PATHWAY
Clinical Trials in Hypertension

Prevention And Treatment of Hypertension With Algorithm based therapY (PATHWAY)

Amiloride-hydrochlorothiazide versus individual diuretic effects on glucose tolerance and blood pressure

PATHWAY-3

Principal Results

Morris Brown, Bryan Williams, Tom Macdonald

on behalf of the British Hypertension Society's PATHWAY Investigators

British Heart Foundation

BHS
British Hypertension Society

NHS
National Institute for Health Research

DECLARATION OF INTEREST

- I have nothing to declare

British Heart Foundation

NHS National Institute for Health Research

PATHWAY
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PATHWAY Executive Committee

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Thomas MacDonald: University of Dundee

Bryan Williams: University College London

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PATHWAY Study Sites and Investigators (11 secondary, 2 primary care)

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Birmingham: (2 sites) Una Martin, Richard Hobbs, Rachel Iles	**Kings College London:** Krzysztof Rutkowski
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Leicester: Adrian G Stanley, Christobelle White, Peter Lacy, Pankaj Gupta, Sheraz A Nazir, Caroline J. Gardiner-Hill	**Manchester:** Handrean Soran, See Kwok, Karthirani Balakrishnan
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St Barts London: David Collier, Nirmala Markandu, Manish Saxena, Anne Zak, Enamuna Enobakhare	**Glasgow:** Scott Muir, Linsay McCallum

Background

- The optimal diuretic for hypertension is uncertain.
- The view that 'low-dose thiazides are maximal', avoiding metabolic consequences, without compromising antihypertensive efficacy, has been disproven.[1]
- Increased risk of diabetes appears linked to potassium-depletion, and might be avoided by use of potassium-sparing diuretics[2]

[1] Hood et al. ***Circulation. 2007;116:268-275;*** [2] Stears et al. ***Hypertension*. 2012;59:934-942;**

Study Methods and Design

PATHWAY 3
Clinical Trials in Hypertension

Screening

Uncontrolled hypertension (SBP > 140 mmHg)

Eligible for diuretic treatment

At least 1 additional component of metabolic syndrome

Study Methods and Design

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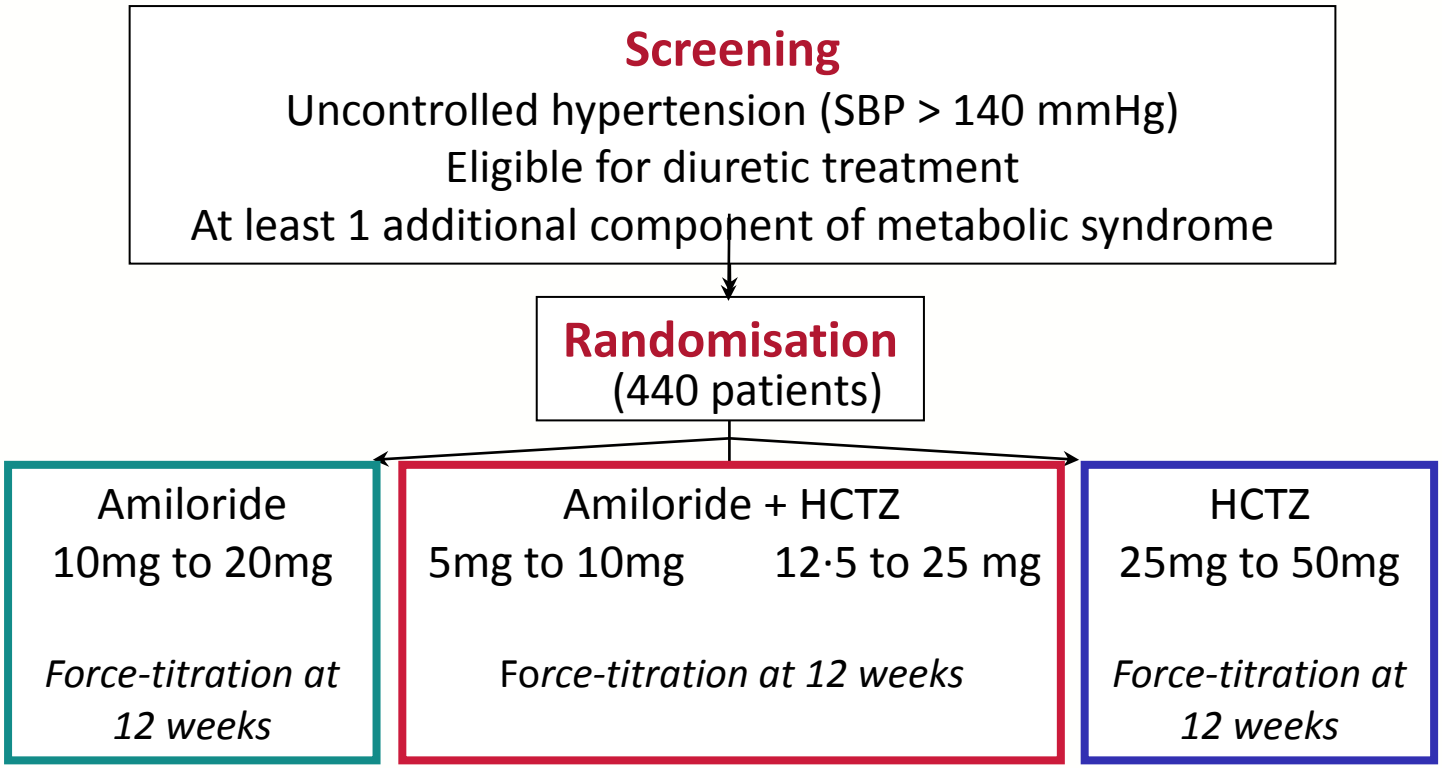

Study Methods and Design

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Clinical Trials in Hypertension

Screening

Uncontrolled hypertension (SBP > 140 mmHg)
Eligible for diuretic treatment
At least 1 additional component of metabolic syndrome

Randomisation
(440 patients)

Amiloride	Amiloride + HCTZ	HCTZ
10mg to 20mg	5mg to 10mg 12·5 to 25 mg	25mg to 50mg
Force-titration at 12 weeks	*Force-titration at 12 weeks*	*Force-titration at 12 weeks*

Primary Outcome

Difference from baseline in 2-hr glucose at 12 & 24 weeks, on oral glucose tolerance test (OGTT)

Principal Secondary Outcome

Difference in home SBP at 12 and 24 weeks.

Hierarchical Primary End-point

i. Difference in change from baseline in OGTT 2-hour glucose between **amiloride** and hydrochlorothiazide

Significant

Not-significant

ii. Difference in change from baseline in OGTT 2-hour glucose between **combination** and hydrochlorothiazide

Secondary Outcome Measures

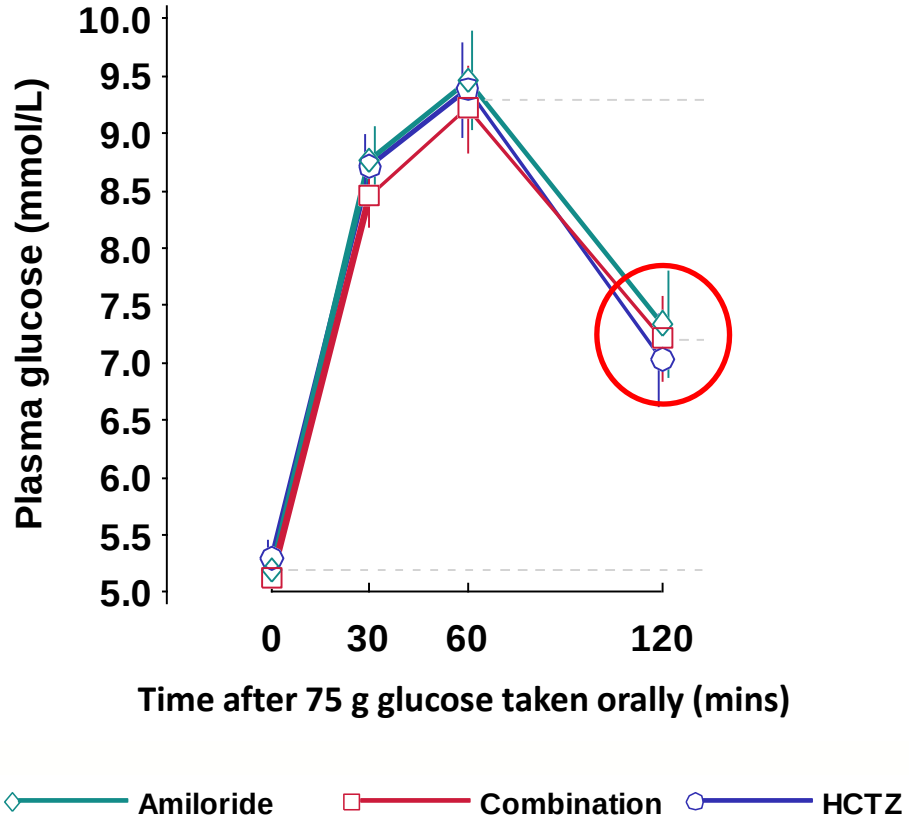
Secondary outcomes include:

- Home systolic BP responses to each treatment
- Serum K^+
- Uric acid
- HbA1c
- Insulin (0 and 30 minutes) and HOMA-ir
- Safety and adverse events

Baseline Patient Demographics

	Amiloride n=132
Age (years)	62 (10)
Female	52 (39%)
Body-mass index (kg/m2)	31 (7·6)
Blood Pressure (mmHg)	154 (11) /91 (10)

Oral glucose tolerance test (OGTT)



Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ

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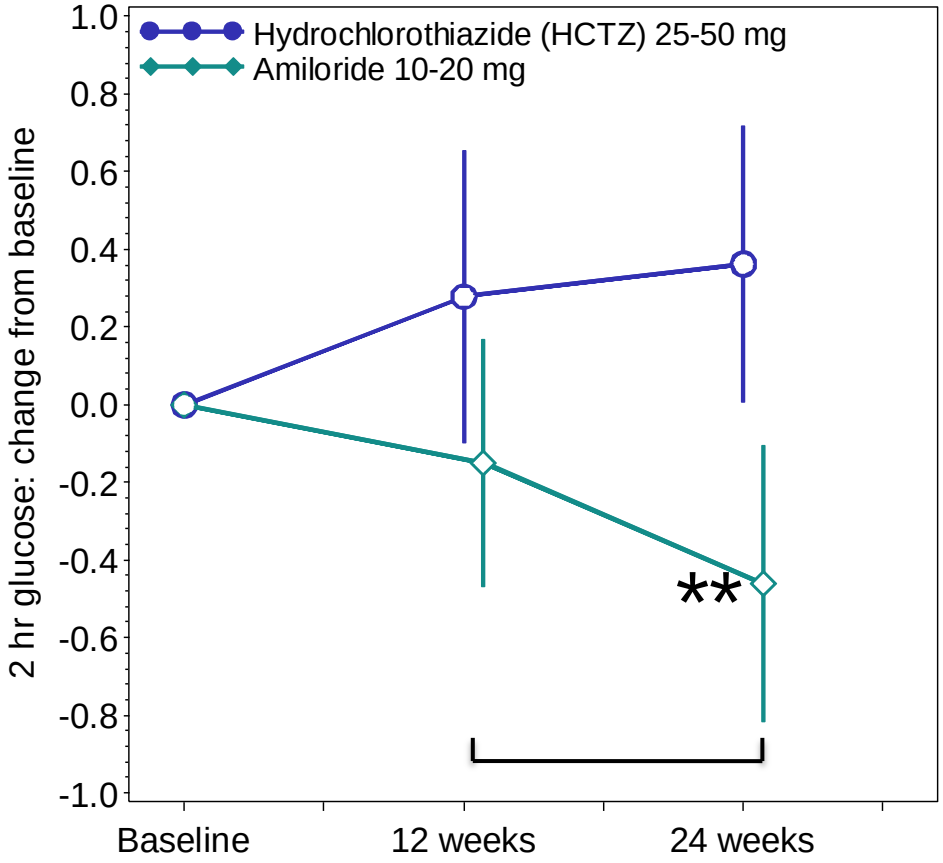


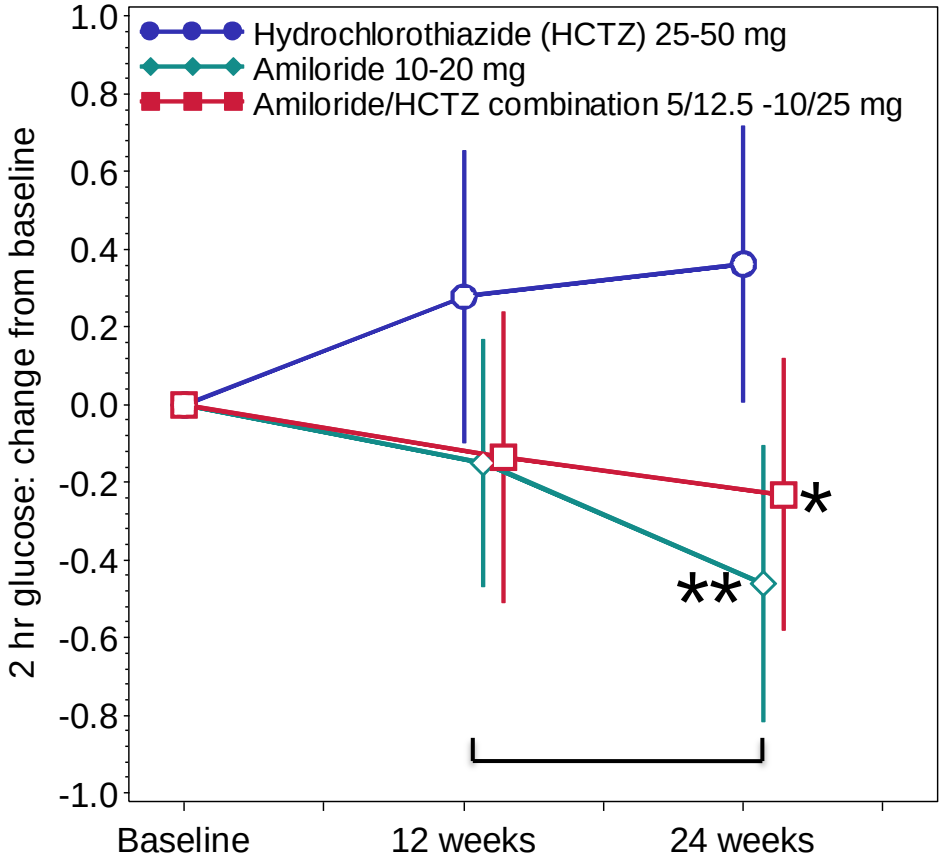
Average difference from HCTZ (mmol/L) (12 & 24 weeks)

Amiloride n=132
-0.55 (-0.14,-0.96)
P=0.009

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ

Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ, [ii] combination vs HCTZ



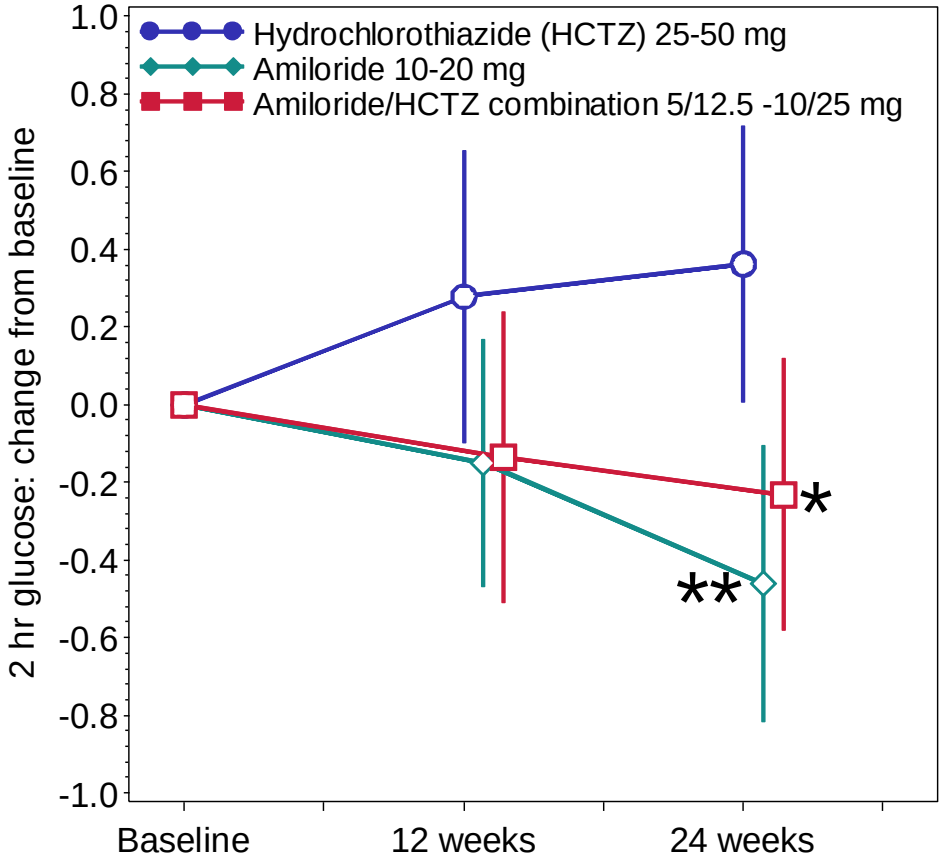
Average difference from HCTZ (mmol/L) (12 & 24 weeks)

Amiloride n=132	Amiloride/HCTZ n=133
-0.55 (-0.14,-0.96)	**- 0.42 (-0.004,-0.84)**
P=0.009	**P=0.048**

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ; *=p<0.05 vs HCTZ

Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ, [ii] combination vs HCTZ



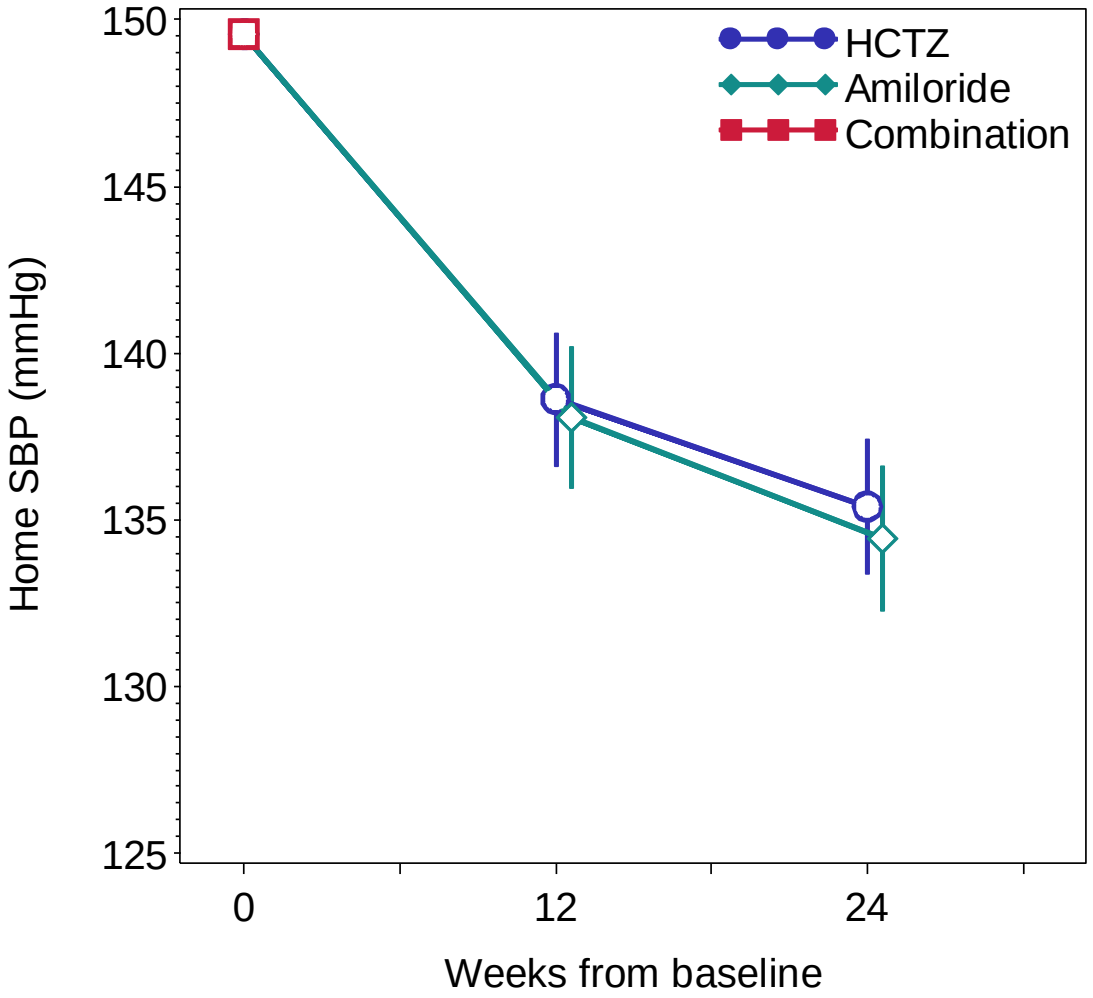
High-dose difference from HCTZ (mmol/L) (24 weeks)

Amiloride n=132	Amiloride/HCTZ n=133
0.71 (0.21,1.21)	0.58 (0.08,1.06)
P=0.005	P=0.024

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ; *=p<0.05 vs HCTZ

Secondary endpoints

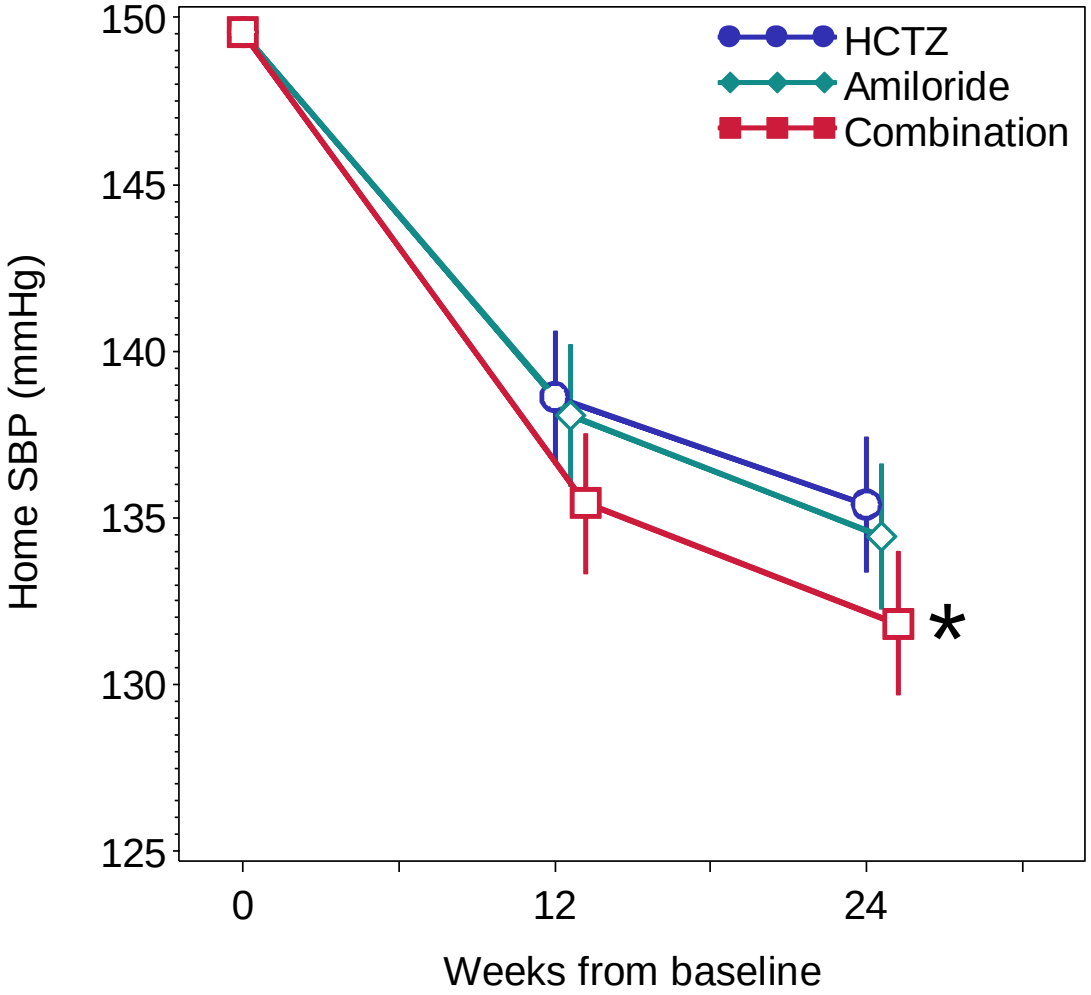
Blood Pressure reduction



Home SBP (mean, 95% CI) adjusting for baseline covariates

Secondary endpoints

Blood Pressure reduction



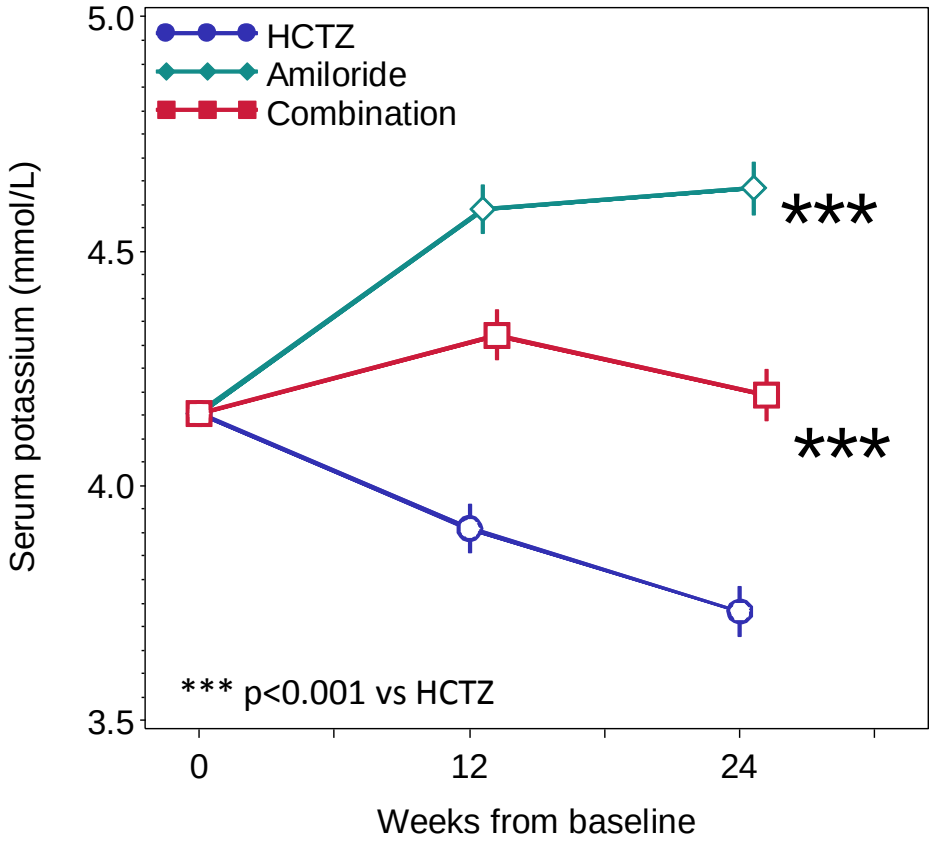
Home SBP (mean, 95% CI) adjusting for baseline covariates

* p=0.02 for combination vs HCTZ at week 24.

Across weeks 12 (low-dose) and 24 (high-dose), BP fall on combination of amiloride and HCTZ was 3·4 (0·9, 5·8) mmHg greater than on HCTZ (p=0·007)

Secondary Outcomes

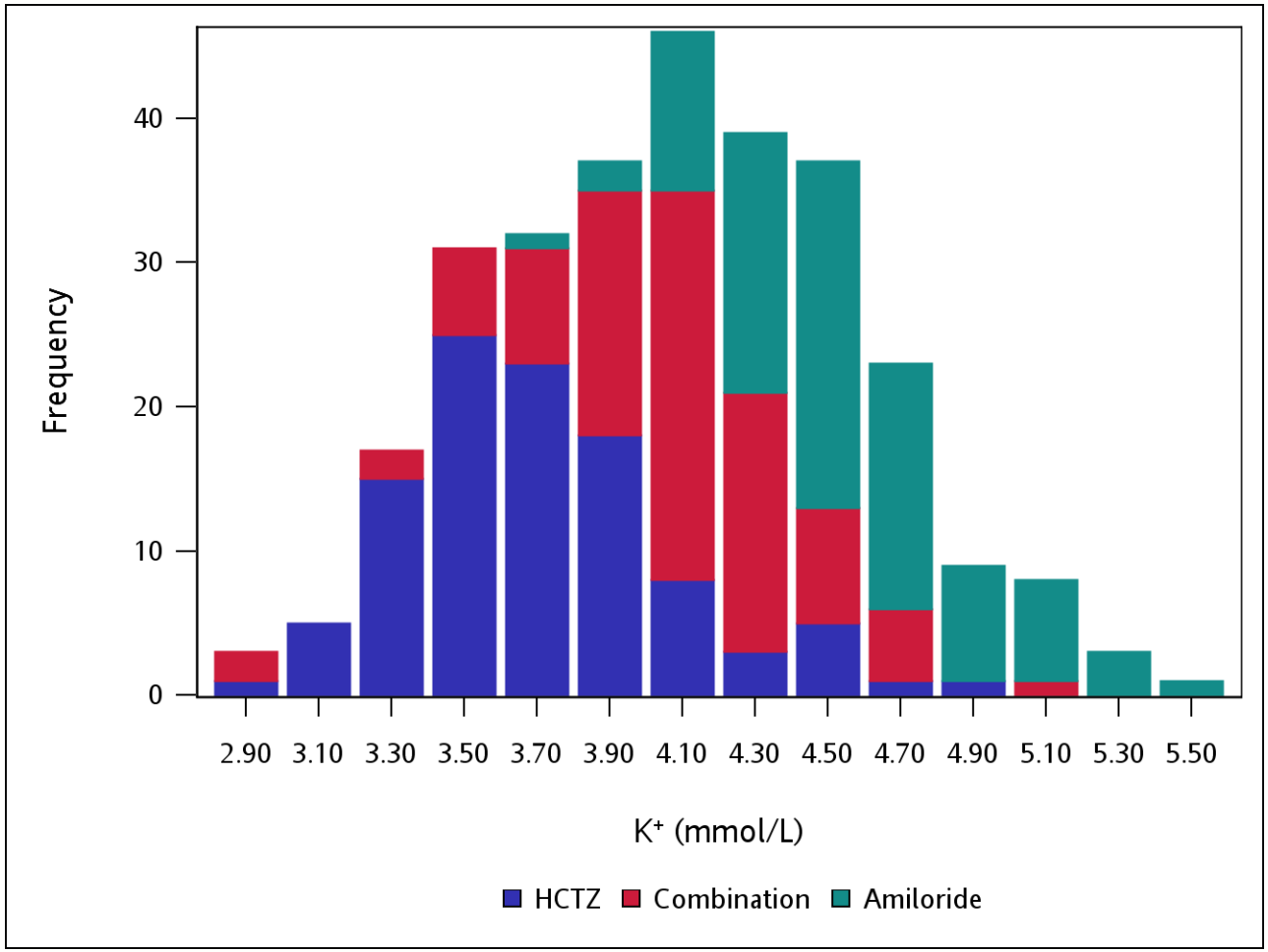
Potassium



Mean (95% CI) serum potassium, on a model adjusting for baseline covariaties

Safety data

Incidence/severity of hypo/hyperkalaemia



Summary - 1

- **Amiloride 10-20 mg** had the opposite effects to HCTZ 25-50 mg on 2-hour glucose and K^+ ($p<0.01$), but achieved the same fall in BP (-14 mmHg)
- **Combination of Amiloride-with-HCTZ** was neutral for glucose and K^+, and reduced BP by 3.4 mmHg more than twice the dose of each single diuretic ($p=0.007$)
- Amiloride was well tolerated, with no instances of K^+ >5.8 mmol/L despite background ACEi/ARB

Implications of findings

- The combination of amiloride and HCTZ is a 'win-win' which at equipotent doses
  - amplifies the desirable effects of each drug on BP,
  - neutralizes the undesirable changes in blood glucose and potassium
- Amiloride-HCTZ is the only diuretic with superiority in outcome trials (vs CCB[1] and beta-blockade[2])
- In summary, PATHWAY-2 and PATHWAY-3 show that K^+-sparing diuretics are effective and safe, and can be preferred choices for the treatment of hypertension

[1]Brown et al. Lancet, **356**:366- 372, 2000; [2]MRC Working Party. *BMJ* 1992; **304**: 405-12