CONCEPTS IN HYPERTENSION

A Journal Article Based Approach to Understanding the Clinical Aspects of Hypertension

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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).

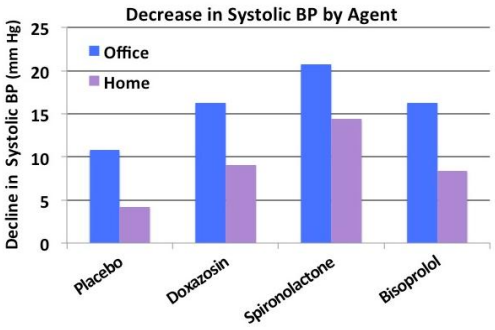
Design, Setting, and Participants

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

-This study is the first randomized controlled trial comparing multiple agents with placebo for resistant hypertension; the mineralocorticoid antagonist spironolactone was the most effective agent.

-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. My editorial in the Lancet offers further insight.

-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. 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 closely monitor elderly patients for evidence of volume depletion given the hemodynamic effects of ACE/ARB, diuretic, and spironolactone triple therapy.