PATHWAY
Clinical Trials in Hypertension

The **P**revention **A**nd **T**reatment of **H**ypertension **W**ith **A**lgorithm based therap**Y**
PATHWAY

Optimal Treatment of Drug Resistant Hypertension
PATHWAY-2

Principal Results

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on behalf of the PATHWAY Investigators

British Heart Foundation
BHS British Hypertension Society
NHS National Institute for Health Research
ESC CONGRESS LONDON 2015
Hot Line presentation
www.escardio.org/ESC2015

DECLARATION OF INTEREST

- The authors have no conflicts to declare in relation to this work which was a British Hypertension Society investigator-initiated and led study, funded by the British Heart Foundation and the National Institute for Health Research

Background

- Resistant hypertension has been defined as uncontrolled blood pressure (BP) despite treatment with maximal tolerated doses of 3 BP-lowering medications
- International guidelines now concur that the 3 BP-lowering medications should usually be; an ACE-inhibitor or ARB + CCB + Thiazide-like Diuretic, i.e. A + C + D
- Prevalence of resistant hypertension is reported to be ~10% of hypertensive patients, equating to ~100 million people globally
- These patients are at especially high risk due to long term exposure to poor BP control and co-morbidities

Myatt A, et al. BMJ 2012, Kjeldsen S, et al. Drugs, 2014, Achelrod D, et al. Am J Hypertens. 2015

Background

- The optimal drug treatment of resistant hypertension remains undefined
- Recent meta-analysis suggests that spironolactone may be an effective treatment based on 3 small trials versus placebo and uncontrolled observational data
- But…there have been no randomised controlled trials directly comparing spironolactone with other BP-lowering drugs to determine whether spironolactone is the most effective treatment for resistant hypertension

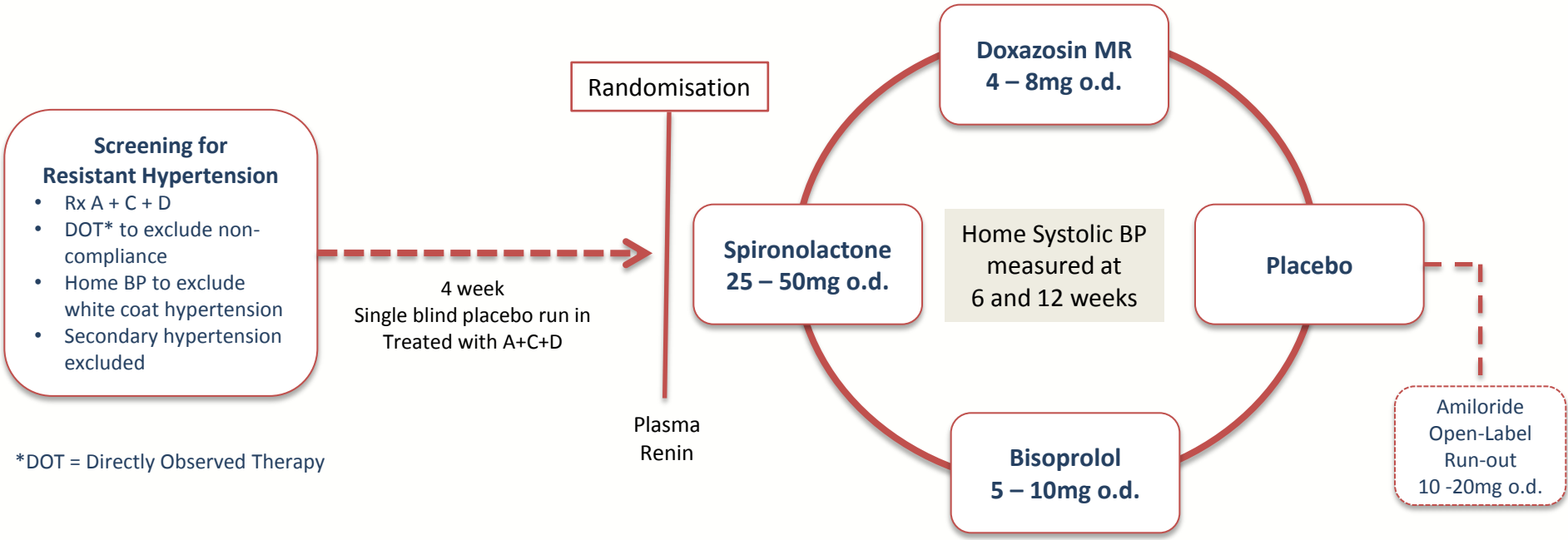
Dahal K, et al. Am J Hypertens, 2015

Hypothesis

- Resistant hypertension is a sodium retaining state that is characterised by an inappropriately low plasma renin level despite treatment with A + C + D
- Further diuretic therapy with spironolactone will be more effective at lowering BP than alternative treatments, targeting different mechanisms, i.e. bisoprolol (β-sympathetic blockade and renin suppression) or doxazosin MR (α-sympathetic blockade and vasodilatation)
- Plasma renin level (whilst treated with A+C+D) will be inversely related to the response to spironolactone

PATHWAY-2 Study Design

Double blind, Randomised, Placebo-Controlled, Cross-over Study



*DOT = Directly Observed Therapy

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

Williams B, et al. BMJ Open, 2015

Primary outcome measures

Hierarchical Primary End-point:

i. Difference in average home systolic BP (HSBP) between spironolactone and placebo

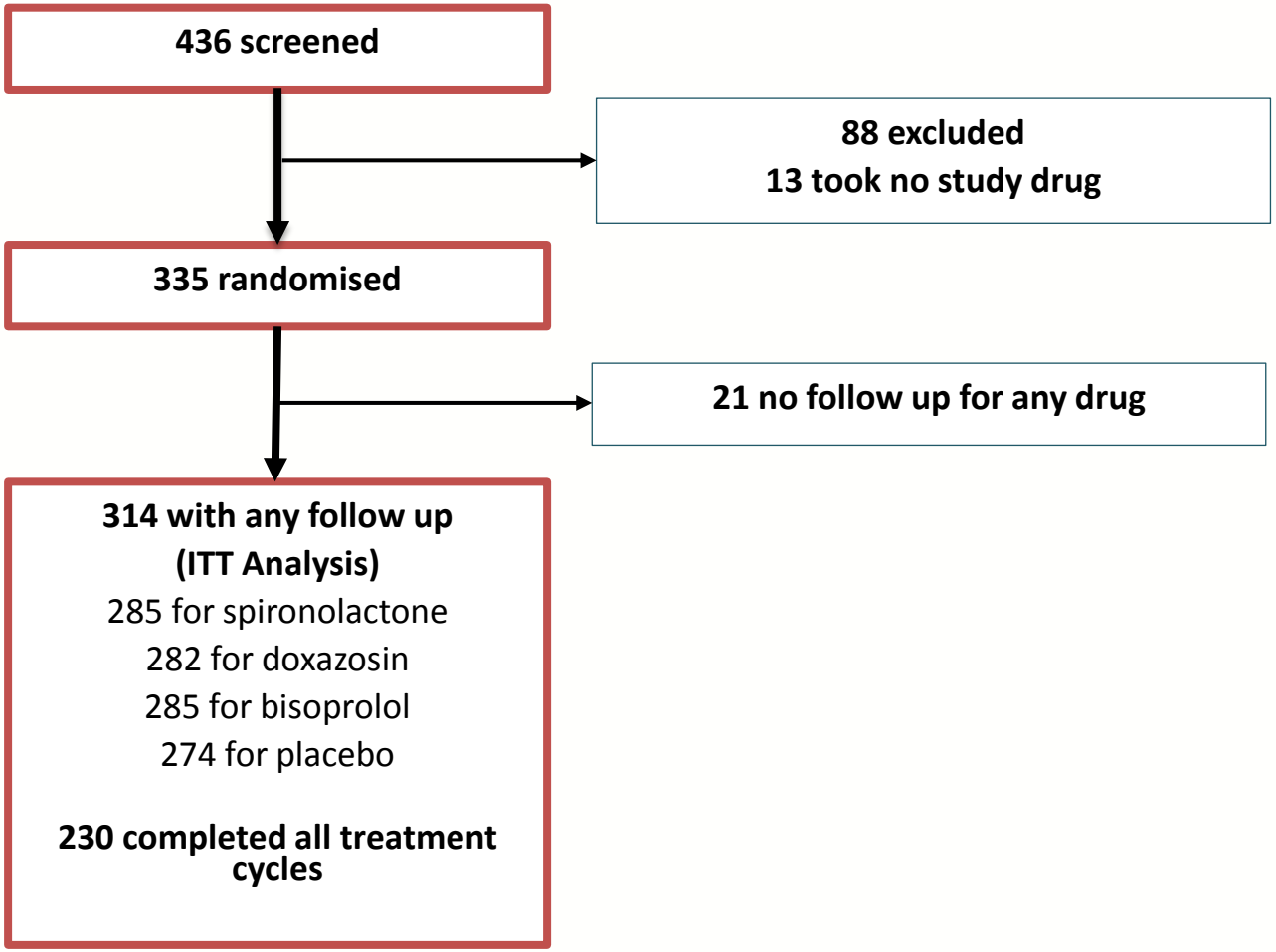
followed, if significant by;

ii. HSBP difference between spironolactone and the average of the other two active drugs(bisoprolol and doxazosin MR)

followed, if significant by;

iii. HSBP difference between spironolactone and each of the other two active drugs

Patient Disposition



Baseline Patient Demographics

		Mean (SD) or N (%)
Age (yrs.)		61.4 (9.6)
Male		230 (68.7%)
Weight (kg)		93.5 (18.1)
Smoker		26 (7.8%)
Home BP (mmHg)	Systolic	147.6 (13.2)
	Diastolic	84.2 (10.9)
Clinic BP (mmHg)	Systolic	157.0 (14.3)
	Diastolic	90.0 (11.5)
Blood electrolytes	Sodium (mmol/L)	140 (3.0)
	Potassium (mmol/L)	4.1 (0.47)
eGFR (mls/min)		91.1 (26.8)
Diabetic		46 (13.7%)

Primary Outcome

Comparators (N=314)	Home Systolic BP difference (mmHg)	p value
Spironolactone vs placebo	-8.70 (-9.72,-7.69)	<0.001

Home systolic BP averaged throughout the treatment cycle from measurements at week 6 and week 12. Analysis used least squares means from mixed effects models adjusted for baseline covariates

Primary Outcome

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Spironolactone vs Doxazosin	-4.03 (-5.04,-3.02)	<0.001
Spironolactone vs Bisoprolol	-4.48 (-5.50,3.46)	<0.001

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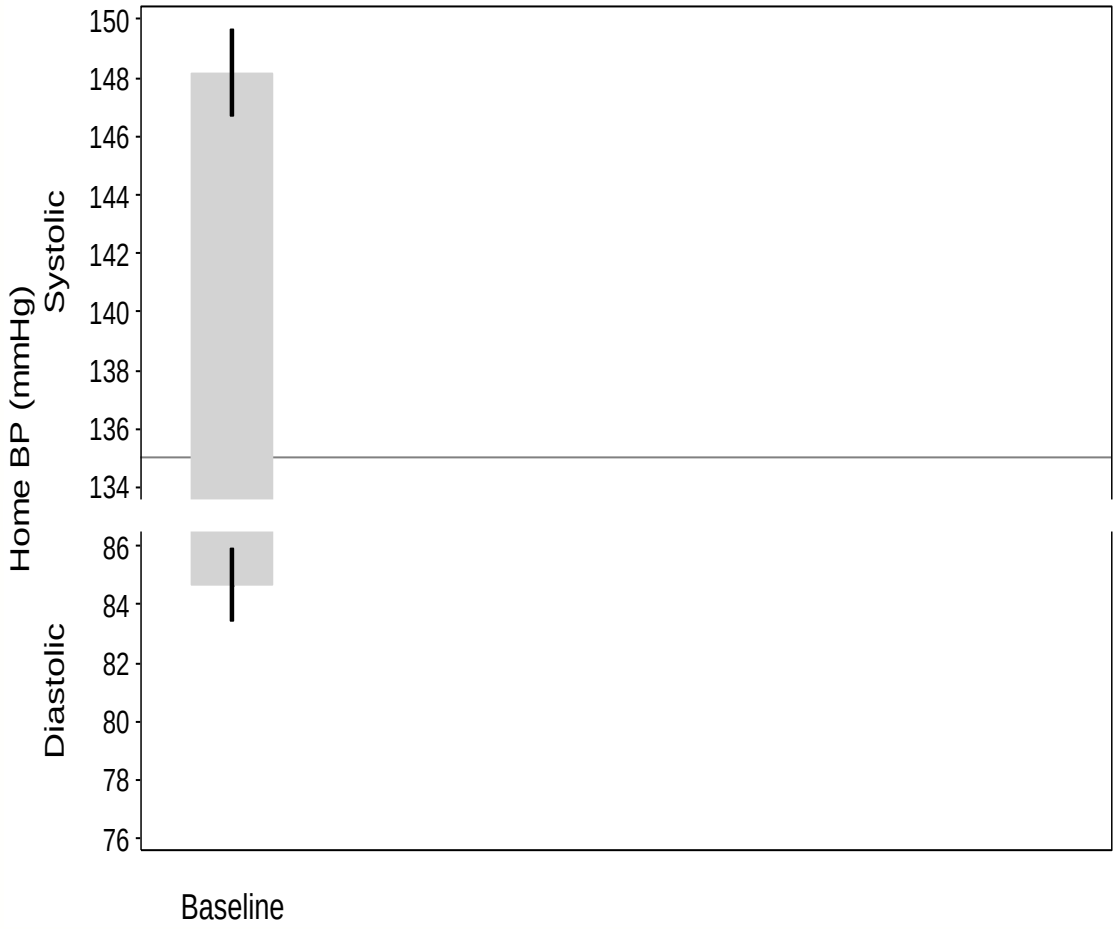
Treatments	Home Systolic BP (mmHg)	Change from baseline
Spironolactone	134.9 (134.0,135.9)	-12.8 (-13.8,-11.8)
Doxazosin	139.0 (138.0,140.0)	-8.7 (-9.7,-7.7)
Bisoprolol	139.4 (138.4,140.4)	-8.3 (-9.3,-7.3)
Placebo	143.6 (142.6,144.6)	-4.1 (-5.1,-3.1)

Primary Outcome



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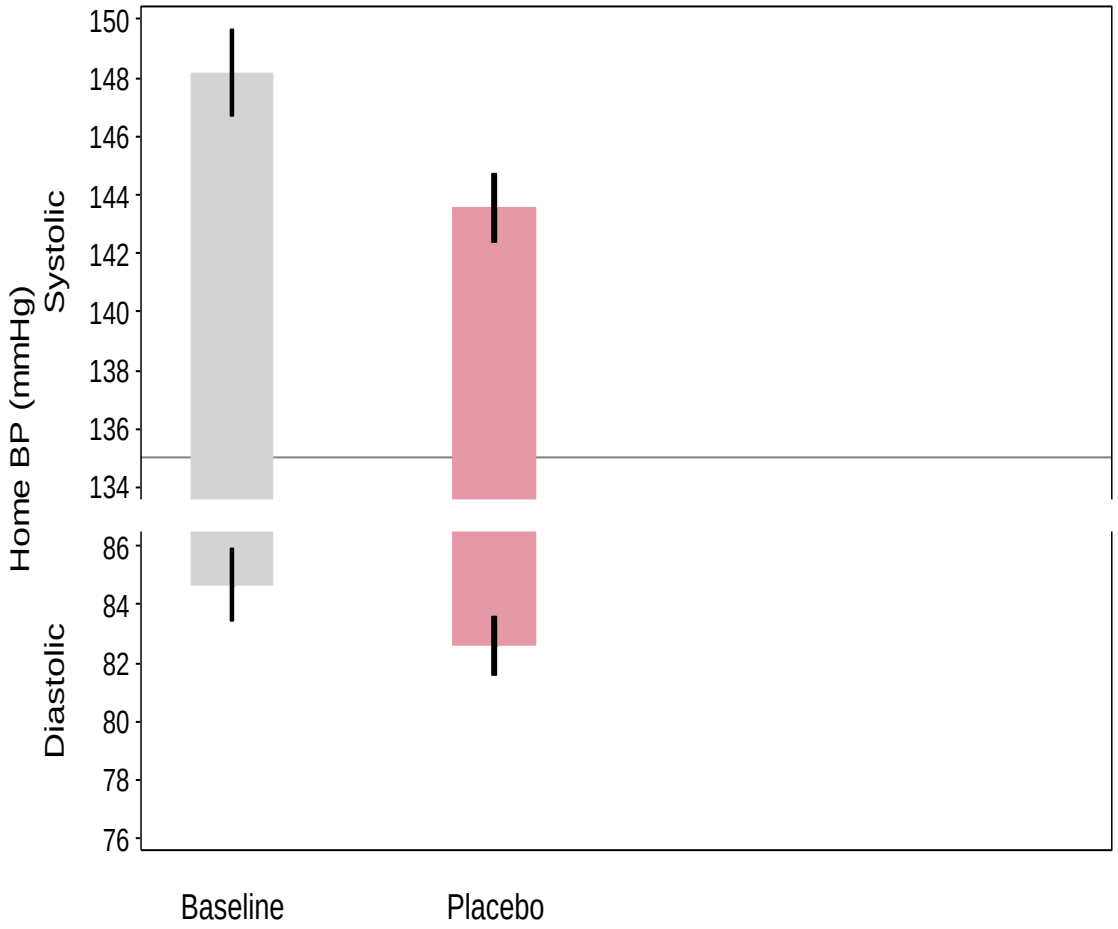
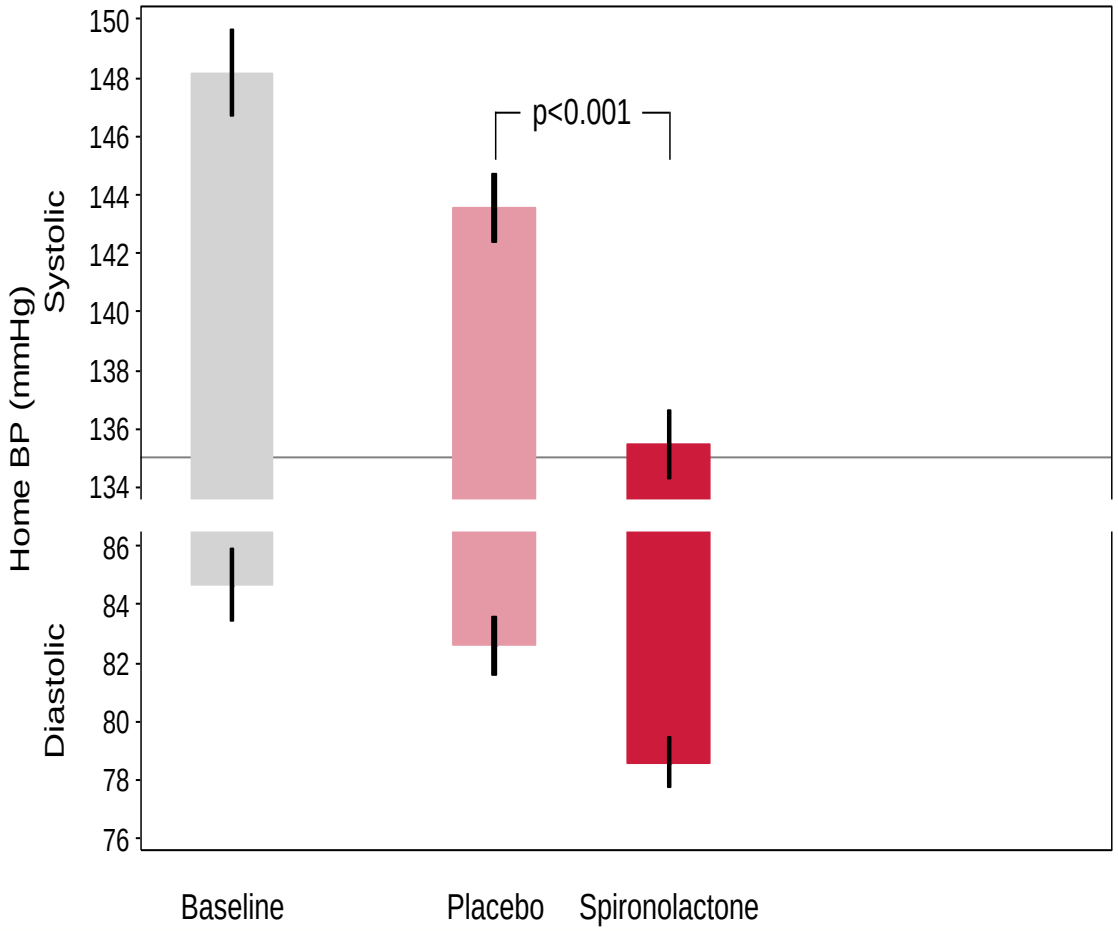
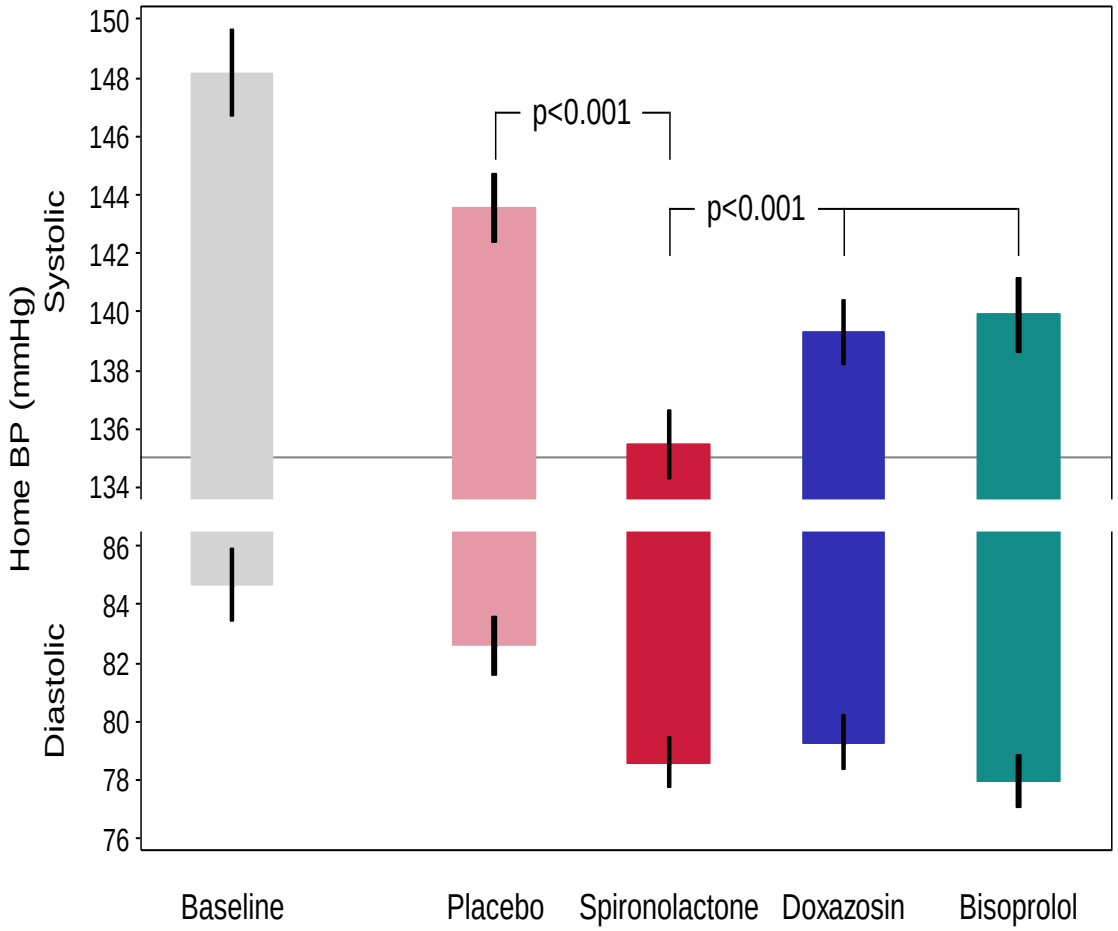


Primary Outcome



Primary Outcome



Secondary Outcomes

Seated Clinic Blood Pressure Mean differences (N=314)	Clinic Systolic BP difference (mmHg)	p value
Spironolactone vs placebo	-9.92 (-11.3,-8.59)	<0.001
Spironolactone vs mean Bisoprolol/Doxazosin	-4.44 (-5.59,-3.28)	<0.001
Spironolactone vs Doxazosin	-4.42 (-5.75,-3.09)	<0.001
Spironolactone vs Bisoprolol	-4.45 (-5.80,-3.11)	<0.001

Means	Clinic Systolic BP (mmHg)	Change from baseline
Spironolactone	136.5 (134.4,138.7)	-20.7 (-22.9,-18.6)
Doxazosin	141.0 (138.8,143.1)	-16.3 (-18.5,-14.2)
Bisoprolol	141.0 (138.8,143.2)	-16.3 (-18.4,-14.2)
Placebo	146.5 (144.3,148.6)	-10.8 (-13.0,-8.7)

BP Control Rates

	Home Systolic BP (mmHg)		Patients	Met target		Least Squares Estimates	Odds ratio	p value
	Baseline	Final	(n)	(r)	r/n (%)			
Spironolactone	148.3	133.9	282	163	57.8	58.0 (52.0,63.7)		
Doxazosin	147.8	138.9	276	115	41.7	41.5 (35.8,46.5)	0.52 (0.37,0.73)	<0.001
Bisoprolol	147.7	139.6	280	122	43.6	43.3 (37.5,49.2)	0.55 (0.39,0.78)	<0.001
Placebo	147.8	143.5	270	66	24.4	23.9 (19.1,29.4)	0.23 (0.16,0.33)	<0.001

BP control rates refer to patients achieving a home systolic BP of <135mmHg.
Odds ratios from logistic regression models adjusted for baseline.

Serious Adverse Events and Withdrawals

	Bisoprolol	Spironolactone	Doxazosin	Placebo	p value
Serious adverse events	8 (2.6%)	7 (2.3%)	5 (1.7%)	5 (1.7%)	0.831
Any adverse event	68 (11.3%)	67 (10.4%)	58 (10.1%)	42 (9.1%)	0.711
Withdrawals for adverse events	2 (2.9%)	3 (3.4%)	8 (10.0%)	2 (2.6%)	0.084

p values for Fisher's exact test

Summary

- We demonstrate for the first time that spironolactone (25-50mg daily) is overwhelmingly the most effective drug treatment for resistant hypertension
- Spironolactone controlled BP in almost 60% of patients with resistant hypertension – and was 3-times as likely to be the a patient's best drug versus doxazosin or bisoprolol
- Spironolactone was well tolerated with no significant excess adverse effects with the caveat that serum potassium levels and renal function should be monitored on treatment and treatment duration was too short to assess incident gynecomastia (~6% in longer-term studies)

Implications of Findings

- PATHWAY-2 is the first RCT to directly compare spironolactone with other active BP-lowering treatments in patients with well characterised resistant hypertension
- The result in favor of spironolactone is unequivocal – Spironolactone is the most effective treatment for resistant hypertension, and these results should influence treatment guidelines globally
- Patients should not be defined as resistant hypertension unless their BP remains uncontrolled on spironolactone

Acknowledgements

- We thank the Patients who participated in our study
- The Investigators who made it happen
- The PATHWAY study programme was funded by the British Heart Foundation and the National Institute for Health Research

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