Chinese Trial on Isolated Systolic Hypertension in the Elderly

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Background: In 1988, the Systolic Hypertension in China (Syst-China) Collaborative Group initiated the placebo-controlled Syst-China trial to investigate whether antihypertensive drug treatment could reduce the incidence of fatal and nonfatal stroke in older Chinese patients with isolated systolic hypertension.

Objectives: To explore (1) whether the benefits of active treatment were evenly distributed across 4 strata, prospectively defined according to sex and previous cardiovascular complications, and (2) whether the morbidity and mortality results were influenced by age, level of systolic or diastolic blood pressure (BP), smoking or drinking habits, or diabetes mellitus at enrollment.

Methods: Eligible patients had to be 60 years or older with a sitting systolic BP of 160 to 219 mm Hg and diastolic BP less than 95 mm Hg. After stratification for center, sex, and previous cardiovascular complications, 1253 patients were assigned to active treatment starting with nitrendipine (10-40 mg/d), with the possible addition of captopril (12.5-50.0 mg/d), and/or hydrochlorothiazide (12.5-50 mg/d). In the 1141 control patients, matching placebos were used similarly.

Results: Male sex, previous cardiovascular complications, older age, higher systolic BP or lower diastolic BP, living in northern China, smoking, and diabetes mellitus significantly and independently increased the risk of 1 or more of the following end points: total or cardiovascular mortality, all fatal and nonfatal cardiovascular end points, all strokes, and all cardiac end points. In the placebo-control group diabetes raised the risk of all end points 2-to-3-fold ($P \leq .05$). However, active treatment reduced the excess risk associated with diabetes to a nonsignificant level ($P$ values ranging from .12-.86) except for cardiovascular mortality ($P = .04$). Cox regression with adjustments applied for significant covariates suggested that active treatment may reduce total mortality more ($P = .06$) in women and stroke more ($P = .07$) in men and that it may provide better protection against cardiac end points in nonsmokers than smokers ($P = .04$). Otherwise, the benefits of active treatment were equally manifest, regardless of the enrollment characteristics of the patients, and regardless of whether active treatment consisted of only nitrendipine or of nitrendipine associated with other active drugs.

Conclusions: In elderly Chinese patients with isolated systolic hypertension, stepwise antihypertensive drug treatment, starting with the dihydropyridine calcium channel blocker nitrendipine, improved prognosis. The benefit was particularly evident in diabetic patients; for cardiac end points it tended to be larger in nonsmokers. Otherwise, the benefit of active treatment was not significantly influenced by the characteristics of the patients at enrollment in the trial.

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PATIENTS AND METHODS

STUDY DESIGN

The Chinese Ministry of Health approved the Syst-China trial. Its design is described in detail elsewhere.1,2,4 Eligible patients consented to be enrolled in the study and were at least 60 years old. While receiving single-blind placebo during the run-in phase, their sitting systolic BP had to range from 160 to 219 mm Hg, with diastolic BP below 95 mm Hg. The sitting BP determining eligibility was the average of 6 readings, 2 at baseline visits 1 month apart. Patients whose serum creatinine concentration exceeded 180 µmol/L (2 mg/dL) and patients with severe concomitant cardiovascular or noncardiovascular disorders were excluded.1,2,4

The 31 Syst-China centers received supplies of the 3 active study drugs, all labeled A, and the 3 matching placebos, all labeled B. After stratification for sex and cardiovascular complications, eligible patients were alternatingly assigned to type A or type B medication. The first patient of each of the 4 strata always received type A medication. Active treatment was initiated with nitrendipine, with the possible addition of captopril, hydrochlorothiazide, or both drugs. The dosage steps for nitrendipine were 10 mg or 20 mg once daily in the evening, or 20 mg twice daily. For captopril and hydrochlorothiazide, the doses were 12.5 mg in the morning, or 12.5 mg or 25 mg twice daily. The study drugs were stepwise titrated and combined to reduce the sitting systolic BP by 20 mm Hg or more to less than 150 mm Hg.2,4 Drugs causing intolerable side effects were substituted by the next-line study medication. Placebos and active drugs were used in the same way. Patients who withdrew from the study medication remained in open follow-up. Patients without any report within the year before the trial ended in each center were classified as lost to follow-up, but were included in the analysis up to the most recent evaluation of their health status.3,2,4

DEFINITIONS AND VALIDATION OF END POINTS

Fatal and nonfatal stroke, the primary end point, and the other secondary end points were defined as in the Systolic Hypertension in Europe (Syst-Eur) trial.3 Stroke was clinically diagnosed as a neurologic deficit with symptoms continuing for more than 24 hours or leading to death with no apparent cause other than vascular. The diagnosis of acute myocardial infarction rested on 2 of the following 3 disorders: typical chest pain, electrocardiographic changes, or increased cardiac enzyme levels. Myocardial infarction excluded silent myocardial infarction. Congestive heart failure required the presence of 3 conditions, namely, symptoms, such as dyspnea; clinical signs, such as ankle edema or rales; and the necessity of treatment with diuretics, vasodilators, or antihypertensive drugs. Sudden death included any death of unknown origin occurring instantly or within 24 hours of the onset of acute symptoms, as well as unattended death for which no likely cause could be established by autopsy or recent medical history. Cardiac end points included fatal and nonfatal heart failure, fatal and nonfatal myocardial infarction, and sudden death.

During the course of the trials end points were logged at the coordinating office in Beijing, People's Republic of China, as reported by the investigators. In 1996 and 1997 the blinded End Point Committee validated all end points by reviewing the local patient files and other source documents, by requesting detailed written information from the investigators, or by both approaches. For the final analysis, the whole Syst-China database was transferred to Leuven, Belgium, in October 1997. The source documents certifying the stroke cases were translated into English and were again reviewed by 2 independent and blinded Syst-Eur investigators.

Diabetes mellitus at enrollment was defined according to the criteria of the World Health Organization.2,4 The diagnosis required the presence of a history of diabetes reported by the clinical investigator, a fasting blood glucose level of 7.8 mmol/L (140 mg/dL) or more, or the use of antidiabetic medication. Smokers and patients who consumed alcohol regularly were identified by questionnaire administered at enrollment.

STATISTICAL ANALYSIS

The statistical analysis by intention-to-treat was done with a commercially available software (SAS, Version 6.12; SAS Institute Inc, Cary, NC), using 2-sided tests. Means and proportions were contrasted by the standard normal z test and the x² statistic, respectively. Relative hazard rates were assessed by single and multiple Cox regression.3 Survival curves were compared using the log rank test.

diovascular complications,2,4 and (2) whether the morbidity and mortality results were influenced by age, level of systolic or diastolic blood pressure (BP), smoking or drinking habits, or diabetes mellitus at enrollment.

RESULTS

In the 2394 enrolled patients the median follow-up by intention-to-treat was 3.0 years (follow-up range, 1.94 months). The number of patient-years in the placebo and active treatment groups were 2892 and 3510, respectively. At 2 years of follow-up, the sitting systolic and diastolic BP had fallen by a mean (±SD) of 11 ± 17 mm Hg and 2 ± 8 mm Hg, respectively, in the placebo group and by 20 ± 16 mm Hg and 5 ± 8 mm Hg, respectively, in the active treatment group. The differences in systolic and diastolic BP between the 2 groups then averaged 9.1 mm Hg (95% confidence interval [CI], 7.6-10.7 mm Hg) and 3.2 mm Hg (95% CI, 2.4-4.0), respectively. The analysis by intention to treat showed that both before (Table 1) and after (Table 2) adjustment for significant covariates, active treatment had reduced the incidence of total mortality (P<.01), fatal and nonfatal stroke (P<.05), and all cardiovascular end points (P<.01). Among the incident cases of stroke, the diagnosis was confirmed by computed tomographic brain scans in 12 (40%) of 30 patients with a fatal event and in 55 (72%) of 76 patients with a nonfatal stroke.

COMPLIANCE WITH ENROLLMENT CRITERIA

Of the enrolled patients, 223 assigned to placebo and 240 of the active treatment group did not comply with 1 or
Fatal and Nonfatal Cardiovascular End Points

The trial included 1541 men (64.4%), 853 women (35.6%), 269 patients with previous cardiovascular complications (11.2%), and 2125 patients without such complications (88.8%). The 4 strata were equally represented in the 2 arms of the trial. Of the 269 patients with cardiovascular complications at enrollment, 224 (9.4%) had symptoms or signs suggestive of coronary heart disease or myocardial infarction, 34 (1.4%) had a history of stroke, and 11 (0.5%) had coronary and cerebrovascular disorders.

Male sex was a significant and strong predictor of all end points. Patients with cardiovascular complications at enrollment experienced significantly more fatal and nonfatal cardiovascular end points (Table 1). With adjustments applied for the covariates listed in Table 2, these associations remained statistically significant. Further analysis showed that in general the benefits of active treatment were evenly distributed across men and women and across patients with and without previous cardiovascular complications. Only for total mortality

Table 1. Crude Relative Hazard Rates According to Various Characteristics in 2394 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cardiovascular</th>
<th>Fatal and Nonfatal Cardiovascular End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving placebo</td>
<td>28.4 (82)</td>
<td>15.2 (44)</td>
</tr>
<tr>
<td>Receiving active treatment</td>
<td>17.4 (61)</td>
<td>9.4 (33)</td>
</tr>
</tbody>
</table>

Relative Hazard Rates*

- Active treatment†: 0.61 (0.44-0.85)▼ 0.62 (0.40-0.98)▼ 0.64 (0.47-0.87)▼ 0.62 (0.42-0.91)▼ 0.64 (0.37-1.09)
- Male sex†: 2.03 (1.39-2.97)▼ 2.52 (1.45-4.38)▼ 2.29 (1.60-3.28)▼ 2.16 (1.38-3.37)▼ 2.44 (1.29-4.65)
- Cardiovascular complications†: 0.84 (0.49-1.43) 0.97 (0.48-1.94) 1.61 (1.08-2.39) 1.55 (0.93-2.57) 1.85 (0.96-3.58)
- Age, y: 1.09 (1.06-1.12)▼ 1.09 (1.05-1.13)▼ 1.06 (1.03-1.10)▼ 1.01 (0.97-1.05)▼ 1.12 (1.08-1.17)
- Increase in systolic blood pressure of 10 mm Hg: 1.32 (1.16-1.51)▼ 1.34 (1.12-1.59)▼ 1.29 (1.14-1.46)▼ 1.12 (0.94-1.32)▼ 1.50 (1.24-1.82)
- Increase in diastolic blood pressure of 5 mm Hg: 0.77 (0.70-0.86)▼ 0.73 (0.64-0.83)▼ 0.80 (0.72-0.88)▼ 0.88 (0.77-1.00)▼ 0.69 (0.60-0.80)
- Residence in northern China†‡ 1.08 (0.77-1.52) 1.10 (0.69-1.75) 1.02 (0.69-1.51) 1.04 (0.67-1.61) 1.34 (0.76-2.37)
- Smoking†§ 1.67 (1.19-2.34) 1.61 (1.01-2.55) 1.72 (1.26-2.35) 1.23 (0.84-1.81) 1.13 (0.64-2.01)
- Drinking alcohol†§ 1.20 (0.92-1.81) 1.56 (0.99-2.45) 1.42 (0.94-1.99) 1.62 (1.09-2.40) 1.22 (0.71-2.11)
- Diabetes mellitus† 2.25 (1.29-3.92) 3.33 (1.71-6.48) 1.97 (1.16-3.36) 2.06 (1.07-3.98) 2.19 (0.87-5.52)

* Relative hazard rates are presented with 95% confidence intervals and levels of statistical significance (a indicates P = .05; b, P = .01; c, P = .001).
† Dichotomous variables were coded 0 or 1 depending on whether the condition was absent or present.
‡ Compared with patients recruited in southern Chinese provinces.
§ Smoking and drinking habits were unknown in 61 (5.4%) and 53 (4.6%) patients of the placebo group; in the active treatment group these numbers were 49 (3.9%) and 41 (3.3%), respectively.

Table 2. Adjusted Relative Hazard Rates* According to Various Characteristics in 2394 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cardiovascular</th>
<th>Fatal and Nonfatal Cardiovascular End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving placebo</td>
<td>61.8 (57)</td>
<td>31.1 (31)</td>
</tr>
<tr>
<td>Receiving active treatment</td>
<td>47.4 (47)</td>
<td>26.4 (26)</td>
</tr>
</tbody>
</table>

Relative Hazard Rates*

- Active treatment†: 0.62 (0.44-0.86)▼ 0.64 (0.41-1.01)▼ 0.63 (0.46-0.85)▼ 0.66 (0.45-0.98)▼ 0.67 (0.39-1.15)
- Male sex†: 2.37 (1.61-3.47)▼ 3.11 (1.78-5.42)▼ 2.68 (1.87-3.84)▼ 2.01 (1.25-3.22)▼ 2.97 (1.56-5.65)
- Cardiovascular complications†: NS (P = .31) NS (P = .62) 1.65 (1.00-2.74) NS (P = .16) NS (P = .18)
- Age, y: 1.06 (1.03-1.09)▼ 1.05 (1.02-1.09)▼ 1.03 (1.00-1.06)▼ NS (P = .92) 1.08 (1.03-1.13)
- Increase in systolic blood pressure of 10 mm Hg: 1.27 (1.10-1.45)▼ 1.13 (1.03-1.23)▼ 1.29 (1.14-1.47)▼ NS (P = .18) 1.47 (1.20-1.79)
- Increase in diastolic blood pressure of 5 mm Hg: 0.62 (0.51-0.76)▼ 0.74 (0.65-0.84)▼ 0.79 (0.72-0.86)▼ 0.87 (0.77-0.99)▼ 0.72 (0.62-0.83)
- Residence in northern China†‡: NS (P = .31) NS (P = .74) NS (P = .10) 1.60 (1.03-2.50)▼ NS (P = .62)
- Smoking†§: NS (P = .22) NS (P = .72) NS (P = .19) 1.64 (1.08-2.48)▼ NS (P = .26)
- Diabetes mellitus†§: 2.25 (1.29-3.96)▼ 3.38 (1.71-6.68)▼ 1.95 (1.14-3.58)▼ 1.60 (1.03-2.51)▼ NS (P = .20)

* Because the relative hazard rates were calculated by stepwise Cox regression with treatment forced into the model, they are automatically adjusted for allocation to active treatment and for all significant covariates listed in the table. Cardiovascular complication at entry and drinking alcohol were not independently and significantly correlated with outcome. NS indicates not significant. See Table 1 for explanation of the remaining footnote symbols.

More of the eligibility criteria. Of these 463 patients (criteria are not mutually exclusive so that numbers do not add up), 43 and 110 had been recruited after only 1 or 2 run-in visits, 89 were 50 to 59 years old, 45 had grade 3 retinopathy, 189 had a sitting systolic BP from 140 to 159 mm Hg, and 91 had a sitting diastolic BP of 95 mm Hg or higher. Noncompliance with all enrollment criteria did not affect the results. For instance, for all fatal and nonfatal cardiovascular end points the relative hazard rate of active vs placebo treatment was 0.67 (95% CI, 0.48-0.94; P < .02) in the 1931 compliant patients and 0.39 (95% CI, 0.17-0.88; P = .02) in the 463 noncompliant patients. The P value for the treatment-by-compliance interaction term was .38.

SEX AND PREVIOUS CARDIOVASCULAR COMPLICATIONS

Before enrollment, the patients had been prospectively stratified for sex and previous cardiovascular complications. The trial included 1541 men (64.4%), 853 women (35.6%), 269 patients with previous cardiovascular complications (11.2%), and 2125 patients without such complications (88.8%). The 4 strata were equally represented in the 2 arms of the trial. Of the 269 patients with cardiovascular complications at enrollment, 224 (9.4%) had symptoms or signs suggestive of coronary heart disease or myocardial infarction, 34 (1.4%) had a history of stroke, and 11 (0.5%) had coronary and cerebrovascular disorders.

Male sex was a significant and strong predictor of all end points. Patients with cardiovascular complications at enrollment experienced significantly more fatal and nonfatal cardiovascular end points (Table 1). With adjustments applied for the covariates listed in Table 2, these associations remained statistically significant. Further analysis showed that in general the benefits of active treatment were evenly distributed across men and women and across patients with and without previous cardiovascular complications. Only for total mortality
(P = .06) and stroke (P = .07), the treatment-by-sex interaction terms approached statistical significance. For all-cause mortality, the relative hazard rates associated with active treatment were 0.74 (95% CI, 0.50-1.09; P = .12) in men and 0.34 (95% CI, 0.16-0.72; P = .005) in women; for stroke these hazard rates were 0.54 (95% CI, 0.34-0.85; P = .008) and 1.24 (95% CI, 0.56-2.74; P = .06), respectively. Thus, these treatment-by-sex interaction terms suggested that active treatment may reduce total mortality more in women and that it may prevent stroke especially in men. The P values for the other treatment-by-sex interactions ranged from .13 to .52; those for the interactions between treatment and previous cardiovascular complications ranged from .09 to .69.

**AGE**

Age at baseline averaged 66.5 (5.5) years (mean [SD]). In single (Table 1) and multiple (Table 2) Cox regression, age was a strong predictor of all end points with the exception of stroke. Plots of the crude relative hazard rates in 3 age strata (≥64, 65-69, and ≥70 years) suggested that for cardiovascular mortality (Figure 1) the effect of active treatment weakened in the oldest (≥70 years) age group. However, this was not the case for all fatal and nonfatal cardiovascular end points (Figure 1).

Furthermore, Cox regression with adjustments applied for the covariates listed in Table 2 demonstrated that age did not influence the effects of active treatment on outcome. Even for cardiovascular mortality (Figure 2), the relative hazard rate for the treatment-by-age interaction term was only 1.03 (95% CI, 0.95-1.11; P = .48); for the other end points the P values of these interaction terms ranged from .45 to .83.

**SYSTOLIC AND DIASTOLIC BP AT ENROLLMENT**

At baseline, the sitting BP averaged 170.5 ± 11.1 mm Hg systolic and 86.0 ± 6.8 mm Hg diastolic BP. In single (Table 1) and multiple (Table 2) regression, all end points with the exception of fatal and nonfatal stroke were positively correlated with systolic BP. Plots of the crude relative hazard rates in 3 strata according to the systolic BP at enrollment (≥169, 170-179, and ≥180 mm Hg) did not show a consistent trend (Figure 1). After adjustment for the covariates listed in Table 2, the interaction terms between treatment and systolic BP were nonsignificant for all end points (Figure 2); the P values ranged from .16 to .78.

Both before and after adjustment (Table 1 and Table 2), a higher diastolic BP was associated with a lower incidence of end points. The latter associations were not influenced by treatment status; after adjustment, the P values for the interactions between treatment and diastolic BP ranged from .27 to .99.

**NORTHERN VS SOUTHERN CHINESE PATIENTS**

Of the 2394 patients, 1579 (66.1%) were residents of northern China. Compared with 815 (33.9%) southern Chinese patients, the northern Chinese were at significantly greater risk of stroke both before (Table 1) and after (Table 2) adjustment for the covariates listed in Table 2. However, with these adjustments applied, there was no statistically significant difference between northern and southern Chinese patients in the effects of treatment on stroke prevention (P = .92). This was also the

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**Figure 1.** Unadjusted relative hazard rates (active treatment vs placebo) for cardiovascular mortality and for all cardiovascular end points in all patients and in various subgroups according to age and systolic blood pressure at enrollment in the study. For each group the 95% confidence interval and the number of subjects are given.

**Figure 2.** Adjusted relative hazard rates (active treatment vs placebo) for total mortality and for all cardiovascular end points according to age and systolic blood pressure at enrollment in the study. The hazard rates were plotted as continuous risk functions with 95% confidence interval and were adjusted for the covariates listed in Table 2. P values refer to the interaction terms between treatment and the independent predictor variables plotted along the horizontal axis.
case for all other end points, for which the P values of the treatment-by-residence interaction terms ranged from .42 to .58.

SMOKING AND DRINKING HABITS

At baseline, 737 patients (30.8%) (626 men [85%] and 111 women [15%]) smoked. In single regression (Table 1), smoking predicted outcome except for all cardiac end points. The proportion of smokers was similar among patients who suffered a cardiac end point and those who did not (29.1% vs 30.8%). After adjustment for the covariates listed in Table 2, smoking was still a significant predictor of fatal and nonfatal stroke. With adjustments for the covariates in Table 2 applied, Cox regression showed a significant interaction between treatment and smoking for all cardiac end points (P = .04). The relative hazard rate for active vs placebo treatment was 0.49 (95% CI, 0.25-0.96; P = .04) in nonsmokers, but it was 1.38 (95% CI, 0.51-3.71; P = .52) in smokers.

At baseline, 748 men (48.5%) and 89 women (10.4%) reported regular alcohol consumption. In single regression (Table 1), alcohol intake was positively correlated with the incidence of stroke and all fatal and nonfatal cardiovascular end points. However, after adjustment for significant covariates, these associations weakened to a non-significant level (P values ranging from .35 to .93). In multiple Cox regression, the P values for the interaction terms between treatment and drinking alcohol ranged from .19 to .87.

NITRENDIPINE ONCE VS TWICE DAILY

Of 1253 patients allocated to active treatment, 735 remained on monotherapy with nitrrendipine and 518 proceeded to twice daily dosing; the mean daily doses of nitrrendipine in these 2 groups were 13.8 mg and 36.9 mg, respectively. Compared with the whole placebo group and with adjustments applied for the covariates listed in Table 2, the benefit of active treatment tended to be slightly larger in patients receiving twice daily dosing (Figure 3). However, only for cardiac end points the P value for the difference between the 2 dosing schemes of active nitrrendipine reached statistical significance; for the other end points the P values ranged from .14 to .65.

DIABETES MELLITUS

At enrollment 55 men and 43 women had diabetes mellitus. Of these 98 patients (4.1%), 21 had a history of diabetes mellitus and 90 had a fasting blood glucose level of 7.8 mmol/L (140 mg/dL); 2 patients were on a diabetic diet and 10 were taking oral antidiabetic drugs. In diabetic patients, compared with the 2296 nondiabetic patients, body mass index (calculated by the weight, in kilograms, divided by the height, in meters, squared) (25.4 vs 23.9, P < .001), blood glucose level (9.7 vs 5.3 mmol/L [174.7 vs 95.5 mg/dL]; P < .001), serum total cholesterol level (5.7 vs 5.1 mmol/L [220 vs 197 mg/dL]; P = .005) and systolic BP at enrollment (172.5 vs 170.2 mm Hg; P = .14) were higher. However, the percentage of patients with previous cardiovascular complications was similar in both groups (12.2% vs 11.2%; P = .75).

Diabetic and nondiabetic patients were treated similarly and their BP decreased to a similar extent (Table 3). At 2 years the net differences between the placebo and active treatment groups were 6.0 mm Hg systolic BP (95% CI, 1.5-13.5 mm Hg; P = .12) and 4.7 mm Hg diastolic BP (95% CI, 0.4-9.1 mm Hg; P = .04) in the diabetic patients; in the 2296 nondiabetic patients, these differences were 9.3 mm Hg (95% CI, 7.7-10.8 mm Hg; P < .001) and 3.1 mm Hg (95% CI, 2.3-3.9 mm Hg; P < .001), respectively. The P values for the differences in the net BP effects between diabetic and nondiabetic patients were .40 systolic and .47 diastolic.

After adjustment for the covariates listed in Table 2, active treatment showed a consistent trend in diabetic patients (Figure 4) in reducing total mortality (59%; P = .15), cardiovascular mortality (57%; P = .22), all cardiovascular end points (74%; P = .03), fatal and nonfatal stroke (45%; P = .42) and all cardiac end points (90%; P = .08). In the nondiabetic patients (Figure 4) active treatment significantly decreased total mortality (36%; P = .01) and all cardiovascular end points (34%, P = .01), while the same tendency was also observed for cardiovascular mortality (33%, P = .10) and total stroke (32%; P = .06). The P values of the interaction terms between active treatment and the presence of diabetes mellitus ranged from .15 to .88.

The incidence of all cardiovascular end points was also calculated separately for patients who continued to receive nitrrendipine monotherapy and for those patients who had any combination regimen of nitrrendipine, captopril, or hydrochlorothiazide (or matching placebos). In the placebo group (Table 3), the cardiovascular event rates in diabetic patients were approximately twice as high as in nondiabetic patients, regardless of the treatment regimen. In the actively treated diabetic patients, the excess cardiovascular risk was reduced to the rates observed in the nondiabetic patients; this was equally true in patients treated with only nitrrendipine as in those on other treatments (Table 3).
Finally, within-group analyses (Table 4) showed that in the placebo group diabetes mellitus significantly enhanced the risk of all end points, with relative hazard rates ranging from 2.23 for all-cause mortality to 3.36 for cardiovascular mortality. In the active treatment group the risk associated with diabetes mellitus was reduced to nonsignificant levels for total mortality and for the combined fatal and nonfatal end points; the relative hazard rates ranged from 0.78 to 2.03.

A major finding of this study was that in the within-group analysis diabetes at enrollment significantly raised the risk of all types of end points in the placebo group, whereas in the active treatment group the CIs of the corresponding relative hazard rates were wide and included unity except for cardiovascular mortality. Cox regression in all patients combined failed to show significant treatment-by-diabetes interaction terms, because the diabetic patients represented only 4.1% of the whole trial population. However, in terms of clinical relevance, our findings suggest that both the relative and the absolute benefit of active treatment were greater for diabetic than for nondiabetic patients. Indeed, the point estimate for the prevention of all cardiovascular end points was 59% in the diabetic patients and only 33% in the nondiabetic; in terms of absolute benefit, at the rates observed in the placebo group, treating 1000 patients for 5 years, could prevent 221 major cardiovascular end points in diabetic patients, but only 51 in the nondiabetic patients.

The Syst-China trial findings must also be interpreted considering the prior probability of a greater treatment effect in hypertensive diabetic patients as observed in the Syst-Eur trial.\(^6\) In the latter study 492 diabetic patients (10.5%) and 4203 nondiabetic patients (89.5%) were randomized to placebo or to active treatment initiated with the dihydropyridine nitrendipine (10-40 mg/d) with the possible addition of enalapril maleate (5-20 mg/d), hydrochlorothiazide (12.5-25.0 mg/d), or both drugs. In diabetic Syst-Eur patients, with adjustments for possible confounders applied, active treatment reduced all-cause mortality by 59%, cardiovascular mortality by 76%, all cardiovascular end points by 69%, fatal and nonfatal stroke by 73% and all cardiac end points by 63%; in the nondiabetic Syst-Eur patients, active treatment decreased all cardiovascular end points by 26% and fatal and nonfatal stroke by 38%.\(^9\) Active treatment reduced total mortality (\(P = .04\)), cardiovascular mortality (\(P = .02\)) and all cardiovascular endpoints (\(P = .01\)) significantly more for diabetic than for nondiabetic Syst-Eur patients. In terms of absolute benefit, the Syst-Eur trial showed that active treatment, per 1000 patients treated for 5 years, could prevent 178 major cardiovascular end points for diabetic patients, and 39 for nondiabetic patients.\(^9\) The Systolic Hypertension in the Elderly Program (SHEP)\(^10\) included 4736 men and women, aged 60 years or older, with isolated systolic hypertension (systolic BP 160-219 mm Hg and diastolic BP <90 mm Hg). At baseline, 583 patients (12.3%) had non-insulin-dependent diabetes mellitus, 4149 patients did not have diabetes, and 4 patients could not be classified.\(^11\) In the SHEP control group, the rate of all cardiovascular complications was 63.0 events per 1000 patient-years in the diabetic patients (\(n = 300\)) and 36.8 events per 1000 patient-years in nondiabetic patients (\(n = 2069\)); in the diabetic (\(n = 283\)) and nondiabetic (\(n = 2080\)) patients randomized to active treatment (chlorthalidone, 12.5-25 mg/d, with the possible addition of atenolol, 25-50 mg/d, or reserpine, 0.05-0.1 mg/d), these rates were reduced to 42.8 and 26.6 events per 1000 patient-years, respectively.\(^11\) Thus, in the SHEP trial, active treatment decreased the incidence of cardiovascular complications to the same extent (34%) in diabetic patients (95% CI, −54% to −6%) and in nondiabetic patients (95% CI, −45% to 21%).\(^11\) In the Hypertension Detection and Follow-up Program

### Table 3. Medication, Blood Pressure Reduction, and Incidence of All Cardiovascular End Points in Treated and Untreated Diabetic and Nondiabetic Patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Active Treatment(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetics ((n = 47))</td>
</tr>
<tr>
<td><strong>No. of Patients on Treatment (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Nitrendipine only</td>
<td>32 (68.1)</td>
</tr>
<tr>
<td>Other study medications(‡)</td>
<td>13 (27.7)</td>
</tr>
<tr>
<td>Open-label drugs</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>None or unknown</td>
<td>2 (4.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean (SD) Decrease in Blood Pressure at 2 Years, mm Hg</th>
<th>Cardiovascular End Points per 1000 Patient-Years, No. of End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>16.5 (16.7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.9 (9.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intention-to-treat</th>
<th>Only nitrendipine</th>
<th>Other study medications(‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76.4 (10)(^\dagger)</td>
<td>31.0 (84)</td>
<td>32.1 (5)(^\dagger)</td>
</tr>
<tr>
<td>Only nitrendipine</td>
<td>97.3 (8)(^\dagger)</td>
<td>34.0 (49)</td>
</tr>
<tr>
<td>Other study medications(‡)</td>
<td>42.1 (2)</td>
<td>26.3 (29)</td>
</tr>
</tbody>
</table>

*Significance levels for the comparison between placebo and active treatment; a indicates \(P = .07\); b, \(P = .05\); c, \(P = .01\); d, \(P = .001\).  
\(\dagger\)Indicates a difference (\(P = .08\)) between diabetic and nondiabetic patients of the same treatment group.  
\(\#\)Any combination of nitrendipine, captopril and/or hydrochlorothiazide, or captopril only; the mean (SD) daily doses in the active treatment group were 19.5 (9.8) mg for nitrendipine, 26.7 (15.4) mg for captopril, and 19.8 (13.9) mg for hydrochlorothiazide.
The stepped-care treatment regimen also started with a diuretic (chlorthalidone, 25-100 mg/d). In all, 1079 (9.9%) of the HDFP participants showed evidence of diabetes at enrollment. In the 9861 nondiabetic patients (90.1%), the mortality rate was significantly lower in the stepped-care (intervention) group than in the referred-care (control) group; the relative benefit amounted to 17.4% (60.1 vs 72.8 deaths per 1000 patient-years). In contrast, in the diabetic HDFP patients there was little (0.8%) difference between the death rates in the stepped-care and referred-care groups (105.8 vs 106.6 deaths per 1000 patient-years).

In diabetic and nondiabetic patients, cardiovascular benefit was equally observed in the patients continuing to receive monotherapy with nifedipine and in those progressing to combined treatment with nifedipine plus captopril, hydrochlorothiazide, or both drugs. These findings are in keeping with the Syst-Eur report, in which diabetic patients treated with thiazides may be particularly vulnerable. In addition, calcium channel blockers may provide better cardiovascular protection than therapy starting with a thiazide. This may be due to the absence of metabolic side effects, such as glucose intolerance and perturbation of the serum lipid profile, to which diabetic patients treated with thiazides may be particularly vulnerable. In addition, calcium channel blockers may provide better cardiovascular protection than thiazides may be further investigated. The ongoing Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) will be informative in this regard, because nearly one third of the ALLHAT patients have diabetes.

The prevalence of diabetes in the Syst-China trial (4.1%) was approximately only one third of that observed in the SHEP and Syst-Eur trials. In the 1980s and early 1990s studies from the Chinese Mainland showed a low prevalence of diabetes, ranging from 0.15% in Guizhou and 0.33% in Guangdong to almost 1% in cities such as Beijing, Shanghai, and Ningxia. More recent epidemiological data demonstrated age-adjusted prevalence rates of 3.6% for diabetes and 4.2% for impaired glucose tolerance in 213 515 subjects aged 25 to 64 years. These numbers confirm the rapid rise in diabetes that has occurred in China in the past 10 years and underscore the possible implications of the present findings for the treatment of hypertensive Chinese patients with type 2 diabetes.

The present analysis identified male sex and previous cardiovascular complications as significant and independent cardiovascular risk factors. Stratification for these characteristics made it possible to test a priori whether the effects of treatment were similar in these 4 strata. Cox regression with adjustments applied for significant covariates, suggested that active treatment may reduce total mortality more (P = .06) in women, but that it may prevent stroke better (P = .07) in men. Whether these findings are influenced by the higher inclusion of men (~66%) in the Syst-China study than in the other trials in isolated systolic hypertension (~33%) is uncertain. However, in Syst-China and in the other trials in isolated systolic hypertension men and women at risk and with

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**Figure 4.** Relative hazard rates (active treatment vs placebo) in diabetic and nondiabetic patients with adjustments for the covariates listed in Table 2. Asterisk indicates P for interaction; dagger, adjusted for sex, age, diabetes mellitus, cardiovascular (CV) complications, enrollment systolic and diastolic blood pressure, smoking, residence in northern China.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Patients (n = 98)</th>
<th>Nondiabetic Patients (n = 2296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.41*</td>
<td>0.64</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>0.43*</td>
<td>0.67</td>
</tr>
<tr>
<td>CV End Points</td>
<td>0.26</td>
<td>0.66</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.55</td>
<td>0.68</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.13</td>
<td>0.76</td>
</tr>
</tbody>
</table>

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**Table 4. Relative Hazard Rates at Enrollment in the Study for Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo Adjusted†</th>
<th>Active Treatment Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>2.23 (1.06-4.68)</td>
<td>2.03 (0.82-5.01)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>3.36 (1.39-8.10)</td>
<td>3.24 (1.04-10.06)</td>
</tr>
<tr>
<td>All cardiovascular end points</td>
<td>2.53 (1.29-4.94)</td>
<td>1.55 (0.61-3.91)</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>2.65 (1.12-6.27)</td>
<td>1.60 (0.56-4.63)</td>
</tr>
<tr>
<td>Fatal and nonfatal</td>
<td>2.99 (1.01-8.85)</td>
<td>0.78 (0.09-7.05)</td>
</tr>
<tr>
<td>cardiac end points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative hazard rates, presented with 95% confidence intervals (levels of statistical significance), were adjusted for sex, age, cardiovascular complications, systolic and diastolic blood pressure at enrollment in the study, smoking, and residence in northern China.
out previous cardiovascular complications, irrespective of race, all benefited from antihypertensive drug treatment.

The question whether the effects of antihypertensive drug treatment are preserved in very old patients has important public health implications in view of the increasing longevity of populations worldwide. In our study the treatment-by-age interaction was not significant. These findings agree with those in 650 patients, aged 80 years or older, randomized in the SHEP trial, in whom the relative risk of stroke on active treatment compared with...
In elderly Chinese patients with isolated systolic hypertension, stepwise antihypertensive drug treatment, starting with the dihydropyridine calcium channel blocker nifedipine, improves prognosis. The benefit was particularly evident in diabetic patients; for cardiac end points it tended to be larger in nonsmokers. Otherwise, the benefit of active treatment was not significantly influenced by the characteristics of the patients at enrollment in the study.

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REFERENCES


