similar across quartiles of risk. However, the numbers needed to treat (NNTs) to prevent one cardiovascular event were progressively smaller according to higher cardiovascular risk quartiles. In participants with baseline CVD, the NNTs to prevent one cardiovascular event were similar to those estimated for CVD-free participants in the highest-risk quartile.

Conclusions—Treatment of systolic hypertension is most effective in older patients who, because of additional risk factors or prevalent CVD, are at higher risk of developing a cardiovascular event. These patients are prime candidates for antihypertensive treatment. (Circulation. 2001;104:1923-1926.)

Key Words: hypertension ■ aging ■ risk factors ■ cardiovascular diseases ■ trials

Present guidelines suggest that the treatment of hypertension is more effective in patients with multiple cardiovascular disease (CVD) risk factors.1–3 This statement is supported by findings of epidemiological studies and clinical trials showing that persons with combined systolic and diastolic hypertension and a high-risk profile experience higher rates of coronary and cerebrovascular diseases.4–8 Although there is evidence that treatment of systolic hypertension in older patients effectively prevents major CVD outcomes,9–11 it remains unclear whether such a treatment is more effective in high-risk patients. In fact, it has been suggested that the natural history of arteriosclerosis in older patients with a high-risk profile may not be substantially modified by treatment.12

Using data from the Systolic Hypertension in the Elderly Program (SHEP), we examined whether the treatment of systolic hypertension is more effective in older patients who have additional CVD risk factors compared with low-risk patients. To test this hypothesis, we calculated the risk of CVD in each participant using the Multiple Risk Factor Assessment Equation proposed by the American Heart Association and the American College of Cardiology and performed an efficiency analysis across quartiles of CVD risk.13

Methods

The SHEP trial is a randomized, double-blind, placebo-controlled clinical trial funded by the National Heart, Lung, and Blood Institute and the National Institute on Aging that tested whether treatment of isolated systolic hypertension (ISH) in older persons prevents stroke.14

Study Population

The study population consisted of community-dwelling persons ≥60 years of age affected by ISH, defined as systolic blood pressure [SBP] 160 to 219 mm Hg and diastolic blood pressure [DBP] <90 mm Hg assessed and averaged over 2 visits, no atrial fibrillation, and no history of myocardial infarction (MI) or stroke in the last 6 months. Subjects taking antihypertensive medications were eligible if after therapy withdrawal, their BPs met the entry criteria for ISH. A total of 2,046 men and 2,690 women were randomized into the study.

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At baseline, health behaviors, medical conditions, and cardiovascular risk factors were ascertained according to standard criteria. Fasting blood samples were analyzed at a central laboratory (MetPath, Teterboro, NJ).

Of the 4,736 SHEP participants, 283 were excluded because of missing data concerning CVD risk factors. These 283 excluded participants had similar age, sex, race, and smoking characteristics as those who were included in the analysis. Participants who at baseline did not report (n=4189) and those who did report previous CHD or stroke (n=264) were considered in separate analyses.

**Intervention**

A stepped-care treatment approach was used, with the goal of decreasing SBP to <160 mm Hg or at least by 20 mm Hg. The first-step therapy was chlorthalidone (12.5 mg/d). Second-step therapy involved addition of atenolol (25 mg/d) or reserpine (0.05 mg/d) if atenolol was not tolerated. Drug treatment in placebo and active treatment groups was increased by doubling the dosage or adding a second-step drug until the BP goal was reached, side effects precluded additional step up, or the highest step was reached.

**Events Adjudication**

Members of a committee who were blinded to participants’ treatment and BP status reviewed the documentation of new cardiovascular events over a 4.5-year follow-up and adjudicated outcome events according to predetermined criteria. The present analysis focused on four types of events: (1) first-occurring major cardiovascular event, including stroke, MI, or heart failure; (2) first-occurring MI; (3) first-occurring stroke, and (4) first clinical diagnosis of congestive heart failure (CHF).

**Calculation of Global Risk Scores**

Baseline information on age, sex, total and HDL cholesterol, SBP, diabetes, and smoking was used to estimate individual risks of developing subsequent cardiovascular events according to the Multiple Risk Factor Assessment Equation. The equation assigns subscores to major risk factors using cut points developed from the Framingham study. A global CVD risk score ranging from −17 to +22 was obtained by adding the subscores. Higher values reflect a more unfavorable risk profile. Because the equation does not provide the age score for persons ≥75 years of age (28.5% of the SHEP population), one additional point was assigned to men and women in this age group compared with those 70 to 74 years of age.

**Data Analysis**

Participants were stratified according to sex-specific quartiles of global cardiovascular risk scores. Cox’s proportional hazards models were fitted to evaluate the effect of active treatment compared with placebo on the time to the first occurrence of a CVD event. Patients who did not develop a CVD event were censored at the time of their last valid follow-up visit or of their death. Relative risks (RRs) and 95% confidence intervals (95% CI) were used as measures of association. The proportionality of hazards was verified by log minus log plots and by testing the interaction of exposure with time. Time to event analyses were conducted separately in all participants free of CVD at baseline, according to strata of global CVD risk, and in those with prevalent CVD. The heterogeneity of the RRs across strata was tested by a likelihood-ratio test comparing a model including only treatment as a predictor and a second model that also included dummy variables for the CVD risk strata and their interaction with treatment. To estimate the absolute benefit of treatment by risk score, we calculated the number needed to treat (NNT) for 1 year to prevent an event as the inverse of the absolute risk reduction attributable to treatment.

**Results**

Major characteristics of the SHEP population that was free of CVD at baseline and had complete data are listed in the Table. Sex-specific scores were assigned according to the Multiple Risk Factor Assessment Equation. Categories of SBP were assigned on the basis of assessment of BP at the first of the 2 screening visits, when 18.1% of men and 16.2% of women had SBP values between 140 and 159 mm Hg.

The threshold scores that divide each sex-specific quartiles of global CVD score and the increments in rate were always statistically significant. Participants with prevalent baseline CVD compared with those free of CVD were more likely to experience any major CVD event (64.9 versus 35.5 events/1000 person-years; RR 1.8; 95% CI 1.4 to 2.4), MI (13.2 versus 8.2 events/1000 person-years; RR 1.4; 95% CI 1.0 to 2.1), stroke (19.3 versus 13.4 events/1000 person-years; RR 1.4; 95% CI 0.9 to 2.8), and CHF (19.3 versus 7.7 events/1000 person-years; RR 1.4; 95% CI 1.0 to 2.0).
For any type of event and for all strata of CVD risk, the relative risks of developing a CVD event indicated a protective effect of treatment. With few exceptions, the magnitude of these relative risks was similar across strata, and, in fact, a formal test of heterogeneity of the relative risks performed for each type of CVD event was never statistically significant. This finding suggests that on a multiplicative scale, the protection conferred by the antihypertensive treatment is independent of the initial CVD risk score. However, because of the greater incidence rates of CVD events, the NNT for 1 year to prevent a CVD event was substantially lower with increasing global CVD risk score (Figure 2).

The NNTs to prevent a CVD event of any type were of comparable magnitude in participants with prevalent baseline CVD and in those free of baseline CVD but with the highest global CVD risk score. These findings suggest that treatment of systolic hypertension is as effective in older patients with high CVD risk profiles as in those with prevalent CVD.

We examined whether the reduced NNTs in the higher risk subgroups could be explained by differences in the magnitude of BP reduction or type of drug used for treatment across groups. Over the first year, participants with and without CVD at baseline experienced an average BP decrease of 28 and 8 mm Hg, respectively, for those on active therapy, and 14 and 3 mm Hg, respectively, for those in the placebo group. The magnitude of the average reduction in SBP and DBP was quite similar and not statistically different according to quartiles of CVD risk. The percentage of participants who required a step-two drug were almost identical across quartiles of CVD risk (participants free of CVD at baseline: first quartile, 25.3%; second quartile, 25%; third quartile, 26%; fourth quartile, 24%; NS) and slightly but not significantly lower in those with CVD (22.8%). Equivalent results were obtained when comparing the percentage of participants who were prescribed a β-blocker.

Discussion

Present guidelines for treatment of hypertension recommend that patients with multiple CVD risk factors should be especially targeted for treatment.1–3,5 However, limited evidence exists to support this recommendation in older patients with ISH.7,16–18 In 1999, it was proposed that the global risk of CVD be assessed with the multiple risk factors equation, a method based on a robust analysis of the relative strength of risk factors for acute coronary events in the Framingham study that is simple enough for routine use in the primary care setting.8,13 Applying this method in >4,000 older persons with ISH enrolled in the SHEP trial, we found that increasing scores of global CVD risk were strongly predictive of major CVD events. The relative protection conferred by the antihypertensive treatment was similar across levels of baseline CVD risk. Consequently, the NNTs to prevent a CVD event were substantially lower in patients in the high CVD risk strata.

These findings suggest that the multiple risk factors equation should be used to forecast the risk of developing future CVD events in older patients with ISH to target the patients in whom the antihypertensive treatment is most effective.
stratification of risk is especially important when facing decisions about treating hypertension in older patients who, because of comorbidity and frequent multidrug treatment, are at high risk of iatrogenesis. The risk-benefit ratio can be positive in high-risk patients because of small NNTs, whereas in low-risk patients, the risk reduction may not be sufficient to justify the side effects and cost of drug treatment.

It has been suggested that the treatment of CVD risk factors such as hypertension may not be as effective in older as in younger patients, because the long-term exposure to risk factors determines cumulative arteriosclerosis and plaque burden that cannot be reversed. In contrast to this view, the NNTs estimated from our analysis were similar to those from trials of drug therapy for systodiastolic hypertension in middle-aged adults and were substantially lower in persons with multiple risk factors.6,19–21 Additionally, it has been suggested that cardiovascular drug therapy oriented toward one specific risk factor may have multiple effects on other associated risk factors, and, thus, it may have other positive, unintended health effects.22 Indeed, except for stroke, we found that the preventive effect of treatment was not completely washed out when we adjusted the analyses for changes in BP (data not shown).

We found that antihypertensive treatment has comparable efficacy in older patients with prevalent CVD and in those free of CVD but with a high-risk profile. These findings suggest that patients at the high end of the spectrum of CVD risk are already affected by subclinical cardiovascular disease.

Our use of the multiple risk factors assessment equation to predict risk of CVD events requires comment. Because Framingham scores estimate risk for persons without clinical manifestations of CHD, at least in theory they should be applied only to primary prevention of CHD.8,13 In clinical practice, however, it is difficult to separate out specific preventive strategies for various types of CVD events, because, to a certain extent, risk factors for developing CHD also represent risk factors for other cardiovascular events, such as stroke.

Despite the strong evidence that treatment of ISH may substantially reduce the risk of negative health outcomes, studies have indicated that this condition is often inadequately controlled.23 The findings of this study provide the best evidence presently available that treatment of ISH in older patients is especially effective in patients with high absolute risk of developing a CVD event, such as those with multiple CVD risk factors or prevalent CVD. These patients should be prime candidates for treatment.

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References

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