Mechanisms for benefit of spironolactone in resistant hypertension in the PATHWAY-2 study

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on behalf of the PATHWAY Investigators

Declaration of interests: None in relation to the content of this work
Declaration of interest

- I have nothing to declare
Background

The PATHWAY-2 study hypothesis:

• That patients with resistant hypertension are retaining too much salt which makes their blood pressure difficult to control

• Giving these patients additional diuretic treatment with spironolactone would be the most effective additional treatment to lower blood pressure

• Spironolactone is a diuretic that specifically antagonises the action of the body’s salt-retaining hormone – aldosterone

The PATHWAY-2 Mechanisms study

• Pre-specified mechanistic sub-studies, embedded within the PATHWAY-2 study

Key Questions addressed by the PATHWAY-2 Mechanisms study

• What is the mechanism for the superior BP-lowering effect of spironolactone in resistant hypertension?
• Would this benefit be replicated by an alternative diuretic, e.g. amiloride, with a similar mechanism of action?
• Can these studies help us better understand why some people develop drug resistant hypertension?
PATHWAY-2 Mechanisms study

**Screening for Resistant Hypertension**
- Treatment A + C + D
- DOT* to exclude non-compliance
- Home BP to exclude white coat hypertension
- Secondary hypertension excluded

**Randomisation**
- 4 week Single blind placebo run in Treated with A+C+D

**Baseline**
- Plasma Renin, Aldosterone, Aldosterone : Renin ratio
- Haemodynamic studies

**Spironolactone 25 – 50mg o.d.**
- Haemodynamic studies

**Bisoprolol 5 – 10mg o.d.**
- Haemodynamic studies

**Doxazosin MR 4 – 8mg o.d.**
- Haemodynamic studies

**Placebo**
- Haemodynamic studies

**Home Systolic BP measured at 6 and 12 weeks**

**Clinic Systolic BP measured at 6 and 12 weeks**

**Amiloride Open-Label 12 week Run-out 10 -20mg o.d.**

**12 weeks per treatment cycle**
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles

**Mean Age: 61yrs**
- 70% male

**Baseline BP: 158/91**
- Already on treatment with A+C+D

*DOT = Directly Observed Therapy*
Impact of baseline Renin, Aldosterone, and Aldosterone/Renin ratio on the BP response to placebo and spironolactone

Placebo
No significant relationships

Similar result for doxazosin and bisoprolol

Spironolactone
Renin mass: $r^2=0.108$, $p<0.0002$
Aldosterone: $r^2=0.025$, $p=0.0524$
Aldo/ Renin: $r^2=0.130$, $p=0.0001$
Impact of treatment of resistant hypertension on haemodynamics

- Spironolactone is the only treatment that reduces fluid volume in the body
- Spironolactone most effective in patients with a hormonal pattern consistent with the most salt retention
- Supports the hypothesis that the underlying problem in resistant hypertension is salt and water retention
- Hormonal pattern suggests excessive production of salt-retaining hormone aldosterone in ~25%

Measurements made at baseline and at the end of each treatment cycle - Cardiodynamics BioZ®
Effects of amiloride versus spironolactone on clinic systolic BP in resistant hypertension

Correlation of BP reduction with amiloride vs spironolactone

Baseline Placebo Amiloride 10 – 20mg Spironolactone 25 – 50mg Doxazosin 4 – 8mg Bisoprolol 5-10mg

Clinic Blood Pressure (mmHg)

Systolic Diastolic

74 76 78 80 82 84 86 88 90 92 94 96 98 100 102 104 106 108 110 112 114 116 118 120

r = 0.64 p<0.0001.
Summary and Conclusions

• We show that resistant Hypertension is predominantly a sodium retaining state (salt and water excess), and the most effective treatment is a diuretic (spironolactone) that eliminates the volume excess by antagonising the effect of the salt retaining hormone aldosterone.

• We also show for the first time that this effect of spironolactone is replicated by a different diuretic, amiloride 10-20mg daily, which also blocks the action of the the salt retaining hormone - this extends the choice of treatment options.

• Why is resistant hypertension a salt retaining state? We demonstrate that a significant proportion of patients with resistant hypertension have levels of the salt-retaining hormone “aldosterone” which are higher than they should be.
# PATHWAY Executive Committee

**Morris J Brown*** | Queen Mary University London  
**Thomas MacDonald** | University of Dundee  
**Bryan Williams** | University College London  
**Steve Morant** | Statistician  

*Chairman

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# PATHWAY Study Sites and Local Investigators

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