The Prevention And Treatment of Hypertension With Algorithm based therapY

PATHWAY
Clinical Trials in Hypertension

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

Professor Bryan Williams FESC
Chair of Medicine | University College London
Tom MacDonald FESC, Steve Morant and Morris Brown FESC
on behalf of the PATHWAY Investigators

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

British Heart Foundation

BHS
British Hypertension Society

NHS
National Institute for Health Research

Declaration of interest

- I have nothing to declare

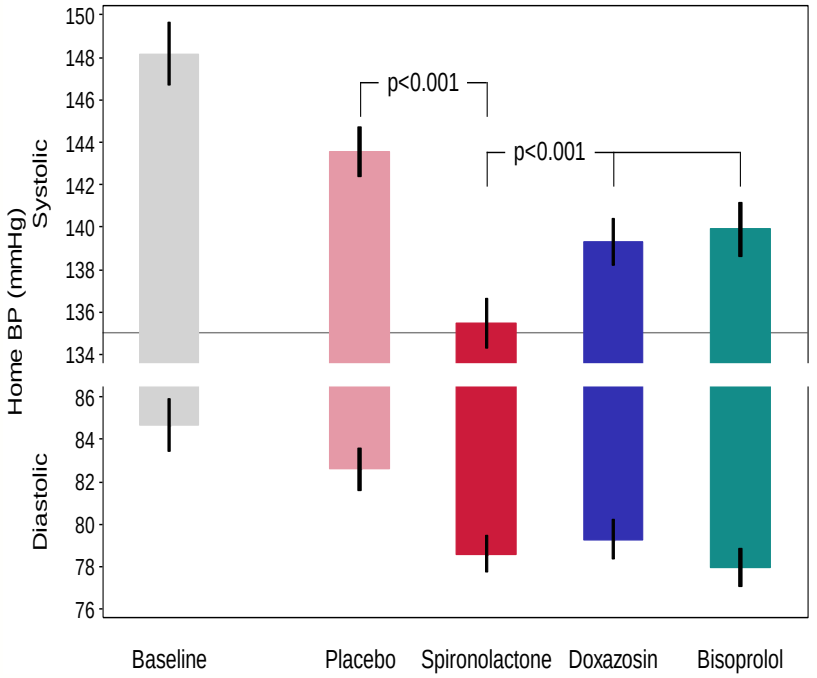
Background

The PATHWAY-2 study hypothesis:

- That patents 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

Williams B, et al. Lancet 2015

PATHWAY-2 Primary Outcome



All patients were already on treatment with 3 drugs to lower blood pressure, including a diuretic

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

PATHWAY Mechanisms Study
Clinical Trials in Hypertension

Screening for Resistant Hypertension

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

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

Randomisation

Baseline

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

Home Systolic BP measured at 6 and 12 weeks

- **Doxazosin MR 4 – 8mg o.d.** — Haemodynamic studies
- **Spironolactone 25 – 50mg o.d.** — Haemodynamic studies
- **Placebo** — Haemodynamic studies
- **Bisoprolol 5 – 10mg o.d.** — Haemodynamic studies

Clinic Systolic BP measured at 6 and 12 weeks

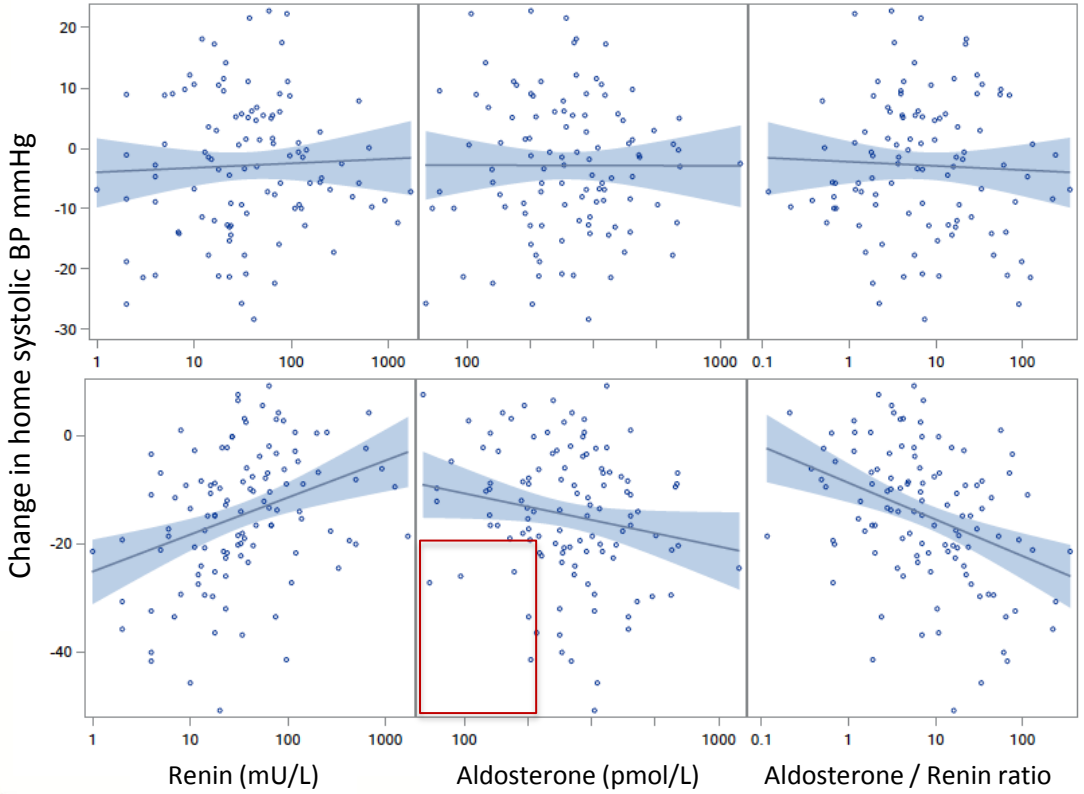
Amiloride Open-Label 12 week Run-out 10 -20mg o.d.

*DOT = Directly Observed Therapy

Mean Age: 61yrs
70% male
Baseline BP: 158/91
Already on treatment with A+C+D

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

Impact of baseline Renin, Aldosterone, and Aldosterone/Renin ratio on the BP response to placebo and spironolactone



Placebo

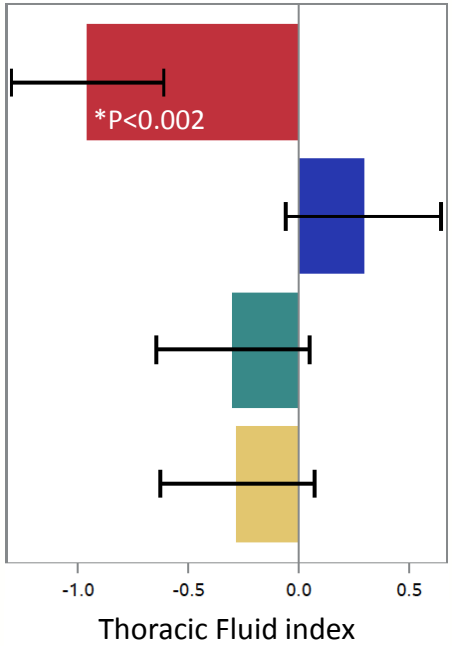
No significant relationships

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

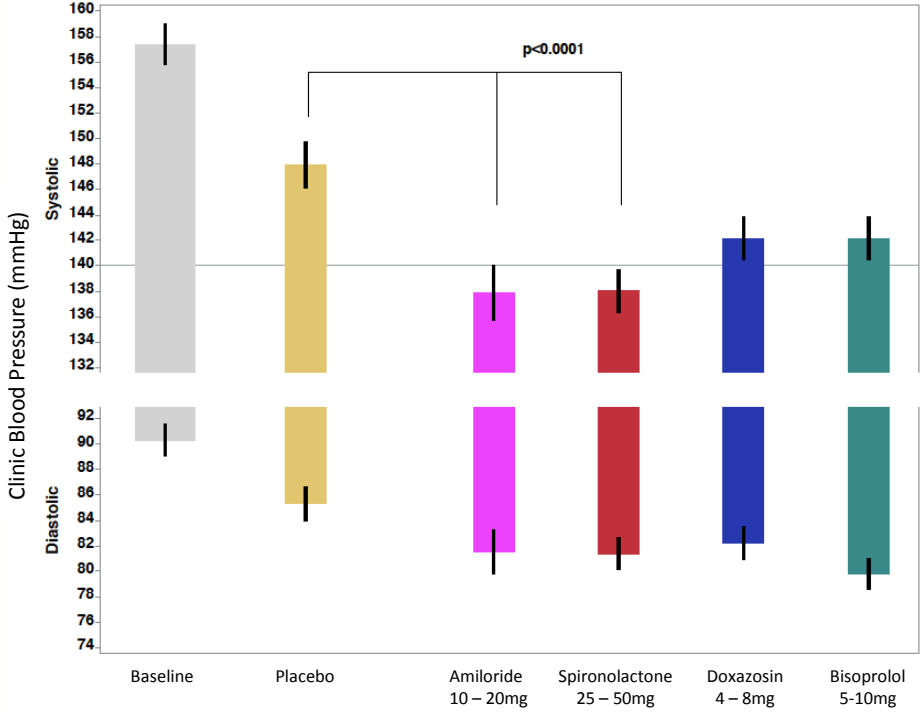


- Spironolactone is the only treatment that reduces fluid volume in the body
- Spironolactone most effective in patients with a hormonal pattern consistent with the most salt retention
- Supports the hypothesis that the underlying problem in resistant hypertension is salt and water retention
- Hormonal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

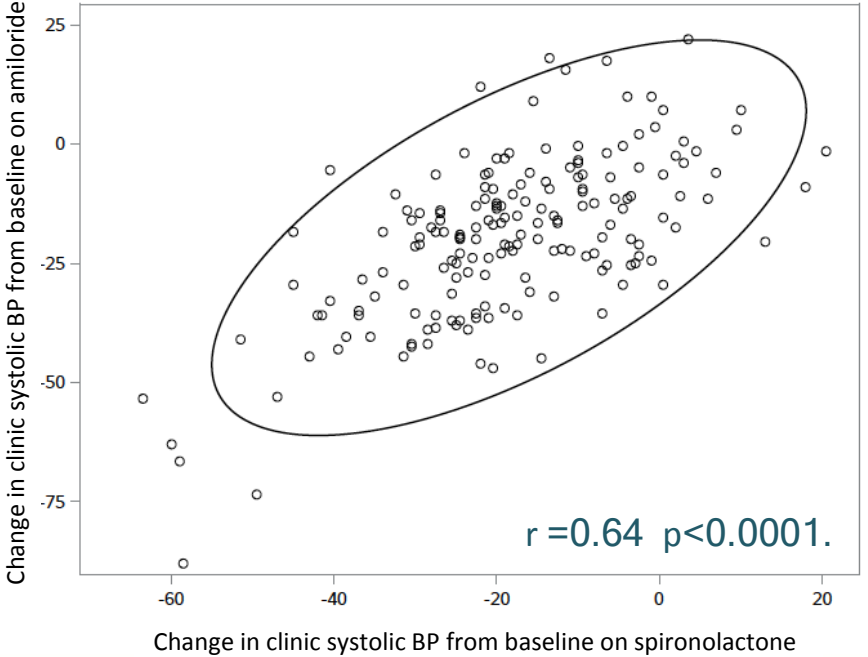
Placebo Spironolactone Doxazosin Bisoprolol

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



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.

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PATHWAY Study Sites and Local Investigators

Cambridge: A Schumann, J Helmy, C Maniero, TJ Burton, U Quinn, L. Hobbs, J Palmer	Ixworth: J Cannon, S Hood
Birmingham: (2 sites) U Martin, R Hobbs, R Iles	Kings College London: K Rutkowski
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