

Article of Interest

Williams, B et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug resistant hypertension (PATHWAY-2). *Lancet*. 2015. ([Click to Access](#))

Context and Study Objective

The optimal additional medication in resistant hypertension (persistent hypertension despite 3 agents including an appropriately dosed diuretic) is unknown. This study sought to determine whether spironolactone, bisoprolol, or doxazosin was the most effective agent; the primary endpoint was change in home systolic blood pressure (BP).

Design, Setting, and Participants

In a double blind fashion, patients received spironolactone (25-50 mg/d), bisoprolol (10mg/d), doxazosin (8 mg/HS), or placebo for 12 weeks in a random but consecutive fashion (no washout period). Inclusion criteria: office systolic pressure >140 mm Hg and home >130 mm Hg despite maximally tolerated doses of an ACE/ARB, a CCB, and thiazide. Exclusion criteria: GFR < 45 cc/min 1.73 m² or a potassium "outside the normal range." The study sponsor had no role in the trial.

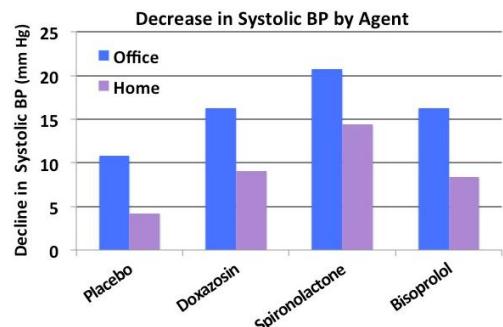
Results

-335 patients were randomized, 230 completed the study. Mean age 61, 70% male. Ethnicity data not provided, home 148/84 mm Hg, office 157/90 mm Hg, K 4.1 mEq/L, Cr 1.0 mg/dL, 24hr urine Na 137 mEq. Baseline ACE/ARB, CCB, thiazide agent/dose were not specified.

-Figure: All agents resulted in statistically significant reductions in systolic pressure compared to placebo; spironolactone resulted in larger reductions than any other agent ($p<0.05$).

-Upon trial completion, K was 4.4 mEq/L in the spironolactone arm (unchanged with other agents), Cr 1.1 mg/dL in all groups.

-Discontinuation rates related to gynecomastia/sexual dysfunction, renal impairment, or hyperkalemia were no higher in the spironolactone group.



Clinical Perspective

-My own experience is compatible with this trial's conclusions. I find 25 mg/day of spironolactone has excellent anti-hypertensive efficacy and I've yet to see sexual side effects/gynecomastia at this dose. It's also highly effective in those with metabolic syndrome. [My editorial](#) in the *Lancet* accompanies this article.

-In those with advanced kidney disease or a baseline K above 4.5 mEq/L, I start at 12.5 mg if I feel the benefits outweigh the risk. I monitor elderly patients for evidence of volume depletion given the hemodynamic effects of ACE/ARB, diuretic, and spironolactone triple therapy.

-Because this is the first randomized, placebo-controlled trial for resistant hypertension, I believe it is a landmark study. It enshrines spironolactone as the agent of choice among those already on a diuretic, calcium channel blocker, and ACEi/ARB.

.-The use of home BP readings ensured the presence of resistant hypertension by excluding a white coat effect; the (expected) marked difference between office and home readings reinforces this phenomenon.

-Limitations: While rates of creatinine elevation and hyperkalemia were insignificant, those with GFR < 45 cc/ mL 1.73 m² or elevated pre-trial K were excluded. It is unclear what thiazide/dose was used; the number of black patients was not specified.

-Disclosures: None to declare.