Diuretics reduced cardiovascular disease events in diabetic and nondiabetic patients

ACP Journal Club. 1997 May-Jun;126:57. ***(All 1997 articles were reviewed for relevancy, and abstracts were revised in October 2002.)***
Evidence-Based Medicine. 1997 May-Jun;2:87.
Curb JD, Pressel SL, Cutler JA, et al. **Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group.** JAMA. 1996;276:1886-92.[PubMed ID: 8968014]

Objective

To determine the efficacy of diuretic-based (chlorthalidone) antihypertensive treatment in patients with type 2 diabetes mellitus compared with nondiabetic patients.

Design

Subgroup analysis of a 5-year randomized, double-blind, placebo-controlled trial (Systolic Hypertension in the Elderly Program [SHEP]).

Setting

United States.

Patients

4736 patients (mean age 62 y, 57% women) who were ≥60 years of age and had isolated systolic hypertension (average systolic blood pressure [SBP] ≥160 mm Hg and diastolic blood pressure < 90 mm Hg during 2 baseline measurements). Exclusion criteria were SBP ≥220 mm Hg, major cardiovascular disease (CVD), other major disease, or such medical management problems as depression or diabetes requiring insulin. Of the 4732 patients included in the analysis, 583 patients (12.3%) were considered to have diabetes because of a diagnosis of diabetes, receipt of oral hypoglycemic agents, or a fasting serum glucose level of ≥7.8 mmol/L.

Intervention

Patients were allocated to oral chlorthalidone, 12.5 mg/d up to a maximum 25 mg/d (n = 2363 [283 patients with diabetes]), or placebo (n = 2369 [300 patients with diabetes]). Atenolol or reserpine was added if goal SBP was not attained.

Main outcome measures

Combined nonfatal and fatal stroke, nonfatal myocardial infarction (MI) or cardiac death, major coronary heart disease (CHD), and major CVD.

Main results

In patients with diabetes, major CVD event rates were lower in patients who received diuretics compared with those who received placebo {P = 0.03}* (Table). In patients without diabetes, CVD event rates were lower in diuretic recipients than in placebo recipients {P < 0.001}* (Table). The

rate of nonfatal MI and fatal CHD in patients with diabetes was lower for diuretic recipients than for placebo recipients {*P* = 0.035}* (Table).

Conclusion

In terms of absolute risk reduction, diuretic-based antihypertensive therapy was more efficacious in patients with type 2 diabetes mellitus than in patients without diabetes.

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*Numbers calculated from data in article.

Diuretics vs placebo on cardiovascular disease outcomes in older patients with isolated systolic hypertension at 5 y†

Outcomes in patients with diabetes	Diuretics	Placebo	RRR (95% CI)	NNT (CI)
Major CVD event	20%	28%	27% (2 to 46)	12 (7 to 169)
Nonfatal MI and fatal CHD	6%	11%	56% (33 to 96)	20 (10 to 281)
Outcomes in patients without diabetes			**RRR (CI)**	**NNT (CI)**
Major CVD event	11%	16%	30% (19 to 40)	20 (14 to 36)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary

The treatment of hypertension in patients with diabetes mellitus should decrease the rate of vascular complications with minimal side effects. In a previous cohort study (1), the use of

thiazide diuretics in patients with type 1 diabetes mellitus and hypertension was associated with increased cardiovascular mortality when compared with a group of patients with type 1 diabetes and untreated hypertension. This has led to a recommendation for the use of angiotensin-converting enzyme inhibitors and β-blockers as the first line of treatment for hypertension in diabetes and avoidance of thiazide diuretics. The deleterious effect of thiazides was thought to be caused by hypokalemia, worsening dyslipidemia, increased insulin resistance, or unknown mechanisms.

The analysis from the SHEP trial did not find an increased rate of cardiovascular complications; on the contrary, it found a decrease that was more marked in diabetic patients than in nondiabetic, hypertensive patients. The first and most important difference between the 2 studies is that, in the SHEP trial, low-dose chlorthalidone was used. The antihypertensive effect of this agent at lower doses is similar to that at higher doses but the rate of side effects is lower. Other important differences between the previous study and the SHEP study are that the latter included only older patients with isolated systolic hypertension and excluded patients who required insulin.

Although cardiovascular events were decreased in the SHEP study, the diabetic patients treated with chlorthalidone had a higher frequency of sexual dysfunction (in men), hyperglycemia, hypokalemia, hyperuricemia, and hyponatremia than the diabetic patients who received placebo.

This study shows that thiazide diuretics should be considered a viable antihypertensive therapy in diabetic patients. They should ideally be used, however, in low doses similar to those used in this study—12.5 to 25 mg/d.

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Reference

1. Warram JH, Laffel LM, Valsania P, Christlieb AR, Krolewski AS. Excess mortality associated with diuretic therapy in diabetes mellitus. Arch Intern Med. 1991;151:1350-6.[PubMed ID: 1823530]