PATHWAY-2 and -3: Potassium-Sparing Diuretics Safe and Effective for Resistant Hypertension

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Spironolactone was significantly more effective in controlling resistant hypertension compared with doxazosin or bisoprolol in the PATHWAY-2 study, and the combination of amiloride and hydrochlorothiazide (HCTZ) amplified the desirable effects of each drug on blood pressure (BP) lowering while neutralizing the undesirable changes in blood glucose and potassium levels in the PATHWAY-3 study. The study results were presented, respectively, by Bryan Williams, MD, University College London, London, United Kingdom, and Morris J. Brown, MD, University of Cambridge, Cambridge, United Kingdom.

PATHWAY-2 was a double-blind, randomized, placebo-controlled, crossover trial [Williams B et al. *BMJ Open*. 2015], with the hypothesis that resistant hypertension is a sodium-retaining state characterized by an inappropriately low plasma renin level despite treatment, and that further diuretic therapy with spironolactone would be more effective at lowering BP than treatments targeting different mechanisms. Although a recent meta-analysis suggested that spironolactone may be effective for resistant hypertension [Dahal K et al. *Am J Hypertens*. 2015], there is no clinical trial evidence comparing it with other BP-lowering drugs.

The primary end point was hierarchical, with the first measure being the difference in average home systolic BP (HSBP) between spironolactone and placebo; if significant, followed by the difference in HSBP with spironolactone vs the average of bisoprolol and doxazosin; if significant, the difference in HSBP with spironolactone vs bisoprolol and vs doxazosin.

A total of 314 patients were included in the intent-to-treat analysis: 285 randomized to spironolactone (25-50 mg OD), 282 to doxazosin (4-8 mg OD), 285 to bisoprolol (5-10 mg OD), and 274 to placebo. Their mean age was 61.4 years, and 68.7% were men; the mean home BP was 147.6/84.2 mm Hg and the mean clinic BP was 157.0/90.0 mm Hg.

In PATHWAY-2, spironolactone produced significantly greater reductions for the average of the HSBP measurements at 6 and 12 weeks for each component of the primary outcome ($P < .001$ for all 4 comparators).

Spironolactone also produced significantly greater seated clinic BP reductions compared with each of the other treatments: –9.92 mm Hg vs placebo, –4.42 mm Hg vs doxazosin, and –4.45 mm Hg vs bisoprolol, respectively (all $P < .001$). The rate of serious adverse events and withdrawals did not vary significantly between the treatment groups.

Prof Williams stated that the BP response to spironolactone was inversely related to plasma renin levels and unlike other active treatments the BP response was dose dependent, supporting the hypothesis that the dominant cause of resistant hypertension is sodium retention despite background treatment with a thiazide diuretic. He concluded that the results unequivocally favored spironolactone (25-50 mg daily) as the most effective treatment for resistant hypertension, and that patients should not be defined as having resistant hypertension unless their BP remains uncontrolled when spironolactone is added to the treatment regimen.

Prof Brown highlighted the need to determine the optimal diuretic treatment for hypertension, noting the apparent link between potassium-depletion with hypertension treatment and the increased risk of diabetes [Stears AJ et al. *Hypertension*. 2012], suggesting possible benefit with potassium-sparing diuretics.

PATHWAY-3 was a parallel-group, randomized, double-blind, multicenter trial, comparing HCTZ 25 to 50 mg, amiloride 10 to 20 mg, and the combination of both diuretics at half of these doses; forced titration occurred at 12 weeks and follow-up was 6 months [Brown MJ et al. *BMJ Open*. 2015]. The hypothesis was that the combination of half-maximal doses of these drugs would neutralize the undesired effects of HCTZ on glucose and potassium levels while potentiating the desired BP lowering.

The hierarchical primary end point was the difference in change from baseline in the 2-hour oral glucose tolerance test (OGTT) with amiloride and HCTZ at 12 and 24 weeks; if significant, the difference in change from baseline in the 2-hour OGTT between the half-dose combination of treatments and HCTZ.

A total of 399 patients were included in the analysis: 132 taking amiloride, 134 taking HCTZ, and 133 taking the combination treatment. The mean age of the patients was 62 years and 39% were women; the home BP was 149/87 mm Hg and the clinic BP was 154/91 mm Hg. At baseline, 44 (33%) patients had impaired glucose tolerance.

Both amiloride and the amiloride/HCTZ combination produced a significantly greater reduction in glucose compared with HCTZ. Amiloride and HCTZ alone produced similar BP reduction at both 12 and 24 weeks. However, the amiloride/HCTZ combination lowered BP by 3.4 mm Hg more than each drug alone (95% CI, 0.9 to 5.8; $P=.007$). The amiloride/HCTZ combination also produced a significantly greater increase in renin levels than HCTZ alone.

The rates of adverse events and withdrawals were comparable between the groups, with the exception of hyperkalemia, which occurred more frequently with amiloride and the combination treatment compared with HCTZ. However, Prof Brown noted there were no increases in potassium > 5.8 mmol/L.

The combination of amiloride and HCTZ did not adversely affect blood glucose and potassium but improved the BP-lowering effect of each drug, concluded Prof Brown. The PATHWAY-2 and PATHWAY-3 trials demonstrated that potassium-sparing diuretics are safe and effective and may be the preferred choice for the treatment of hypertension.

Long-term Euro-ASA Registry Data: Alcohol Septal Ablation Is Safe and Effective

Written by Muriel Cunningham

The long-term safety of alcohol septal ablation (ASA) to decrease the pressure gradient of the left ventricle (LV) in patients with hypertrophic cardiomyopathy has been questioned despite single-center trials and the establishment of national registries. Josef Veselka, MD, PhD, Charles University, Prague, Czech Republic, presented long-term clinical outcomes from the multinational Euro-ASA registry. The study end points were (1) survival and clinical outcome in patients treated with ASA; (2) predictors of mortality events and clinical outcome; and (3) relationships among the dose of alcohol injected during ASA, the improvement of LV outflow tract pressure gradient, and the occurrence of complete heart block.

Table 1. Baseline and Follow-up Characteristics

Characteristic	Baseline	Follow-up[a]	*P* Value
Age, y	58 ± 14	63 ± 13	—
Dyspnea, NYHA class	2.9 ± 0.5	1.6 ± 0.7	< .001
Angina, CCS class	1.3 ± 1.2	0.7 ± 0.8	< .001
Episodes of syncope, %	22	7	< .001
LV outflow gradient, mm Hg	67 ± 36	16 ± 21	< .001
LV diameter, mm	43 ± 6	46 ± 6	< .001
LV ejection fraction, %	70 ± 10	66 ± 10	< .001
Basal septum thickness, mm	20 ± 4	15 ± 4	< .001

CCS, Canadian Cardiovascular Society; LV, left ventricular.

[a]The median (interquartile range) follow-up for survival was 5 y (2.1 to 8.2).

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The study population included 1275 consecutive patients treated with ASA at 10 centers in Europe. The mean age of the patients was 58 ± 14 years, and 49% were female. Patient characteristics at baseline and follow-up are presented in Table 1.

Thirteen patients (1%) died within 30 days of ASA, and 16 patients (1.3%) experienced intraprocedural and early (within 2 days) postprocedural sustained ventricular tachycardia/ventricular fibrillation requiring electrical cardioversion. Thirty-seven percent of patients (n = 468) had intraprocedural complete heart block, with 151 cases (12%) requiring permanent pacemaker implantation. There was a significant association between higher doses of alcohol and complete heart block (HR, 1.19; 95% CI, 1.05 to 1.35; $P=.006$). Optimal doses of alcohol appear to be 1.5 to 2.5 mL.

A lower LV outflow tract gradient at the last clinical visit was independently associated with the final NYHA class ≤ 2 (HR, 0.98; 95% CI, 0.97 to 0.99; $P<.01$).

A total of 171 patients (13%) died during follow-up, resulting in a post-ASA all-cause mortality rate of 2.42 deaths per 100 patient-years (95% CI, 2.07 to 2.82). Significant independent predictors of all-cause mortality included higher age at ASA (HR, 1.06; 95% CI, 1.05 to 1.08; $P<.01$), septum thickness before ASA (HR, 1.05; 95% CI, 1.01 to 1.09; $P<.01$), NYHA class before ASA (HR, 1.5; 95% CI, 1.00 to 2.10; $P=.047$), and the LV gradient at the last check-up (HR, 1.01; 95% CI, 1.00 to 1.01; $P=.048$).

Sixty-eight patients (5.3%) had a sudden mortality event (0.98 per 100 patient-years; 95% CI, 0.76 to 1.12). The only independent predictor of sudden death was septum thickness before ASA (HR, 1.07; 95% CI, 1.01 to 1.12; $P=.014$).

"After 2 decades of the introduction of ASA, we can state that this procedure is safe and this procedure is effective," Prof Veselka said. Because the residual obstruction post ASA is a significant factor influencing both long-term functional status and survival, clinicians should take steps to eliminate LV outflow obstruction in these patients.