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Resistant hypertension? Time to consider this fourth-line drug

For most adults with resistant hypertension, spironolactone is superior to doxazosin and bisoprolol as an adjunct to triple therapy.

PRACTICE CHANGER

When a triple regimen of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide diuretic fails to achieve the target blood pressure, try adding spironolactone.

STRENGTH OF RECOMMENDATION

C: Based on a high-quality disease-oriented randomized controlled trial.¹

Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386:2059-2068.

ILLUSTRATIVE CASE

Willie S, a 56-year-old with chronic essential hypertension, has been on an optimally dosed 3-drug regimen of an ACE inhibitor, a calcium channel blocker, and a thiazide diuretic for more than 3 months, but his blood pressure is still not at goal.

What is the best antihypertensive agent to add to his regimen?

Resistant hypertension—defined as inadequate blood pressure (BP) control despite a triple regimen of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide diuretic—affects an estimated 5% to 30% of those being treated for hypertension.^{1,2} Guidelines from the 8th Joint National Committee (JNC-8) on the management of high BP, released in 2014, recommend beta-blockers, alpha-

blockers, or aldosterone antagonists (AAs) as equivalent choices for a fourth-line agent. The recommendation is based on expert opinion.³

Hypertension guidelines from the UK's National Institute for Health and Care Excellence, released in 2011, recommend an AA if BP targets have not been met with the triple regimen. This recommendation, however, is based on lower-quality evidence, without comparison with beta-blockers, alpha-blockers, or other drug classes.⁴

More evidence since guideline's release

A 2015 meta-analysis of 15 studies and a total of more than 1200 participants (3 randomized controlled trials [RCTs], one nonrandomized placebo-controlled comparative trial, and 11 single-arm observational studies) demonstrated the effectiveness of the AAs spironolactone and eplerenone on resistant hypertension.⁵ In the 4 comparative studies, AAs decreased office systolic blood pressure (SBP) by 24.3 mm Hg (95% confidence interval [CI], 8.65-39.87; $P=.002$) and diastolic blood pressure (DBP) by 7.8 mm Hg (95% CI, 3.79-11.79; $P=.0001$) more than placebo. In the 11 single arm studies, AAs reduced SBP by 22.74 mm Hg (95% CI, 18.21-27.27; $P <.00001$), and DBP by 10.49 mm Hg (95% CI, 8.85-12.13; $P <.00001$).

The previous year, a randomized, placebo-controlled trial examined the effect of low-dose (25 mg) spironolactone compared with placebo in 161 patients with resistant

TABLE

Home SBP after 12 weeks of treatment¹

Treatment	Mean SBP, mm Hg (95% CI)	Change from baseline (95% CI)
Spironolactone	133.5 (132.3 to 134.8)	-14.4 (-15.6 to -13.1)
Doxazosin	138.8 (137.6 to 140.1)	-9.1 (-10.3 to -7.8)
Bisoprolol	139.5 (138.2 to 140.8)	-8.4 (-9.7 to -7.1)
Placebo	143.7 (142.5 to 145)	-4.2 (-5.4 to -2.9)

CI, confidence interval; SBP, systolic blood pressure.

hypertension.⁶ At 8 weeks, 73% of those receiving spironolactone reached a goal SBP <140 mm Hg vs 41% of patients on placebo ($P=.001$). The same proportion (73%) achieved a goal DBP <90 mm Hg in the spironolactone group, compared with 63% of those in the placebo group ($P=.223$).

Ambulatory BP was likewise assessed and found to be significantly improved among those receiving spironolactone vs placebo, with a decrease in SBP of 9.8 mm Hg (95% CI, -14.2 to -5.4; $P<.001$), and a 3.2 mm Hg decline in DBP (95% CI, -5.9 to -0.5; $P=.013$).⁶

STUDY SUMMARY

First study to compare spironolactone with other drugs

The study by Williams et al—a double-blind, randomized placebo-controlled crossover trial conducted in the UK—was the first RCT to directly compare spironolactone with other medications for the treatment of resistant hypertension in adults already on triple therapy with an ACE inhibitor or ARB, a CCB, and a thiazide diuretic.¹ The trial randomized 335 individuals with a mean age of 61.4 years (age range 18 to 79), 69% of whom were male; 314 were included in the intention-to-treat analysis.¹

Enrollment criteria for resistant hypertension specified a clinic-recorded SBP of ≥ 140 mm Hg (or ≥ 135 mm Hg in those with diabetes) and home SBP (in 18 readings over 4 days) of ≥ 130 mm Hg.¹ To ensure fidelity to treatment protocols, the investigators directly observed therapy, took tablet counts, measured serum ACE activity, and assessed BP measurement technique, with all participants adhering to a minimum of 3 months on a maximally dosed triple regimen.

Diabetes prevalence was 14%; tobacco use was 7.8%; and average weight was 93.5 kg (205.7 lbs).¹ Because of the expected inverse relationship between plasma renin and response to AAs, plasma renin was measured at baseline to test whether resistant hypertension was primarily due to sodium retention.¹

Participants underwent 4, 12-week rotations

All participants began the trial with 4 weeks of placebo, followed by randomization to 12-week rotations of once daily oral treatment with 1) spironolactone 25 to 50 mg, 2) doxazosin modified release 4 to 8 mg, 3) bisoprolol 5 to 10 mg, and 4) placebo.¹ Six weeks after initiation of each study medication, participants were titrated to the higher dose. There was no washout period between cycles.

The primary outcome was mean SBP measured at home on 4 consecutive days prior to the study visits on Weeks 6 and 12. Participants were required to have at least 6 BP measurements per each 6-week period in order to establish a valid average. Primary endpoints included: the difference in home SBP between spironolactone and placebo, the difference in home SBP between spironolactone and the mean of the other 2 drugs, and the difference in home SBP between spironolactone and each of the other 2 drugs.

■ **The results:** Spironolactone lowered SBP more than placebo, doxazosin, and bisoprolol (TABLE),¹ and clinic measurements were consistent with home BP readings.

Overall, 58% of participants achieved goal SBP <135 mm Hg on spironolactone, compared with 42% on doxazosin, 44% on bisoprolol, and 24% on placebo.¹ The effective-



Nearly 60% of trial participants achieved their target SBP on spironolactone.

➤ Only 1% of trial participants discontinued spironolactone due to adverse events.

ness of spironolactone on SBP reduction was shown to exhibit an inverse relationship to plasma renin levels, a finding that was not apparent with the other 2 study drugs. However, spironolactone had a superior BP lowering effect throughout nearly the entire renin distribution of the cohort. The mean difference between spironolactone and placebo was -10.2 mm Hg; compared with the other drugs, spironolactone lowered SBP, on average, by 5.64 mm Hg more than bisoprolol and doxazosin; 5.3 mm Hg more than doxazosin alone, and 5.98 mm Hg more than bisoprolol alone.

Only 1% of trial participants had to discontinue spironolactone due to adverse events—the same proportion of withdrawals as that for bisoprolol and placebo and 3 times less than for doxazosin.¹

WHAT'S NEW

Evidence of spironolactone's superiority

This is the first RCT to compare spironolactone with 2 other commonly used fourth-line antihypertensives—bisoprolol and doxazosin—in patients with resistant hypertension. The study demonstrated clear superiority of spironolactone in achieving carefully measured ambulatory and clinic-recorded BP targets vs a beta-blocker or an alpha-blocker.

CAVEATS

Findings do not apply across the board

Spironolactone is contraindicated in patients with severe renal impairment. Although multiple drug trials have demonstrated the drug's safety and effectiveness, especially in patients with resistant hypertension, we should factor in the need for monitoring electrolytes and renal function within weeks of initiating treatment and periodically thereafter.^{7,8} In this study, spironolactone increased potassium levels, on average, by 0.45 mmol/L. No gynecomastia (typically seen in about 6% of men) was found in those taking spironolactone for a 12-week cycle.¹

This single trial enrolled mostly Caucasian men with a mean age of 61 years. Although smaller observational studies that included African American patients have shown promising results for spironolactone,

the question of external validity or applicability to a diverse population has yet to be decisively answered.⁹

CHALLENGES TO IMPLEMENTATION

Potential for adverse reactions, lack of patient-oriented results

The evidence supporting this change in practice has been accumulating for the past few years. However, physicians treating patients with resistant hypertension may have concerns about hyperkalemia, gynecomastia, and effects on renal function. More patient-oriented evidence is likewise needed to assist with the revision of guidelines and wider adoption of AAs by primary care providers. **JFP**

ACKNOWLEDGEMENT

The PURLs Surveillance system was supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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References

- Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386:2059-2068.
- Rosa J, Widimsky P, Tousek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 Study. *Hypertension*. 2015;65:407-413.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. *JAMA*. 2014;311:507-520.
- Hypertension in adults: diagnosis and management (Clinical Guideline CG127). (NICE), National Institute for Health and Care Excellence. 2011. Available at: <https://www.nice.org.uk/guidance/cg127>. Accessed March 4, 2016.
- Dahal K, Kunwar S, Rijal J, et al. The effects of aldosterone antagonists in patients with resistant hypertension: a meta-analysis of randomized and nonrandomized studies. *Am J Hypertens*. 2015;28:1376-1385.
- Václavík J, Sedláč R, Jarkovský J, et al. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). *Medicine (Baltimore)*. 2014;93:e162.
- Wei L, Struthers AD, Fahey T, et al. Spironolactone use and renal toxicity: population based longitudinal analysis. *BMJ*. 2010;340:c1768.
- Oxlund CS, Henriksen JE, Tarnow L, et al. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus. *J Hypertens*. 2013;31:2094-2102.
- Nishizaka M, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens*. 2003;16:925-930.