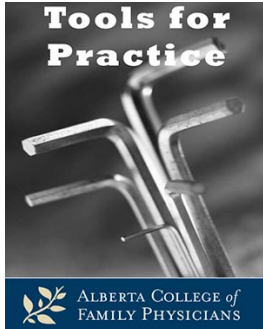


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Three drugs and still hypertensive: What's Left?

Clinical Question: Which drug lowers blood pressure (BP) best in patients with resistant hypertension?

Bottom-line: Spironolactone provides the largest BP reduction for "4th line therapy" in resistant hypertension (10/4 mmHg), causing an additional one in every three patients treated to reach target. Potassium rises on average ~0.4 mmol/L (and should be monitored), causing around 2% to stop due to hyperkalemia (≥ 5.5 mmol/L). Hard outcome data is lacking.

Evidence:

- Only data on BP (not hard outcomes).
 - High-quality cross-over Randomized Controlled Trial (RCT)¹ of 348 patients with resistant hypertension. Each patient cycled through six weeks low-dose and six weeks high-dose of spironolactone 25-50 mg, doxazosin 4-8 mg, bisoprolol 5-10 mg, and placebo.
 - Over both doses, average reduction in office BP versus placebo: Spironolactone 10/4 mmHg, bisoprolol 5/5 mmHg, or doxazosin 5/3 mmHg.
 - High dose decreased systolic BP more than low dose: Spironolactone 5 mmHg, bisoprolol 2 mmHg, or doxazosin 1 mmHg.
 - Patients achieving target home systolic BP (<135 mmHg): Spironolactone 58%, bisoprolol 44%, doxazosin 42%, placebo 24%.
 - Number Needed to Treat (NNT) versus placebo: Spironolactone NNT=3, bisoprolol or doxazosin NNT=6.
 - Serum K >6.0 in 2% of patients with spironolactone.
 - Notes: Excluded patients with abnormal serum K or eGFR <45 mL/min.
 - Three systematic reviews²⁻⁴ missed studies and pooled inappropriately (heterogeneity $\geq 90\%$).
 - Five remaining spironolactone (generally 25 mg/day) RCTs (17-167 patients, 4-16 weeks):⁵⁻⁹
 - Two smallest trials (Iran and Cameroon) with randomization concerns had largest BP changes (19-21/10-17 mmHg): Likely unreliable.^{8,9}
 - Three remaining RCTs: Spironolactone reduced BP 10-16/3-7 mmHg.⁵⁻⁷

- Serum K increases ~0.3-0.4 mmol/L⁵⁻⁹ and ~2% stop due to hyperkalemia (K \geq 5.5 mmol/L).^{5,7}

Context:

- Resistant hypertension is defined as office BP \geq 140/90 mmHg while receiving (and adherent to) \geq 3 BP-lowering drugs of different classes at optimal doses.^{10,11}
 - Thiazides, ACE/ARB, and dihydropyridine calcium channel blockers all have evidence for reducing cardiovascular endpoints.
- Prevalence of resistant hypertension is likely around 13% or less.¹²
- Lower baseline potassium may be associated with better response to spironolactone.^{7,13}

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Disclosure:

Authors do not have any conflicts to disclose.

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