Update on Hypertensive Cardiovascular Disease

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Case Presentation
Pre

Lesions

Balloon
Outline

> Effects of blood pressure on the risks of cardiovascular diseases
  > Epidemiological studies
> Effects of antihypertensive treatment
  > Randomized trials comparing the major drug classes

Stroke mortality in each decade of age by usual SBP at the start of that decade

11,274 deaths at ages 50 - 89

Age at risk: 20 mmHg ↓ SBP

- 80-89 33% ↓ risk
- 70-79 50% ↓ risk
- 60-69 57% ↓ risk
- 50-59 62% ↓ risk
- (40-49) 64% ↓ risk
CHD mortality in each decade of age by usual SBP at the start of that decade

33 867 deaths at ages 40 - 89

Age at risk 20 mmHg ↓ SBP
80-89 31% ↓ risk
70-79 40% ↓ risk
60-69 46% ↓ risk
50-59 50% ↓ risk
40-49 51% ↓ risk

Mortality from other vascular causes (not stroke or CHD): Hazard ratios for 20 mmHg lower usual SBP

9 790 deaths at ages 40-89

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Mean age at death</th>
<th>No. of deaths</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>68</td>
<td>746</td>
<td>0.55 (0.48-0.59)</td>
</tr>
<tr>
<td>Aortic Aneurysm</td>
<td>68</td>
<td>705</td>
<td>0.55 (0.49-0.62)</td>
</tr>
<tr>
<td>Hypertensive HD</td>
<td>68</td>
<td>649</td>
<td>0.22 (0.20-0.25)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>72</td>
<td>508</td>
<td>0.48 (0.42-0.55)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>60</td>
<td>553</td>
<td>0.49 (0.43-0.56)</td>
</tr>
<tr>
<td>Inflammatory HD</td>
<td>67</td>
<td>320</td>
<td>0.63 (0.53-0.75)</td>
</tr>
<tr>
<td>Rheumatic HD</td>
<td>64</td>
<td>255</td>
<td>0.74 (0.61-0.89)</td>
</tr>
<tr>
<td>Other HD (excl. IHD)</td>
<td>69</td>
<td>1682</td>
<td>0.62 (0.58-0.67)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>67</td>
<td>296</td>
<td>0.72 (0.60-0.87)</td>
</tr>
<tr>
<td>Other circulatory</td>
<td>65</td>
<td>182</td>
<td>0.56 (0.44-0.71)</td>
</tr>
</tbody>
</table>

Hazard ratio (& 95% CI) for 20 mmHg lower usual systolic BP
Coronary disease by usual SBP

Coronary heart disease: SBP and cholesterol
Conclusions

> Blood pressure continuously associated with risks of most cardiovascular diseases
> Associations steeper in younger than older individuals
> Similar associations in Asian and Caucasian populations
> Independent effects of blood pressure and cholesterol on risk

Outline

> Effects of antihypertensive treatment
  > Randomized trials comparing the major drug classes
A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B. Dahlof (Co-chair), P. Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O’Brien, J. Östergren, on behalf of the ASCOT Investigators

Study design

ASCOT-BPLA

19,257 hypertensive patients
atenolol ± bendroflumethiazide
PROBE design
amlodipine ± perindopril

ASCOT-LLA

10,305 patients
TC ≤ 6.5 mmol/L (250 mg/dL)
atorvastatin 10 mg
Double-blind
placebo

Investigator-led, multinational randomised controlled trial
Patient Population: LLA

Eligibility criteria

> SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (untreated) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (treated)
> TC ≤6.5 mmol/L (≤250 mg/dL) and TGs ≤4.5 mmol/L (≤400 mg/dL)
> 40-79 years of age
> 3+ CVD risk factors
> No history of CHD


ASCOT LLA: Patient Population Risk Factor Profile

All patients in ASCOT have hypertension plus ≥3 risk factors for CHD

Reductions in Total and LDL Cholesterol


Primary End Point: Nonfatal MI and Fatal CHD

Secondary End Point: Fatal and Nonfatal Stroke

- **Atorvastatin 10 mg**
  - Number of events: 89

- **Placebo**
  - Number of events: 121

Cumulative incidence (%): 27% reduction

HR = 0.73 (0.56-0.96)  \( P = 0.0236 \)

Years: 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

Secondary End Point: All CV Events and Procedures

- **Atorvastatin 10 mg**
  - Number of events: 389

- **Placebo**
  - Number of events: 486

Cumulative incidence (%): 21% reduction

HR = 0.79 (0.69-0.90)  \( P = 0.0005 \)

Years: 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

Summary and Conclusions

In well-managed hypertensive patients at modest risk of CHD and with normal to mildly elevated cholesterol levels, atorvastatin is associated with:

- A highly significant reduction in the primary end point of CHD (36%, $P=0.0005$)
- Significant reductions in the secondary end points of stroke (27%, $P=0.0236$), all cardiovascular events and procedures (21%, $P=0.0005$), and total coronary events (29%, $P=0.0005$)
- These reductions in major cardiovascular events are large given the short follow-up time (median 3.3 years) and occurred earlier than in many other statin trials
- There was no significant heterogeneity among pre-specified subgroups


CAMELOT
Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis

NORMALISE
Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation
CAMELOT / NORMALISE

Overview

> Double-blind, randomized trial comparing effect of Norvasc® (amlodipine besylate) vs enalapril vs placebo on CV events in 1991 normotensive CHD patients
> Norvasc significantly reduced composite CV endpoint by 31% vs placebo
  > 42% reduction in time to hospitalization for angina
  > 27% reduction in coronary revascularizations
> IVUS substudy in 274 patients showed that patients on Norvasc did not experience progression of plaque in the coronary arteries
  > Norvasc significantly reduced progression in patients with blood pressure greater than the mean

NORMALISE Study Design
NOrvasc for Regression of Manifest Atherosclerotic Lesions Intravascular Sonographic Evaluation

PTCA & Angiogram

431 Patients

IVUS & QCA

Amlodipine besylate
10 mg

Enalapril 20 mg

Placebo

24 Months

Repeat IVUS & QCA:
274 Patients

End Points
Change of atheroma volume by intravascular ultrasound


1991 Patients at 100 Centers, North America and Europe
Symptomatic CAD, Coronary Angiography With >20% Stenosis Diastolic BP ≤100 mm Hg

Baseline Intravascular Ultrasound in 431 Participants

Placebo

Enalapril 20 mg

Amlodipine 10 mg

24 Months Treatment

Intent-to-Treat Analysis of CV Events (1991 Patients)
Repeat IVUS Examination (274 Patients)

## CAMELOT Baseline Data

### Baseline Characteristics, Mean (SD) or Percentage of Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=655)</th>
<th>Enalapril (n=673)</th>
<th>Norvasc® (amlodipine besylate) (n=663)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years</td>
<td>57.2 (9.5)</td>
<td>58.5 (9.9)</td>
<td>57.3 (9.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Male Sex</td>
<td>73.0%</td>
<td>71.9%</td>
<td>76.3%</td>
<td>.16</td>
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<tr>
<td>White</td>
<td>89.0%</td>
<td>89.3%</td>
<td>89.4%</td>
<td>.97</td>
</tr>
<tr>
<td>BMI</td>
<td>29.7±5.0</td>
<td>29.7±5.5</td>
<td>29.9±5.5</td>
<td>.72</td>
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<tr>
<td>History of Hypertension</td>
<td>60.3%</td>
<td>59.7%</td>
<td>61.4%</td>
<td>.82</td>
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<tr>
<td>BP, mm Hg</td>
<td>128/78</td>
<td>129/77</td>
<td>130/78</td>
<td>N/A</td>
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<tr>
<td>History of Dyslipidemia</td>
<td>84.4%</td>
<td>83.7%</td>
<td>83.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>LDL-Cholesterol, mg/dL</td>
<td>100 (32)</td>
<td>101 (31)</td>
<td>104 (32)</td>
<td>.04</td>
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<tr>
<td>Diabetes</td>
<td>19.8%</td>
<td>17.5%</td>
<td>17.3%</td>
<td>.42</td>
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<tr>
<td>Unstable Angina†</td>
<td>9.9%</td>
<td>8.3%</td>
<td>8.1%</td>
<td>.45</td>
</tr>
<tr>
<td>Prior Bypass Surgery</td>
<td>8.2%</td>
<td>6.8%</td>
<td>8.0%</td>
<td>.59</td>
</tr>
<tr>
<td>Prior MI</td>
<td>37.7%</td>
<td>40.3%</td>
<td>37.4%</td>
<td>.50</td>
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<tr>
<td>Current Smoker</td>
<td>27.9%</td>
<td>24.8%</td>
<td>27.0%</td>
<td>.41</td>
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<tr>
<td>One-Vessel Disease‡</td>
<td>28.2%</td>
<td>27.8%</td>
<td>30.6%</td>
<td>.47</td>
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<tr>
<td>Two-Vessel Disease‡</td>
<td>34.1%</td>
<td>36.1%</td>
<td>32.7%</td>
<td>.42</td>
</tr>
<tr>
<td>Three-Vessel Disease‡</td>
<td>36.5%</td>
<td>34.8%</td>
<td>34.7%</td>
<td>.74</td>
</tr>
</tbody>
</table>

*Calculated by analysis of variance or χ². †Number of vessels with at least 1 stenosis >20% by visual estimation.


## CAMELOT: Treatments Received and Concomitant Medications

### Mean (SD) or Percentage of Patients

<table>
<thead>
<tr>
<th>Treatments Received</th>
<th>Placebo (n=655)</th>
<th>Enalapril (n=673)</th>
<th>Norvasc® (amlodipine besylate) (n=663)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titrated to Full Target Dosage</td>
<td>89.8%</td>
<td>84.3%</td>
<td>86.7%</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (SD) Dose Received, mg</td>
<td>N/A</td>
<td>17.4 (3.7)</td>
<td>8.6 (2.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Completed Trial</td>
<td>93.7%</td>
<td>92.4%</td>
<td>93.4%</td>
<td>.62</td>
</tr>
<tr>
<td>Discontinued Study Medication</td>
<td>31.1%</td>
<td>35.1%</td>
<td>29.3%</td>
<td>.07</td>
</tr>
<tr>
<td>Concomitant Medication (Percentage of Patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>84.3%</td>
<td>81.7%</td>
<td>83.1%</td>
<td>.46</td>
</tr>
<tr>
<td>Diuretics</td>
<td>33.4%</td>
<td>26.8%</td>
<td>32.1%</td>
<td>.02</td>
</tr>
<tr>
<td>β-blockers</td>
<td>78.8%</td>
<td>74.7%</td>
<td>74.2%</td>
<td>.11</td>
</tr>
<tr>
<td>Aspirin</td>
<td>95.4%</td>
<td>94.7%</td>
<td>94.4%</td>
<td>.69</td>
</tr>
<tr>
<td>ACEIs</td>
<td>12.8%</td>
<td>7.0%</td>
<td>7.4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ARBs</td>
<td>2.3%</td>
<td>1.6%</td>
<td>1.7%</td>
<td>.61</td>
</tr>
<tr>
<td>CCBs</td>
<td>12.1%</td>
<td>6.1%</td>
<td>5.0%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Analysis of variance. P value.

CAMELOT Primary Composite End Point

Adverse CV Events*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>655</td>
<td>655</td>
<td>588</td>
<td>558</td>
<td>525</td>
<td>488</td>
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<tr>
<td>673</td>
<td>673</td>
<td>608</td>
<td>572</td>
<td>553</td>
<td>529</td>
<td></td>
</tr>
<tr>
<td>663</td>
<td>663</td>
<td>623</td>
<td>599</td>
<td>574</td>
<td>535</td>
<td></td>
</tr>
</tbody>
</table>

31% Risk Reduction for Norvasc® (amlodipine besylate) vs Placebo (P=.003)
19% Risk Reduction for Norvasc vs Enalapril (P=.10)
15% Risk Reduction for Enalapril vs Placebo (P=.16)

CV death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina, hospitalization for CHF, fatal/nonfatal stroke or TIA, any new diagnosis of PVD.


CAMELOT: Time to Hospitalization for Angina

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>23.1%</td>
<td>20.2%</td>
<td>16.6%</td>
<td>15%</td>
<td>12.8%</td>
<td></td>
</tr>
</tbody>
</table>

42% Risk Reduction for Norvasc® (amlodipine besylate) vs Placebo (P=.002)
41% Risk Reduction for Norvasc vs Enalapril (P=.003)

7.7%

Data on file, Pfizer Inc.
CAMELOT: Time to Coronary Revascularization

27% Risk Reduction for Norvasc® (amlodipine besylate) vs Placebo ($P=.03$)
16% Risk Reduction for Norvasc vs Enalapril ($P=.24$)

Enalapril
Norvasc
Placebo

0 2 4 6 8 10 12 14 16 18
0 4 8 12 16 20 24
Event Rate (%) Time (Months)

Data on file, Pfizer Inc.

Ultrasound Measurement of Atheroma Area
Precise Manual Planimetry of EEM and Lumen Borders

EEM Area
Lumen Area
Atheroma Area

Image courtesy of Steven E. Nissen, MD.
IVUS Computation of Atheroma Volume

NORMALISE: Primary Intravascular Ultrasound End Point

Change in Percent Atheroma Volume = \[ \frac{\sum_{n} \frac{\text{EEM}_{\text{area}} - \text{LCS}_{\text{area}}}{\text{EEM}_{\text{area}}}}{\text{EEM}_{\text{area}}} \times \frac{\sum_{n} \frac{\text{EEM}_{\text{area}} - \text{LCS}_{\text{area}}}{\text{EEM}_{\text{area}}}}{\text{EEM}_{\text{area}}} \times 100 \]

Image courtesy of Steven E. Nissen, MD.

NORMALISE IVUS Progression: Percent Atheroma Volume

All Randomized Patients

Patients With BP > Mean

Change in Percent Atheroma Volume (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size</th>
<th>Change in Percent Atheroma Volume (%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>95</td>
<td>0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Enalapril</td>
<td>88</td>
<td>1.2</td>
<td>.08</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>91</td>
<td>1.6</td>
<td>=.31</td>
</tr>
</tbody>
</table>

Change in BP, mm Hg

LOWESS Plot of Change in Percent Atheroma Volume vs Change in BP in the Combined Treatment Group

The solid line represents the continuous relationship, surrounded by the dashed lines representing 95% CIs.

LOWESS = locally weighted scatterplot smoothing.

Adapted from Nissen et al, for the CAMELOT investigators. JAMA. 2004;292:2217-2226.
In normotensive patients with CAD treated with a standard of care regimen, including high rates of statin and aspirin use, addition of amlodipine besylate reduced:

> The primary end point, major adverse CV event, by 31%
> Hospitalization for angina by 42% vs placebo and 41% vs enalapril
> Coronary revascularization by 27%
> Enalapril was not statistically different vs placebo
> IVUS results demonstrate that patients on amlodipine did not experience atherosclerotic progression


Additional Implications for **CADUET®**
(amlodipine besylate / atorvastatin calcium)

CAMELOT / NORMALISE data also show

> Caduet may be an excellent choice for patients with CAD who require antianginal, antihypertensive, and antiatherosclerotic treatment
> Both parent components of Caduet, amlodipine besylate and atorvastatin calcium, appear to slow plaque progression in the coronary arteries

Background: **EUTOPIA**

- Atherosclerosis recognized as chronic vascular inflammation (1)
- IL-6 independently predicts cv events in established CHD and healthy populations (2)
- hsCRP – biomarker of IL-6 – is a better predictor of cv events than LDL-C [RR: 4.4 vs 2.4] (3)
- Weight loss, aspirin & statins can lower hsCRP (4)
- Pravastatin reduces events even when matched for LDL (5)
- However, evidence on ARBs is scant, despite the fact that angiotensin II is known to be pro-inflammatory (6)

Pathophysiology: Endothelial Dysfunction

Causes of endothelial dysfunction:
- ↑ LDL; free radicals due to smoking, HT, diabetes mellitus; genetic mutations
- ↑ homocysteine; HSV, Chlamydia infections
- Injury to endothelium results in inflammation (vasoactive molecules, cytokines, growth factors)
- Vessel wall thickening ('remodelling') if inflammation continues unabated
- Chronic inflammatory cells comprise macrophages & lymphocytes

Injury to endothelium results in inflammation (vasoactive molecules, cytokines, growth factors)

- Vessel wall thickening ('remodelling') if inflammation continues unabated
- Chronic inflammatory cells comprise macrophages & lymphocytes

Pathophysiology: Fatty Streak

- Fatty streak – the earliest pathological lesion – is infiltrated with lipid-laden inflammatory cells
- Formation of these foam cells is mediated by oxidized LDL, macrophage CSF, TNF-α, IL-1
- Markers of macrophage accumulation include fibrinogen, CRP

Formation of these foam cells is mediated by oxidized LDL, macrophage CSF, TNF-α, IL-1
Pathophysiology: Fibrin Cap or Plaque

- Advanced lesions – tend to form fibrous cap – becomes walled off
- This is a form of healing or fibrous response
- Fibrous cap contains necrotic core formed from apoptosis
- When chronic inflammation leads to uneven thinning of cap – plaque can rupture
- Plaque rupture usually occurs in non-occlusive lesions – difficult to diagnose by angiography
- This thrombotic process can ultimately lead to acute occlusion (ACS, AMI)

Pathophysiology: Atherogenicity of Angiotensin II

- Activated inflam cells in atherosclerotic plaque produces ACE
- Ang II induces inflam cell recruitment by increasing reactive-O-species
- Reactive-O-species induce chemokines (IL-6, MCP-1) & adhesion molecules (VCAM, ICAM)
- Thus, Ang II is pro-athergenic in vascular inflammation

Aims of study: **EUTOPIA**

> Evaluation of the anti-inflammatory and antihypertensive effect of olmesartan in patients with essential hypertension and signs of vascular micro-inflammation (hsCRP >3 mg/dL)
> Comparison of the anti-inflammatory effect of olmesartan with placebo using vascular inflammatory markers
> Examine effect of combination therapy with olmesartan & pravastatin

**Methods: EUTOPIA**

> Study design
  > Phase IIIB, randomized, PBO-controlled, double-blind, parallel
  > 2-wk anti-HT & washout & 2-wk PBO run-in
> Patients
  > 160 patients with essential hypertension
> Drugs
  > Olmesartan (20 mg) or placebo for 12 weeks
  > HCTZ (12.5/25 mg) added after 6 weeks (if SeDBP ≥ 90 mmHg)
  > Pravastatin (20 mg) added to both groups after 6 weeks
> Study duration
  > 12 weeks
> Endpoints
  > hsCRP, hsTNF-α, IL-6, ICAM-1, MCP-1
  > TC, LDL, HDL, TG
Inclusion Criteria: **EUTOPIA**

- Essential hypertension (SeDBP 95-110 for treatment-naive or washed out)
- Diagnosed atherosclerotic disease (CHD, PVD, CVD)
- Type II diabetes (HbA1C 8-12%) and/or LDL-cholesterol (3.89-6.48 mmol/L)
- No significant renal disease (creatinine >150 µmol/L, proteinuria >100 g/dL)
- No acute inflammation and/or hsCRP >20 mg/dL
- No statin intake within 3 months
- SeSBP ≤200 mmHg
- No other anti-HT drugs, lipid-lowering drugs, TCAs, long-acting nitrates

**Patient Demographics: EUTOPIA**

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Data and Inflammation Markers at Baseline of Patients With Essential Hypertension Treated With Olmesartan or Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan</td>
</tr>
<tr>
<td>(n=100)</td>
</tr>
<tr>
<td>Gender, M/F</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Necessity of taper-off of antihypertensive drugs, n</td>
</tr>
<tr>
<td>Atherosclerotic disease, n</td>
</tr>
<tr>
<td>Hypercholesterolemia, n</td>
</tr>
<tr>
<td>Diabetes mellitus type 2, n</td>
</tr>
<tr>
<td>Abnormal ECG at screening, n</td>
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<td>Smokers, n</td>
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<tr>
<td>Atriai fibril, n</td>
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<tr>
<td>hsCRP, mg/L</td>
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<tr>
<td>hsMIF-α, pg/ml</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
</tr>
<tr>
<td>MCP-1, pg/ml</td>
</tr>
</tbody>
</table>

*P<0.05, olmesartan vs placebo.

- No overall differences in randomized groups
- Apart more diabetic patients on placebo (offset benefits of active treatment)
Change from baseline in hsCRP:

**EUTOPIA**

![Change from baseline in hsCRP diagram](image)

Changes in serum concentrations of hsCRP (A) hsTNF-α (B), IL-6 (C), and MCP-1 (D) in patients with essential hypertension after 6 and 12 weeks of therapy with olmesartan (n=100) or placebo (n=98). Piroxicam was added to both treatment arms at week 6. *P<0.05, **P<0.01 vs baseline, #P<0.05, olmesartan vs placebo.

Change from baseline in hsTNF-α:

**EUTOPIA**

![Change from baseline in hsTNF-α diagram](image)

Changes in serum concentrations of hsCRP (A) hsTNF-α (B), IL-6 (C), and MCP-1 (D) in patients with essential hypertension after 6 and 12 weeks of therapy with olmesartan (n=100) or placebo (n=98). Piroxicam was added to both treatment arms at week 6. *P<0.05, **P<0.01 vs baseline, #P<0.05, olmesartan vs placebo.
Change from baseline in IL-6: **EUTOPIA**

C

<table>
<thead>
<tr>
<th>Week</th>
<th>Change from Baseline in IL-6</th>
<th>Omesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
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</tbody>
</table>

Changes in serum concentrations of IL-6 in patients with essential hypertension: after 6 and 12 weeks of therapy with olmesartan (n=100) or placebo (n=99). Pravastatin was added to both treatment arms at week 6. *P=0.05, **P=0.02, ***P=0.01 vs baseline. #P=0.05, olmesartan vs placebo.

Change from baseline in MCP-1: **EUTOPIA**

D

<table>
<thead>
<tr>
<th>Week</th>
<th>Change from Baseline in MCP-1</th>
<th>Omesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
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</tbody>
</table>

Changes in serum concentrations of MCP-1 in patients with essential hypertension: after 6 and 12 weeks of therapy with olmesartan (n=100) or placebo (n=99). Pravastatin was added to both treatment arms at week 6. *P=0.05, **P=0.02, ***P=0.01 vs baseline. #P=0.05, olmesartan vs placebo.
Effects on BP and lipids: EUTOPIA

Olmesartan reduced DBP and SBP at 6 and 12 weeks

Olmesartan did not affect lipid levels during first 6 wks

Compared to baseline, pravastatin reduced LDL cholesterol at 12 weeks (but did not appear to affect HDL/TG levels)

Conclusions

Olmesartan has been demonstrated to reduce markers of vascular inflammation (as early as 6 weeks compared to baseline; and specifically in TNF-α at 12 weeks)

This finding was observed in hypertensive patients with relatively high risk (eg established cv disease, metabolic syndrome)

Anti-inflammatory effect of olmesartan observed independently, as well as when combined with a statin

Interestingly, combination of olmesartan and pravastatin appears to further reduce inflammatory markers of atherosclerosis
Management of Heart Failure

Hypertension
- Left ventricular hypertrophy
- Diastolic dysfunction
- Systolic dysfunction
- Left ventricular remodeling

Atrial fibrillation

Coronary artery disease
- Myocardial infarction

Smoking
- Hyperlipidemia
- Diabetes
- Obesity

Progression of symptoms
↓↓ ↓↓
- Left ventricular function
- Exercise capacity

Heart failure

Tse HF 2006 (in press)
Heart Failure: How Big is the Problem Really?

Despite advances in diagnosis and treatment of HF, over 1 million patients will be hospitalized this year. HF hospitalizations continue to be one of the largest expenses for Centers for Medicare & Medicaid Services. There are currently no national guidelines for acute heart failure management.

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>4,900,000</td>
<td>550,000</td>
<td>50% within 5 years</td>
<td>1,000,000</td>
<td>$24.3 billion</td>
</tr>
</tbody>
</table>

AHA Statistics

Renin–Angiotensin–Aldosterone System

Weber KT. NEJM 2004;345:1689
Mechanisms of Hypertension

L Opie, Heart physiology, 2004

Serum Aldosterone and HT

Vasan RS, et al. NEJM, 2004; 351:33
RAAS in Heart Failure

Weber KT. NEJM 2004;345:1689

RAAS blockade in the management of CVS disease
### Major Outcomes Trials for ARBs

<table>
<thead>
<tr>
<th>Trials</th>
<th>Subject</th>
<th>Drugs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE</td>
<td>CHF</td>
<td>Losartan &gt;</td>
<td>Captopril</td>
</tr>
<tr>
<td>ELITE II</td>
<td>CHF</td>
<td>Losartan =</td>
<td>Captopril</td>
</tr>
<tr>
<td>RESOLVE</td>
<td>CHF</td>
<td>Candesartan=</td>
<td>Enalapil</td>
</tr>
<tr>
<td>ValHeFT</td>
<td>CHF</td>
<td>Valsartan</td>
<td>Add-on benefit</td>
</tr>
<tr>
<td>CHARM</td>
<td>CHF</td>
<td>Candesartan=</td>
<td>ACEI, Add-on benefit</td>
</tr>
<tr>
<td>OPTIMAAL</td>
<td>MI</td>
<td>Losartan =</td>
<td>Captopril</td>
</tr>
<tr>
<td>VALIANT</td>
<td>MI</td>
<td>Valsartan =</td>
<td>Captopril</td>
</tr>
<tr>
<td>LIFE</td>
<td>HT</td>
<td>Losartan &gt;</td>
<td>Atenolol</td>
</tr>
<tr>
<td>SCOPE</td>
<td>HT</td>
<td>Losartan =</td>
<td>Captopril</td>
</tr>
</tbody>
</table>

### Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM)

Completed of three trials comparing candesartan to placebo in patients with symptomatic heart failure

Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM)


Hypertension:
> ARBs and ACEI are equally effective agents for first-line therapy in hypertension, but ARBs do not cause cough
> However, no direct comparison between them on LVH regression or clinical outcome is available.

Heart failure:
> Insufficient data to recommend ARBs as first-line therapy for heart failure as ACE I
> ARBs should be considered in patients who are intolerance (alternative) or refractory (add-on) to ACEI (Esp. in pts not treated with BB)

ARBs Vs ACEI
**Potential advantages of ARBs**

> Complete and sustained blockade of the RAAS, independent of the pathway of angiotensin II production

> Placebo-level tolerability
  > no accumulation of bradykinin
  > compared with ACE inhibitors, virtually no cough

> Stimulation of AT₂ receptor may be associated with clinical benefits and anti-proliferative activity

> Future guidelines are likely to emphasize lower BP goals and well-tolerated agents to help meet those goals

RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin-converting enzyme; BP, blood pressure

Spironolactone

> Aldosterone blocker

Indications:
> Primary hyperaldosteronism
> Edematous conditions in:
  > Congestive heart failure
  > Cirrhosis of liver
  > Nephrotic syndrome
> Essential hypertension
> Hypokalemia

Spironolactone for Resistant HT

- 76 pts with refractory HT to diuretic and ACEI/ARB
- 34 pts with biochemical primary aldosteronism
- Similar and significant BP reduction in pts with or without primary aldosteronism

Spironolactone

Adverse events:

- Digestive: gastric bleeding, ulceration, gastritis, diarrhea & cramping, nausea, vomiting
- Endocrine: gynecomastia, inability to achieve or maintain erection, irregular menstruation or amenorrhea, postmenopausal bleeding
- Hematologic: agranulocytosis
- Hypersensitivity: fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis
- Nervous system: mental confusion, ataxia, headache, drowsiness, lethargy
- Renal: renal dysfunction

Randomized Aldactone Evaluation Study (RALES)

Hyperkalemia after RALES

Prescription

Hyperkalemia Hospitalization

Juurlink et al. NEJM 2004;351:543

Eplerenone

> Eplerenone selectively binds to mineralcorticoid receptors relative to glucocorticoid, progesterone, and androgen receptors
> More selectively blocks aldosterone relative to its effects on sex hormones
> Associated with low incidence of sex hormone-related adverse events
> Increase long-term patient compliance
Eplerenone vs Losartan: Low Renin Hypertension


Eplerenone vs Losartan: Low Renin Hypertension

Eplerenone EPHESUS Study

Background
- Aldosterone blockade prevents ventricular remodeling and collagen formation after AMI
- Spironolactone reduces death rate and hospitalisation (RALES study, NEJM 1999), but most patients were not on BB

Current Trial
- Eplerenone is a selective mineralocorticoid blocker (not on glucocorticoid, progesterone, or androgen receptors)
  - less side effects such as gynaecomastia and impotence

* N Eng J Med 2003; 348: 1309-21 (1)
Spironolactone vs. Eplerenone

> **Hypertension:**
> Spironolactone and eplerenone are equally effective agents for refractory hypertension (? Low renin HT), but eplerenone has less side effects.
> In general, 25 mg of spironolactone is equivalent to 50 mg of eplerenone in terms of mineralocorticoid effects.
> However, no direct comparison between them on clinical efficacy or outcome is available.

> **Heart failure:**
> Insufficient data to replace spironolactone for severe HF, except for intolerant.

Pharmacological Treatment of Systolic Heart Failure

**Treatment of Patients with Chronic Heart Failure and reduced LV systolic function**

- **NYHA class II/III**
  - Proven ACE-I or Valsartan 160 mg twice daily or/and Candesartan 32 mg once daily
- **NYHA class III/IV**
  - Spironolactone 25 mg once daily

**Severity of symptoms**

Proven Beta-blocker

CIBIS-2/MERIT-HF/COPERNICUS

CONSENSUS/SOLVD-T/Val-HeFT/CHARM

**RALES**

McMurray: Circulation, 2004;110:3281-3288
Pharmacological Treatment of Systolic Heart Failure in AMI

Early Treatment of Patients with AMI complicated by LVSD/Acute HF

Clinical Severity

LVSD or Acute HF

- Antiplatelet agent
- Beta-blocker
- Statin

LVSD and Acute HF

- Proven ACE-I
- Valsartan 160 mg twice daily
- Eplerenone 25–50 mg once daily

SAVE/AIRE/TRACE VALIANT EPHESUS

McMurray: Circulation 2004;110:3281-3288

Pharmacological Treatment of Systolic Heart Failure

Improving survival in CHF

1 year mortality

- SOLVD-T (1991) RRR 23%
- CIBIS-2 (1999) RRR 33%
- CHARM-Added (2003) beta blocker subgroup RRR 30%

McMurray: Circulation 2004;110:3281-3288
Conclusions

> Hypertension and heart failure remains to major global health burdens
> Latest agents (ARBs and aldosterone antagonists) which targeted at the RAAS can improve blood pressure control and/or clinical outcome in pts with hypertension and heart failure

Thank You!!