ONLINE EXCLUSIVE

Q/ How effective is spironolactone for treating resistant hypertension?

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EVIDENCE-BASED ANSWER

A/ **VERY EFFECTIVE.** Spironolactone reduces systolic blood pressure (SBP) by 11 to 17 mm Hg and diastolic blood pressure (DBP) by up to 6 mm Hg in patients with resistant hypertension taking 3 or more medications (strength of recommendation [SOR]: **C**, meta-analysis of randomized controlled trials [RCTs] of disease-oriented evidence).

Evidence summary

A 2017 meta-analysis of 4 RCTs (869 patients) evaluated the effectiveness of prescribing spironolactone for patients with resistant hypertension, defined as above-goal blood pressure (BP) despite treatment with at least 3 BP-lowering drugs (at least 1 of which was a diuretic).[1] All 4 trials compared spironolactone 25 to 50 mg/d with placebo. Follow-up periods ranged from 8 to 16 weeks. The primary outcomes were systolic and diastolic BPs, which were evaluated in the office, at home, or with an ambulatory monitor.

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.[2] 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).

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Spironolactone reduces systolic blood pressure by 11 to 17 mm Hg and diastolic blood pressure by up to 6 mm Hg in patients with resistant hypertension taking 3 or more medications.

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 (I^2 = 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 (I^2 = 21% for SBP and I^2 = 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 methyldopa 750 mg) in 1 trial.[3] 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 adding 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.[4]

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.[5]

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. **JFP**

References

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