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
DECLARATION OF INTEREST

- I have nothing to declare
**PATHWAY Executive Committee**

<table>
<thead>
<tr>
<th>Morris J Brown (Chairman): University of Cambridge</th>
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<tr>
<td>Thomas MacDonald: University of Dundee</td>
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<td>Bryan Williams: University College London</td>
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**Data Centre and Monitor**

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Sharon Kean, Richard Papworth, Robbie Wilson, Ian Ford  
**Monitor:** Elizabeth Sprunt

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

- **Cambridge:** Anne Schumann, Jo Helmy, Carmela Maniero, Timothy J Burton, Ursula Quinn, Lorraine Hobbs, Jo Palmer,  
  **Ixworth:** John Cannon, Sue Hood  
- **Birmingham:** (2 sites) Una Martin, Richard Hobbs, Rachel Iles  
- **Dundee:** Alison R McGinnis, JG Houston, Evekyn Findlay, Caroline Patterson,  
  **Kings College London:** Krzysztof Rutkowski  
- **Leicester:** Adrian G Stanley, Christobelle White, Peter Lacy, Pankaj Gupta, Sheraz A Nazir, Caroline J. Gardiner-Hill  
- **Imperial College London:** Judith Mackay, Simon A McG Thom, Candida Coghlan  
- **Edinburgh:** Vanessa Melville, Iain M MacIntyre  
- **Manchester:** Handrean Soran, See Kwok, Karthirani Balakrishnan  
- **St Barts London:** David Collier, Nirmala Markandu, Manish Saxena, Anne Zak, Enamuna Enobakhare  
- **Norwich:** Khin Swe Myint, Judith Gowlett  
- **Glasgow:** Scott Muir, Linsay McCallum

**PATHWAY Steering Committee**

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<thead>
<tr>
<th>Morris J Brown – Chairman</th>
<th>Gordon McInnes,</th>
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<tr>
<td>Thomas MacDonald</td>
<td>Peter Sever</td>
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<td>Bryan Williams</td>
<td>Isla MacKenzie</td>
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<td>Jackie Salsbury – Co-ordinator</td>
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<td>J Kennedy Cruickshank</td>
<td>Steve Morant - Statistician</td>
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<td>Ian Ford</td>
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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 diuretics²

Study Methods and Design

Screening

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

Randomisation
(440 patients)

Amiloride
10mg to 20mg
Force-titration at 12 weeks

Amiloride + HCTZ
5mg to 10mg  12.5 to 25 mg
Force-titration at 12 weeks

HCTZ
25mg to 50mg
Force-titration at 12 weeks
Randomisation
(440 patients)

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

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

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

Not-significant
SecondaryOutcome 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

<table>
<thead>
<tr>
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<th>Amiloride n=132</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62 (10)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (39%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>31 (7.6)</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>154 (11) / 91 (10)</td>
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</table>
Oral glucose tolerance test (OGTT)

Plasma glucose (mmol/L)

Minutes

0 30 60 120

Time after 75 g glucose taken orally (mins)

Plasma glucose (mmol/L)

5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

Amiloride Combination HCTZ

Baseline 12 weeks 24 weeks

** *
Hierarchical primary endpoints

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

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

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

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

<table>
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<tr>
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<th>Amiloride 10-20 mg</th>
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<tbody>
<tr>
<td>n</td>
<td>132</td>
</tr>
<tr>
<td>Average difference from HCTZ</td>
<td>-0.55 (-0.14,-0.96)</td>
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<tr>
<td>P</td>
<td>0.009</td>
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</tbody>
</table>
**Hierarchical primary endpoints**

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

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

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 covariates

*** p<0.001 vs HCTZ
Safety data

Incidence/severity of hypo/hyperkalaemia
• **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