Is hydrochlorothiazide the best thiazide diuretic for hypertension?

Clinical Question: When choosing a thiazide diuretic for hypertension, is hydrochlorothiazide (HCTZ) the best choice?

Evidence:

No trials specifically compare hydrochlorothiazide (HCTZ) to other thiazide diuretics on cardiovascular or mortality outcomes. We must rely on less rigorous study designs and other outcomes:

- Meta-analysis\(^1\) (19 trials): Compared to patients treated with other major antihypertensive drug classes, 24-hour BP was higher with 12.5-25mg HCTZ
  - Systolic 4.5-6.2 mmHg and diastolic 2.9-6.7mmHg higher
- Chlorthalidone reduces systolic BP better than HCTZ at equivalent doses with similar effects on potassium.\(^2\)
- Chlorthalidone 25mg, compared to HCTZ 50mg, provided superior BP 24-hr (12 versus 7mmHg) and nighttime (13 versus 6mmHg).\(^3\)
- Retrospective (and thus not considered definitive) analysis of the MRFIT trial: Chlorthalidone-based regimen reduced mortality versus HCTZ-based regimen.\(^4\)
- Major trials using chlorthalidone (like ALLHAT\(^5\) and SHEP\(^6\)) have demonstrated reductions in cardiovascular endpoints whereas HCTZ trials have mixed results.
- Meta-analysis of 5 trials\(^7\) comparing chlorthalidone to other thiazides did not find differences in cardiovascular outcomes. However,
  - These were indirect comparisons
  - Other thiazides were not just HCTZ (as many reviewers assumed)
    - Two were HCTZ combined with potassium sparing diuretics.
    - One was indapamide (not HCTZ).

Context:

- Thiazide diuretics are considered a first line drug for hypertensive patients without a compelling indication for an alternate drug.\(^8\)-\(^11\)
- Indapamide is another thiazide-like diuretic with good evidence as first-line\(^12\) or second-line antihypertensive.\(^13\)
- Chlorthalidone has a longer half-life than HCTZ (50-60 versus 9-10 hours), which may explain the superior BP control.\(^14\)
- HCTZ has one advantage in that it is available in many combination preparations, and this facilitates a reduction in overall drug burden.
**Bottom-line:** The available data suggest that chlorthalidone is at least equal to and very likely superior to HCTZ in reducing BP and improving clinical outcomes. Consider prescribing chlorthalidone (12.5mg increasing to 25mg daily) when initiating thiazide diuretic therapy for hypertension.

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