



Chlorthali-D'OH!: What is the best thiazide diuretic for hypertension?

CLINICAL QUESTION

Which thiazide diuretic is best at reducing cardiovascular events in hypertension?

BOTTOM LINE

Chlorthalidone and hydrochlorothiazide reduce the risk of cardiovascular events similarly, but the risk of hypokalemia hospitalization increases from 1.1% with hydrochlorothiazide to 1.5% with chlorthalidone over 2.4 years.

EVIDENCE

- Results statistically different unless indicated.
- One recent systematic review with meta-analysis included 4 randomized controlled trials (RCTs) and 4 observational studies comparing the effects of hydrochlorothiazide and chlorthalidone in patients with hypertension.¹ The one RCT reporting cardiovascular events is described below.²
- Open-label, primary-care RCT, 13,523 patients (average age 72, systolic blood pressure 139 mm Hg) taking hydrochlorothiazide 25-50 mg/day (95% received 25 mg/day) to either switch to chlorthalidone 12.5-25 mg/day or continue their current hydrochlorothiazide dose.² After 2.4 years:
 - No statistical difference in cardiovascular events, all-cause death, or blood pressure;
 - More patients receiving chlorthalidone (versus hydrochlorothiazide):
 - Potassium <3.1 mmol/L: 5.0% versus 3.6%

- Hospitalized for hypokalemia: 1.5% versus 1.1%
 - Crossed over to the other thiazide: ~15% versus ~4%
- Limitations: Predominantly (97%) male patients; excluded patients receiving hydrochlorothiazide in a combination pill; benefit in subgroup with myocardial infarction/stroke history is likely a chance finding;³ exclusively enrolled patients already taking hydrochlorothiazide and continued or switched (should not affect relative efficacy between the two drugs).
- These findings are consistent with the meta-analysis results, except that the meta-analysis found chlorthalidone provided greater blood pressure reduction than hydrochlorothiazide.
- No head-to-head clinical-outcome comparisons with indapamide.

CONTEXT

- A previous Tools for Practice suggested hydrochlorothiazide might be inferior to chlorthalidone,⁴ cautioning that this was based on trials of surrogate outcomes and observational studies.
- Canadian hypertension guidelines recommend thiazides first-line, with chlorthalidone or indapamide preferred based on an indirect comparison of placebo-controlled trials.⁵
- Thiazides used for hypertension reduce the risk of myocardial infarction, stroke, heart failure, and death.^{6,7}
- Hydrochlorothiazide combination products, which increase adherence and patient convenience, are widely available.⁸
- Hydrochlorothiazide is associated with an increased risk of squamous cell carcinoma (estimated absolute risk increase of 0.01% per year).^{9,10} It is unclear if this association is causal, or differs between thiazides.

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