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Article of Interest

Kostis JB, et al. Long Term Effect of Diuretic-Based Therapy on Fatal Outcomes in Subjects with Isolated Systolic Hypertension With and Without Diabetes. Am J Card. 2005. ([Click to Access](#))

Context and Study Objective

Diuretic-based anti-hypertensive therapy is associated with an increased incidence of diabetes but improved clinical outcomes nonetheless. While the landmark [Systolic Hypertension in the Elderly Program \(SHEP\)](#) study showed chlorthalidone to be superior to placebo with respect to short term cardiovascular (CV) events, Kostis assessed the incidence of new onset diabetes mellitus (DM) and its effects on long term clinical outcomes.

Design, Setting, and Participants

The randomized SHEP trial evaluated the benefits of improved blood pressure (BP) control with a chlorthalidone (up to 25mg) based regimen among elderly hypertensives. Upon termination at 4.5 years, all cause mortality was determined after an additional 10 years. Because outcomes from the extended followup were determined retrospectively, BP and incidence of DM were not available; anti-hypertensive selection was not dictated.

Results

- Study characteristics: 4700 patients. Mean age 72. Entry BP 170/77 mm Hg. Study Completion: active 144/68 mm Hg, placebo 155/71 mm Hg. Entry potassium was 4.5mEq/L and fell by 0.3mEq/L more in the active arm.

- Upon SHEP termination at 4.5 yrs, the incidence of new onset DM was 12% in the chlorthalidone and 9.0% in the placebo arm.

- At 14.5 years, all cause mortality and cardiovascular mortality were lower among the chlorthalidone group.

- In the chlorthalidone arm, those who developed DM did not have more CV events compared to those who did not develop DM. Conversely, among placebo treated patients, those with developed DM had worse health outcomes than those who did not.

Impact of Treatment with Chlorthalidone (vs Placebo)

Pts needed to treat for 4 years resulting in 1 new case of DM	33
Pts needed to treat for 14 years to prevent 1 death	50
Pts needed to treat for 14 years to prevent 1 death from CV dz	37

Clinical Perspective

- Clinicians often limit diuretic use to avoid precipitating DM. However, given the high rate of new onset diabetes among placebo controlled patients, this trial demonstrates that the majority of newly diagnosed cases are not attributable to thiazide use.

- Even among the minority of patients who develop DM on diuretics, clinical outcomes are not worse than treated patients who didn't develop diabetes.

- While treating 50 patients for 14 years to prevent one death may seem underwhelming, improving overall survival is *the* most difficult endpoint to achieve. Few therapies in the modern era have done so. These results are particularly impressive given the marked decline in BP among the placebo arm.

- Elevations in fasting blood sugar are multifactorial and include the severity of diuretic induced hypokalemia and the use of β -blockers such as atenolol.

- Shortcomings: Since SHEP, metabolically neutral agents (CCBs, ACEi, ARBs) have become widely available with the [ALLHAT](#) trial exploring whether similar BP targets could be achieved without the attendant metabolic effects.