

THERAPEUTICS

# Diuretic-based therapy reduced cardiovascular mortality in older patients with isolated systolic hypertension and diabetes

Kostis JB, Wilson AC, Freudenberger RS, et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol.* 2005;95:29-35.

**QUESTION**

In older patients with isolated systolic hypertension (ISH) with or without diabetes, what is the long-term effectiveness of a diuretic-based, stepped-care antihypertensive therapy compared with placebo?

**METHODS**

**Design:** Randomized placebo-controlled trial (Systolic Hypertension in the Elderly Program [SHEP]).

**Allocation:** Concealed.\*

**Blinding:** Blinded {clinicians, patients, data collectors, outcome assessors, and data analysts}†.\*

**Follow-up period:** Median 14.3 years.

**Setting:** {16 clinical centers in the United States}†.

**Patients:** 4736 patients ≥ 60 years of age who had ISH (systolic blood pressure [BP] 160 to 219 mm Hg and diastolic BP < 90 mm Hg). Patients with type 1 diabetes or those who required diuretic therapy were excluded.

**Intervention:** Stepped-care therapy with chlorthalidone, 12.5 to 25.0 mg/d (*n* = 2363), or placebo (*n* = 2369) to achieve a systolic BP decrease ≥ 20 mm Hg to < 160 mm Hg. If the goal BP was not reached, atenolol or matching placebo was added.

**Outcomes:** All-cause mortality and cardiovascular (CV) mortality (included the following causes of death: stroke, rapid or sudden death, myocardial infarction, left ventricular failure, and other CV causes).

**Patient follow-up:** 4732 patients (> 99%) (mean age 72 y, 58% women, 17% diabetes). Analysis was by intention to treat.

**MAIN RESULTS**

At the end of the extended follow-up, the stepped care and placebo groups did not differ for all-cause mortality (Table). Fewer patients who received stepped care died from CV causes than did those who received placebo (Table). During follow-up, diabetes developed in 258 patients (13%) in the stepped-care group and in 169 patients (8.7%) in the placebo group (*P* < 0.001). Patients with diabetes at baseline had higher mortality rates than did those without diabetes at baseline in both the stepped care and placebo groups. Patients who developed diabetes during follow-up had higher mortality rates than did those who did not develop diabetes in the placebo group (47% vs 40%, hazard ratio [HR] 1.3, 95% CI 1.1 to 1.7) but not in the stepped-care group (39% vs 40%, HR 1.2, CI 0.9 to 1.4). A similar pattern was seen for CV mortality. Patients who

had diabetes at baseline or who developed diabetes during follow-up and received stepped care had lower all-cause (44% vs 52%, HR 0.8, CI 0.7 to 0.95) and CV (20% vs 29%, HR 0.7, CI 0.5 to 0.8) mortality rates than did those who received placebo.

**CONCLUSIONS**

In older patients with isolated systolic hypertension, diuretic-based, stepped-care antihypertensive therapy reduced long-term cardiovascular mortality. Patients who had diabetes at baseline or who developed diabetes during follow-up and received stepped care had lower mortality rates than did those who received placebo.

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\*See Glossary.

†Information provided by author.

**Stepped care with chlorthalidone vs placebo for older patients with isolated systolic hypertension at median 14.3 years‡**

Outcomes	Stepped care	Placebo	Adjusted hazard ratio (95% CI) <sup>§</sup>	RRR (CI)	NNT (CI)
All-cause mortality	41%	43%	0.92 (0.84 to 1.01)	5.9% (-0.7 to 12)	Not significant
Cardiovascular mortality	19%	22%	0.85 (0.75 to 0.97)	13% (2.5 to 23)	36 (21 to 186)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from hazard ratios in article.

§Adjusted for 12 baseline demographic and clinical factors.

**COMMENTARY**

The study by Kostis and colleagues reports the long-term effects of diuretic-based therapy in the SHEP trial. During the extended 10-year follow-up, diuretic-based therapy was associated with a lower rate of CV mortality, which was not observed during the 4.3-year double-blind phase of the study. These results add more support to the JNC VII recommendation to use thiazide-type diuretics as the initial therapy for uncomplicated hypertension.

It is clear from recent, large hypertension trials that several newer classes of drugs, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium-channel blockers, reduce the complications of hypertension and can be used as first-line therapy, but diuretics are as effective and cost less (1). The use of diuretics as first-line therapy for uncomplicated hypertension was shown to result in substantial cost savings (2).

The uncontrolled nature of the extended follow-up period for this study is its most important limitation. The analysis is based on a conservative assumption that after the double-blind phase of the SHEP trial, most patients in the diuretic-based therapy group continued

diuretic therapy, whereas a smaller proportion of those randomized to placebo initiated diuretic-based therapy.

During the double-blind phase of the SHEP trial, mean systolic and diastolic BP were lower in the chlorthalidone group by 11.1 mm Hg and 3.4 mm Hg, respectively, which could explain the better long-term outcomes associated with chlorthalidone. Additional support for this explanation comes from the recently published VALUE trial, in which amlodipine was superior to valsartan in BP control and in preventing myocardial infarction (3). Both SHEP and VALUE suggest that the degree of BP control is the most important predictor of favorable CV outcomes regardless of the antihypertensive agent used.

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**References**

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3. Julius S, Kjeldsen SE, Weber M, et al. *Lancet.* 2004;363:2022-31.