Q. How effective is spironolactone for treating resistant hypertension?

EVIDENCE-BASED ANSWER

Spironolactone markedly lowers systolic and diastolic BP
A statistically significant reduction in SBP occurred in the spironolactone group compared with the placebo group (weighted mean difference [WMD] = −16.7 mm Hg; 95% confidence interval [CI], −27.5 to −5.8 mm Hg). DBP also decreased (WMD = −6.11 mm Hg; 95% CI, −9.34 to −2.88 mm Hg).

Because significant heterogeneity was found in the initial pooled results ($I^2 = 96\%$ for SBP; $I^2 = 85\%$ for DBP), investigators performed an analysis that excluded a single study with a small sample size. The re-analysis continued to show significant reductions in SBP and DBP for spironolactone compared with placebo (SBP: WMD = −10.8 mm Hg; 95% CI, −13.16 to −8.43 mm Hg; DBP: WMD = −4.62 mm Hg; 95% CI, −6.05 to −3.2 mm Hg; $I^2 = 35\%$), confirming that the excluded trial was the source of heterogeneity in the initial analysis and that spironolactone continued to significantly lower BP for the treatment group compared with controls.

Add-on treatment with spironolactone also reduces BP
A 2016 meta-analysis of 5 RCTs with a total of 553 patients examined the effectiveness of add-on treatment with spironolactone (25-50 mg/d) for patients with resistant hypertension, defined as failure to achieve BP < 140/90 mm Hg despite treatment with 3 or more BP-lowering drugs, including one diuretic. Spironolactone was compared with placebo in 4 trials and with ramipril in the remaining study. The follow-up periods were 8 to 16 weeks. Researchers separated BP outcomes into 24-hour ambulatory systolic/diastolic BPs and office systolic/diastolic BPs.

The 24-hour ambulatory BPs were significantly lower in the spironolactone group compared with the control group (24-hour SBP: WMD = −10.5 mm Hg; 95% CI, −12.3 to −8.71 mm Hg; 24-hour DBP: WMD = −4.09 mm Hg; 95% CI, −5.28 to −2.91 mm Hg).
No significant heterogeneity was noted in these analyses.

Office-based BPs also were markedly reduced in spironolactone groups compared with controls (office SBP: WMD = −17 mm Hg; 95% CI, −25 to −8.95 mm Hg); office DBP: WMD = −6.18 mm Hg; 95% CI, −9.3 to −3.05 mm Hg). Because the office-based BP data showed significant heterogeneity (I² = 94% for SBP and 84.2% for DBP), 2 studies determined to be of lower quality caused by lack of detailed methodology were excluded from analysis, yielding continued statistically significant reductions in SBP (WMD = −11.7 mm Hg; 95% CI, −14.4 to −8.95 mm Hg) and DBP (WMD = −4.07 mm Hg; 95% CI, −5.6 to −2.54 mm Hg) compared with controls. Heterogeneity also decreased when the 2 studies were excluded (I² = 21% for SBP and I² = 59% for DBP).

How spironolactone compares with alternative drugs
A 2017 meta-analysis of 5 RCTs with 662 patients evaluated the effectiveness of spironolactone (25-50 mg/d) on resistant hypertension in patients taking 3 medications compared with a control group—placebo in 3 trials, placebo or bisoprolol (5-10 mg) in 1 trial, and an alternative treatment (candesartan 8 mg, atenolol 100 mg, or alpha methylldopa 750 mg) in 1 trial. Follow-up periods ranged from 4 to 16 weeks. Researchers evaluated changes in office and 24-hour ambulatory or home BP and completed separate analyses of pooled data for spironolactone compared with placebo groups, and spironolactone compared with alternative treatment groups.

Investigators found a statistically significant reduction in office SBP and DBP among patients taking spironolactone compared with control groups (SBP: WMD = −15.7 mm Hg; 95% CI, −20.5 to −11 mm Hg; DBP: WMD = −6.21 mm Hg; 95% CI, −8.33 to −4.1 mm Hg). A significant decrease also occurred in 24-hour ambulatory home SBP and DBP (SBP: MD = −8.7 mm Hg; 95% CI, −8.79 to −8.62 mm Hg; DBP: WMD = −4.12 mm Hg; 95% CI, −4.48 to −3.75 mm Hg).

Patients treated with spironolactone showed a marked decrease in home SBP compared with alternative drug groups (WMD = −4.5 mm Hg; 95% CI, −4.63 to −4.37 mm Hg), but alternative drugs reduced home DBP significantly more than spironolactone (WMD = 0.6 mm Hg; 95% CI, 0.55-0.65 mm Hg). Marked heterogeneity was found in these analyses, and the authors also noted that reductions in SBP are more clinically relevant than decreases in DBP.

Recommendations
The 2017 American Heart Association/American College of Cardiology evidence-based guideline recommends considering a mineralocorticoid receptor agonist to treatment regimens for resistant hypertension when: office BP remains ≥ 130/80 mm Hg; the patient is prescribed at least 3 antihypertensive agents at optimal doses including a diuretic; pseudoresistance (nonadherence, inaccurate measurements) is excluded; reversible lifestyle factors have been addressed; substances that interfere with BP treatment (such as nonsteroidal anti-inflammatory drugs and oral contraceptive pills) are excluded; and screening for secondary causes of hypertension is complete.

The United Kingdom's National Institute for Health and Care Excellence (NICE) evidence-based guideline recommends considering spironolactone 25 mg/d to treat resistant hypertension if the patient’s potassium level is 4.5 mmol/L or lower and BP is higher than 140/90 mm Hg despite treatment with an optimal or best-tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus a calcium-channel blocker and diuretic.

Editor’s takeaway
The evidence from multiple RCTs convincingly shows the effectiveness of spironolactone. Despite the SOR of C because of a disease-oriented outcome, we do treat to blood pressure goals, and therefore, spironolactone is a good option.

References

