

# Best thiazide diuretic for hypertension

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## Clinical question

Is hydrochlorothiazide (HCTZ) a better choice than chlorthalidone for hypertension?

## Evidence

No trials compare HCTZ with other thiazide diuretics in terms of cardiovascular or mortality outcomes. We must rely on less rigorous study designs and other outcomes.

- Chlorthalidone reduces systolic blood pressure (BP) better than HCTZ at equivalent doses with similar effects on potassium levels<sup>1</sup>:  
-25 mg of chlorthalidone, compared with 50 mg of HCTZ, provided superior BP reduction overall (12 vs 7 mm Hg on 24-hour monitor) and at nighttime (13 vs 6 mm Hg).<sup>2</sup>
- Retrospective (and thus not definitive) analysis of the MRFIT trial found that the chlorthalidone-based regimen reduced mortality compared with the HCTZ-based regimen (hazard ratio 0.79, 95% CI 0.68 to 0.92,  $P=.0016$ ).<sup>3</sup>
- Large trials using chlorthalidone (like ALLHAT<sup>4</sup> and SHEP<sup>5</sup>) have demonstrated reductions in cardiovascular end points; evidence for HCTZ is less robust.
- A network meta-analysis of 5 trials<sup>6</sup> comparing chlorthalidone with other thiazides did not find differences in cardiovascular outcomes. However,  
-these were indirect comparisons and  
-the “other thiazides” were not just HCTZ, as many reviewers assumed: 2 were HCTZ combined with potassium-sparing diuretics; 1 was indapamide (not HCTZ).

## Context

- Thiazide diuretics are first-line for hypertensive patients without compelling indications for alternate drugs.<sup>7-9</sup>
- Meta-analysis<sup>10</sup> of 19 trials found 24-hour BP was higher with 12.5- to 25-mg doses of HCTZ compared with other antihypertensive drugs (systolic BP 4.5 to 6.2 mm Hg higher, diastolic BP 2.9 to 6.7 mm Hg higher).
- Chlorthalidone has a longer half-life than HCTZ (50 to 60 vs 9 to 10 hours), which might explain the superior BP control, especially at nighttime.<sup>11</sup>
- The advantage of HCTZ is its availability in many combination preparations, which can improve adherence.<sup>12</sup>
- Indapamide is another thiazide-like diuretic with good evidence for reduction in cardiovascular end points as first- or second-line antihypertensive therapy.<sup>13,14</sup>

## Bottom line

Available data suggest HCTZ is at best equal to and very likely inferior to chlorthalidone for improving BP and clinical outcomes. Consider chlorthalidone when initiating thiazide diuretics for hypertension.

## Implementation

Prescribe 12.5 mg of chlorthalidone daily; this can be increased to 25 mg daily (quarter and half a 50-mg tablet, respectively). Higher doses tend to cause more side effects (including hypokalemia) but minimal further BP reduction.<sup>15</sup> Precautions and bloodwork monitoring for chlorthalidone are similar to those for HCTZ. Patients requiring antihypertensives should be reminded that dietary sodium restriction (< 1500 mg/d)<sup>16</sup> remains key to BP management—handouts could be given with each prescription.<sup>17</sup>

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The opinions expressed in this Tools for Practice article are those of the authors and do not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.

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