BLOOD PRESSURE CONTROL IN EUROPE

Comparing EUROASPIRE II and IV
**THERAPEUTIC CONTROL OF BLOOD PRESSURE* (%) EUROASPIRE III VS. IV**

<table>
<thead>
<tr>
<th>Country</th>
<th>Bulgaria</th>
<th>Croatia</th>
<th>Poland</th>
<th>Romania</th>
<th>UK</th>
<th>Overall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+23.5%</td>
<td>+6.3%</td>
<td>+0.9%</td>
<td>+0.7%</td>
<td>+7.0%</td>
<td>+8.5%</td>
<td>P=0.12</td>
</tr>
</tbody>
</table>

* SBP/DBP <140/90 mmHg in patients using blood pressure lowering drugs
  140/80 mmHg in diabetes

K. Koteseva (London, UK), FP 5069
Resistant hypertension has been defined as uncontrolled blood pressure (BP) despite treatment with maximal tolerated doses of 3 BP-lowering medications, usually; an ACE-inhibitor or ARB + CCB + Thiazide-like Diuretic,

The optimal drug treatment of resistant hypertension remains undefined.

There have been no RCTs directly comparing spironolactone with other BP-lowering drugs to determine whether spironolactone is the most effective treatment for resistant hypertension.

HYPOTHESIS: Further diuretic therapy with spironolactone will be more effective at lowering BP than alternative BP-lowering treatments, targeting different mechanisms.
**PATHWAY-2 STUDY DESIGN**

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

- **314 Patients with Resistant Hypertension**
  - Rx 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

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

- **Plasma Renin**

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

- Baseline Clinic BP (mmHg) **157/90**
- Baseline Home BP (mmHg) **148/84**

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

*DOT = Directly Observed Therapy*
## PRIMARY OUTCOME

<table>
<thead>
<tr>
<th>Comparators (N=314)</th>
<th>Home Systolic BP difference (mmHg)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone vs placebo</td>
<td>-8.70 (-9.72,-7.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs mean Bisoprolol/Doxazosin</td>
<td>-4.26 (-5.13,-3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Doxazosin</td>
<td>-4.03 (-5.04,-3.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Bisoprolol</td>
<td>-4.48 (-5.50,3.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### SERIOUS ADVERSE EVENTS AND WITHDRAWALS

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol</th>
<th>Spironolactone</th>
<th>Doxazosin</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>8 (2.6%)</td>
<td>7 (2.3%)</td>
<td>5 (1.7%)</td>
<td>5 (1.7%)</td>
<td>0.831</td>
</tr>
<tr>
<td><strong>Any adverse event</strong></td>
<td>68 (11.3%)</td>
<td>67 (10.4%)</td>
<td>58 (10.1%)</td>
<td>42 (9.1%)</td>
<td>0.711</td>
</tr>
<tr>
<td><strong>Withdrawals for adverse events</strong></td>
<td>2 (2.9%)</td>
<td>3 (3.4%)</td>
<td>8 (10.0%)</td>
<td>2 (2.6%)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

*p values for Fisher’s exact test*
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 was 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.
Use of thiazide diuretics for hypertension has been complicated by glucose intolerance and hypokalemia, which has resulted in them being used in lower doses.

Potassium-sparing diuretics such as amiloride have been avoided because of a perceived lack of BP-lowering efficacy and increased risk of hyperkalemia on a background of increasing use of RAS blockers.

Increased risk of diabetes with thiazides appears linked to potassium-depletion – could this be avoided by using potassium-sparing diuretics, alone or in combination?
STUDY METHODS AND DESIGN

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

(440 patients)

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.

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

M. J. Brown (Cambridge, UK) FP 4140

PATHWAY
Clinical Trials in Hypertension

ESC CONGRESS
LONDON 2015
Congress Highlights
www.escardio.org/ESC2015
**HIERARCHICAL PRIMARY ENDPOINTS**

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

![Graph showing glucose change from baseline for amiloride and HCTZ](image)

- **Amiloride 10-20 mg**
  - Average difference from HCTZ (mmol/L) (12 & 24 weeks)
    - **Amiloride n=132**
      - **-0.55 (-0.14, -0.96)**
      - **P=0.009**

**M. J. Brown (Cambridge, UK) FP 4140**
**HIERARCHICAL PRIMARY ENDPOINTS**

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

### Graphical Representation

- **Line Graph**: Comparing changes in 2 hr glucose from baseline over 24 weeks with different treatments.

### Table: High-Dose Difference from HCTZ (mmol/L) (24 weeks)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Amiloride (0.21,1.21)</th>
<th>Amiloride/HCTZ (0.08,1.06)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>132</td>
<td>0.71</td>
<td>0.58</td>
</tr>
<tr>
<td>Amiloride/HCTZ combination</td>
<td>133</td>
<td><strong>0.58 (0.08,1.06)</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Statistical Significance

- **P = 0.005** for Amiloride group.
- **P = 0.024** for Amiloride/HCTZ combination group.

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*M. J. Brown (Cambridge, UK) FP 4140*
SECONDARY ENDPOINTS
BLOOD PRESSURE REDUCTION

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

- HTCZ
- Amiloride
- Combination

* p=0.02 for combination vs HCTZ

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SECONDARY OUTCOMES
POTASSIUM

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

- Hydrochlorothiazide (HCTZ) 25-50 mg
- Amiloride 10-20 mg
- Combination (Amiloride/HCTZ 5/12.5-10/25 mg)

*** p<0.001 vs HCTZ

M. J. Brown (Cambridge, UK) FP 4140
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\(^2\))

PATHWAY-2 and PATHWAY-3 show that K\(^+\)-sparing diuretics are effective and safe for the treatment of hypertension

M. J. Brown (Cambridge, UK) FP 4140
ARB/NEPRILYSIN INHIBITOR (ARNI) IN PATIENTS WITH SYSTOLIC HYPERTENSION

PARAMETER Study
NOVEL MECHANISM OF ACTION OF LCZ696, A FIRST-IN-CLASS ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR (ARNI)

NP system

Inactive fragments

Inactive fragments

Neprilysin

Natriuretic peptides (NPs)

Angiotensin receptor neprilysin inhibitor (sacubitril/valsartan)

RAAS

Inactive fragments

Neprilysin

AT₁ receptor

Ang II

Natriuresis/diuresis

Renin secretion

Sodium and water retention

Vasodilation

Blood pressure

Large artery stiffness

Vasoconstriction

Blood pressure

Vascular remodeling

Hypertrophy

Fibrosis

Sympathetic outflow

NP, natriuretic peptides;

RAAS, renin-angiotensin-aldosterone system
PARAMETER: STUDY DESIGN

Multicenter, randomized, double-blind, active-controlled, 52-week study to evaluate the safety and efficacy of an LCZ696 regimen on central aortic pressures and arterial stiffness in elderly hypertensive patients.

Patient population: Isolated Systolic Hypertension with Stiff Arteries

- 454 patients aged ≥60 years
- Elevated SBP (≥150 mmHg) & wide pulse pressure (>60 mmHg)
PARAMETER Study:
PRIMARY AND KEY SECONDARY OUTCOMES:
CHANGE FROM BASELINE IN MEAN CASP AND CPP AT WEEK 12

**SBP – 12 week**
- LCZ696: -12.6 mmHg (p=0.016)
- Olmesartan: -8.9 mmHg

**PP – 12 week**
- LCZ696: -6.4 mmHg
- Olmesartan: -4.0 mmHg (p=0.013)

BP, blood pressure; PP, pulse pressure; SBP, systolic blood pressure
CHANGE IN BRACHIAL SBP AND PP AT WEEK 12

BP, blood pressure; PP, pulse pressure; SBP, systolic blood pressure

∆ BP (mmHg)

SBP – 12 week

-13.7

N=207

Δ-3.8 mmHg (p=0.016)

PP – 12 week

-7.7

N=207

-4.9

N=206

Δ-2.8 mmHg (p=0.013)

LCZ696

Olmesartan

BP, blood pressure; PP, pulse pressure; SBP, systolic blood pressure
24-HOUR BRACHIAL AND CENTRAL AORTIC SBP AT WEEK 12

Mean Δ SBP: -4.1 mmHg, p<0.001 (-13.2 (LCZ696) vs. -9.1 (OLM) mmHg)
Mean Δ cSBP: -3.35 mmHg, p<0.001 (-12.1 (LCZ696) vs. -8.7 (OLM) mmHg)
CHANGE FROM BASELINE IN NT-proBNP AND URINARY cGMP AT WEEK 12

**NT-proBNP**
- Baseline: 93 pg/ml, N=196
- Week 12: 87 pg/ml, N=200
- Change: ↓20% (-27, -12%)
- % change in geometric means from baseline, 95% CI

**Urinary cGMP**
- Baseline: 460 nmol/L, N=197
- Week 12: 441 nmol/L, N=201
- Change: ↑59% (43, 78%)

NT-proBNP, N-terminal pro brain natriuretic peptide; cGMP, cyclic guanosine monophosphate

LCZ696  Olmesartan

0 (-9, 10%)
PARAMETER study - Conclusions

- PARAMETER is the first randomized study demonstrating the ability of LCZ696 to reduce central BP and PP, more effectively than an ARB, in high-risk older patients with systolic hypertension and an increased pulse pressure.

- These results suggest that LCZ696 provides beneficial effects on central aortic haemodynamics and function, that could provide a therapeutic advantage beyond those observed with RAS blockade alone.
BP control rates in Europe have improved but are still inadequate

Hypertension Treatments ‘Old and New’

The ‘Old’ – A potassium-sparing diuretic ‘renaissance’

Spironolactone very effective and safe in resistant hypertension

Higher dose amiloride as effective as a thiazide at lowering BP and the potential to reduce risk of diabetes and hypokalemia associated with thiazides

The ‘New’ – Angiotensin receptor neprilysin inhibitor (ARNI) – reduces aortic and brachial BP and NT-proBNP in systolic hypertension – where next?
CLINICAL REALITY OF PRIMARY PREVENTION IN PEOPLE AT HIGH CARDIOVASCULAR RISK IN EUROPE

A comparison of EUROASPIRE III and IV surveys in general practice

Kornelia Kotseva
National Heart and Lung Institute, Imperial College London, UK on behalf of EUROASPIRE IV Investigators
STUDY POPULATION

- EUROASPIRE III & IV Countries
  - Bulgaria, Croatia, Poland, Romania, UK

<table>
<thead>
<tr>
<th>Survey</th>
<th>Time period</th>
<th>Patients</th>
<th>Women n (%)</th>
<th>Age (years) mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUROASPIRE III</td>
<td>2007-2008</td>
<td>1985</td>
<td>1194 (60)</td>
<td>58±10</td>
</tr>
<tr>
<td>EUROASPIRE IV</td>
<td>2014-2015</td>
<td>1842</td>
<td>1002 (54)</td>
<td>59±12</td>
</tr>
</tbody>
</table>

8 year time trend in the management of patients at high risk of cardiovascular disease

K. Koteseva (London, GB), FP 5069
OBESE PATIENTS EVER BEEN TOLD BY A HEALTH CARE PROFESSIONAL THAT THEIR DIET IS UNHEALTHY (%)

<table>
<thead>
<tr>
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<th>Bulgaria</th>
<th>Croatia</th>
<th>Poland</th>
<th>Romania</th>
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<th>Overall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-7.6%</td>
<td>+0.9%</td>
<td>+1.5%</td>
<td>-6.0%</td>
<td>-11.3%</td>
<td>-3.7%</td>
<td>P=0.24</td>
</tr>
</tbody>
</table>

*Body mass index $\geq 30 \text{ kg/m}^2$*

→ Over 80% of high CVD risk patients were overweight or obese.

K. Koteseva (London, GB), FP 5069
Proportions at goal for CVD prevention

<table>
<thead>
<tr>
<th>Lifestyles (%)</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No smoking</td>
<td>78</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Not obese</td>
<td>60</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Physically active</td>
<td>34</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Risk factor management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP &lt;140/90 mm Hg (&lt;140/80 if diabetes)</td>
<td>37</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>LDL-C &lt;2.5 mmol/L (100 mg/dL)</td>
<td>23</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>
Risk factors are not adequately managed in patients at high risk of cardiovascular disease.

More concerted efforts are required to promote a healthy lifestyle and achieve therapeutic goals.
PREVENTION AND HYPERTENSION

R. Ferrari