PREVENTION

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Conflicts of Interest
DISCLOSURE

- Consultant / Member of Advisory Boards and Committees:
  Bristol Myers Squibb, NILE Therapeutics, Novartis, Servier, Torrent

- Speaker:
  AstraZeneca, BMS, GlaxoSmithKline, MSD, Menarini, Sanofi-Aventis, Servier
STUDIES / TRIALS

- Euroaspire
- TECOS
- New onset diabetes in Improve IT
- Benefit of adding Ezetemibe to Statin therapy on CV outcomes in patients with and without diabetes
- Hypertension
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
OBESE PATIENTS EVER BEEN TOLD BY A HEALTH CARE PROFESSIONAL THAT THEIR DIET IS UNHEALTHY (%)

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulgaria</td>
<td>-7.6%</td>
</tr>
<tr>
<td>Croatia</td>
<td>+0.9%</td>
</tr>
<tr>
<td>Poland</td>
<td>+1.5%</td>
</tr>
<tr>
<td>Romania</td>
<td>-6.0%</td>
</tr>
<tr>
<td>UK</td>
<td>-11.3%</td>
</tr>
<tr>
<td>Overall</td>
<td>-3.7%</td>
</tr>
</tbody>
</table>

P = 0.24

*Body mass index ≥30 kg/m²*

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

K. Koteseva (London, GB), FP 5069
**EUROASPIRE IV: PRIMARY CARE**

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.
IMPACT OF SITAGLIPTIN ON HEART FAILURE AND RELATED OUTCOMES

Frans Van de Werf, MD, PhD
University of Leuven, Belgium
PRIMARY COMPOSITE CARDIOVASCULAR OUTCOME* PER PROTOCOL ANALYSIS FOR NONINFERIORITY

HR (95% CI): 0.98 (0.88, 1.09)
Noninferiority P<0.001

Median FU 2 years

* CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina

F. Van de Werf (Leuven, BE), FP 4128
TIME TO FIRST HOSPITALIZATION FOR HEART FAILURE*

HR (95% CI): 1.00 (0.84–1.20)
P = 0.95

* ITT population

F. Van de Werf (Leuven, BE), FP 4128
Sitagliptin can be safely used in type 2 DM without concern for new onset or worsening heart failure.
NEW-ONSET DIABETES MELLITUS IN THE IMPROVE-IT TRIAL

Michael A. Blazing, Darren K. McGuire, Christopher P Cannon; Robert P. Giugliano, Peter P. Toth, Jennifer A. White, Yuliya V. Lokhnygina, Andrew M. Tershakovec, Thomas A. Mussliner and Eugene Braunwald on behalf of the IMPROVE-IT Investigators
Patients stabilized post ACS ≤ 10 days:
LDL-C 1.3*–3.2† mM/L (or 1.3*–2.6** mM/L if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

Placebo / Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

*50 mg/dL
**100 mg/dL
†125 mg/dL

90% power to detect ~9% difference

CP. Cannon, NEJM 2015;372:2387-2397
PRIMARY OUTCOME

- New onset diabetes mellitus = hyperglycemic medication and/or 2 fasting glucose concentrations > 7 mmol/L
- Median follow up 67 months
- 1,414 (13.3%) patients with New Onset Diabetes Mellitus

**HR 1.04 (CI 0.94-1.15) p=0.46**

Decreased risk with Ez/Simva

Increased risk with Ez/Simva

M. Blazing (Durham, US), FP 5774
Addition of Ezetimibe to simvastatin compared to placebo is not associated with an increase in the incidence of diabetes mellitus.
BENEFIT OF ADDING EZETIMIBE TO STATIN THERAPY ON CARDIOVASCULAR OUTCOMES AND SAFETY IN PATIENTS WITH VS. WITHOUT DIABETES

IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial

RP Giugliano, CP Cannon, MA Blazing, JC Nicolau, R Corbalan, J Spinar, JG Park, JA White, E Braunwald on behalf of the IMPROVE-IT Investigators
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>No DM (N=13,202)</th>
<th>DM (N=4933)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Body mass index (Kg/M²)</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>MI prior to index ACS</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>PCI / CABG prior to index ACS</td>
<td>18 / 8</td>
<td>24 / 14</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Aspirin prior to index ACS</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55</td>
<td>78</td>
</tr>
<tr>
<td>B-blocker / RAA inhibitor prior</td>
<td>31 / 34</td>
<td>44 / 60</td>
</tr>
<tr>
<td>Current smoker</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>ST-Elevation MI</td>
<td>32</td>
<td>21</td>
</tr>
</tbody>
</table>

Data shown are % unless otherwise indicated

P < 0.001 for each No DM vs DM comparison; P=NS for comparisons by randomized Rx, stratified by DM

R.P. Giugliano (Boston, US), FP 1947
PRIMARY ENDPOINT — ITT

- Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

\[ P_{int} = 0.023 \]

<table>
<thead>
<tr>
<th></th>
<th>DM Present</th>
<th>7 yr KM rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plac/Simva</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>EZE/Simva</td>
<td>40.0%</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.86 (0.78, 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No DM</th>
<th>7 yr KM rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plac/ Simva</td>
<td>30.8%</td>
<td></td>
</tr>
<tr>
<td>EZE/ Simva</td>
<td>30.2%</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.98 (0.91, 1.04)</td>
<td></td>
</tr>
</tbody>
</table>

R.P. Giugliano (Boston, US), FP 1947
In the IMPROVE-IT study population, patients with diabetes mellitus showed greater relative and absolute benefit with aggressive lipid lowering compared to patients without diabetes.

The greater benefit in diabetic patients was driven by the reduction in the risk of myocardial infarction and ischaemic stroke.
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
DRUG TREATMENT OF RESISTANT HYPERTENSION

PATHWAY-2
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
BACKGROUND

- 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

B. Williams (London, UK) FP 4137
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

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

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

- Home Systolic BP measured at 6 and 12 weeks

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

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

*DOT = Directly Observed Therapy

B. Williams (London, UK) FP 4137
<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*

B. Williams (London, UK) FP 4137
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.
RE-EVALUATING DIURETICS FOR HYPERTENSION

PATHWAY-3
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)

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

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

HCTZ
25mg to 50mg
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.

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Amiloride 10-20 mg</th>
<th>Hydrochlorothiazide (HTCZ) 15-50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks change from baseline (mmol/L)</td>
<td>-0.55 (-0.14, -0.96)</td>
<td></td>
</tr>
<tr>
<td>24 weeks change from baseline (mmol/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>2 hr glucose change from baseline</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>132</td>
<td>-0.71 (0.21, 1.21)</td>
<td>0</td>
<td>-0.5</td>
<td>-0.2</td>
</tr>
<tr>
<td>Amiloride/HCTZ combination</td>
<td>133</td>
<td>0.58 (0.08, 1.06)</td>
<td>0.58</td>
<td>0.08</td>
<td>0.06</td>
</tr>
</tbody>
</table>

P = 0.005 for Amiloride vs HCTZ
P = 0.024 for Amiloride/HCTZ combination vs HCTZ

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

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

* p=0.02 for combination vs HCTZ

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

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

Neprilysin

NPs

NP system

Inactive fragments

Neprilysin

NP, natriuretic peptides; RAAS, renin-angiotensin-aldosterone system

RAAS

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

B. Williams (London, UK) FP 4143
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)

B. Williams (London, UK) FP 4143
PARAMETER Study: PRIMARY AND KEY SECONDARY OUTCOMES: CHANGE FROM BASELINE IN MEAN CASP AND CPP AT WEEK 12

- **SBP** - 12 week
  - LCZ 696: -12.6 mmHg (p=0.016)
  - Olmesartan: -8.9 mmHg
  - N=207

- **PP** - 12 week
  - LCZ 696: -6.4 mmHg
  - Olmesartan: -4.0 mmHg
  - N=206

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

B. Williams (London, UK) FP 4143
CHANGE IN BRACHIAL SBP AND PP AT WEEK 12

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

<table>
<thead>
<tr>
<th></th>
<th>SBP – 12 week</th>
<th>PP – 12 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>-13.7 (N=207)</td>
<td>-7.7 (N=207)</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>-9.9 (N=206)</td>
<td>-4.9 (N=206)</td>
</tr>
</tbody>
</table>

Δ-3.8 mmHg (p=0.016)  Δ-2.8 mmHg (p=0.013)

B. Williams, (London, UK) FP 4143
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)
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.

B. Williams (London, UK) FP 4143
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?