Declaration of Interest Related to the Present Topic

R. Ferrari received Honararia and research grants from Servier, Phizer, Bayer and Knoll
Multiple Antihypertensive agents are needed to reach BP goal

<table>
<thead>
<tr>
<th>Trial (Achieved SBP)</th>
<th>Average no. of antihypertensive medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-BPLA (136.9 mmHg)</td>
<td>2</td>
</tr>
<tr>
<td>ALLHAT (138 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>IDNT (138 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>RENAAL (141 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>UKPDS (144 mmHg)</td>
<td>2</td>
</tr>
<tr>
<td>ABCD (132 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>MDRD (132 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>HOT (138 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>AASK (128 mmHg)</td>
<td>3</td>
</tr>
<tr>
<td>LIFE (144 mmHg)</td>
<td>4</td>
</tr>
</tbody>
</table>

+ ONTARGET ADVANCE ACCOMPLISH

Monotherapy versus combination strategies

Mild BP elevation
Low/moderate CV risk
Conventional BP target

Choose between

Marked BP elevation
High/very CV high risk
Lower BP target

Single agent at low dose

Two-drug combination at low dose

If goal BP not achieved

Previous agent at full dose
Switch to different agent at low dose

If goal BP not achieved

Two-to three-drug combination at full dose
Full dose monotherapy

Two-three drug combination at full doses

Previous combination at full dose

Add a third drug at low dose

ESH-ESC Guidelines, J Hypertens 2007
Combination therapy in hypertension rationale

- Action on various mechanisms of hypertension
- Neutralization of counter-regulatory mechanisms
- Improved efficacy-tolerability ratio
- Better compliance
Combining 2 classes of drug is 5 times more effective than doubling the dose of 1 drug

Meta-analysis of 11,000 patients

Which combination therapy?  
2007 ESH–ESC recommendations

- Diuretics
- β-blockers
- α-blockers
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Calcium channel blockers (CCBs)

Preferred combinations
Other possible combinations

Clinical evidence

Diuretics

ASCOT

β-blockers

Calcium channel blockers (CCBs)

Angiotensin-converting enzyme (ACE) inhibitors

ASCOT
Reduction in cardiovascular events in hypertensive patients at CV risk

Selected end-points

**Primary**
- Non-fatal MI (incl silent) + fatal CHD

**Secondary**
- Total coronary end point
- Total CV event and procedures
- All-cause mortality
- Cardiovascular mortality
- Fatal and non-fatal stroke

**Tertiary**
- New-onset diabetes mellitus
- New-onset renal impairment

**Post hoc**
- Primary end point + revascularization
- CV death + MI + stroke

Unadjusted Hazard ratio (95% CI)
- 0.90 (0.79-1.02)
- 0.87 (0.79-0.96)
- 0.84 (0.78-0.90)
- 0.89 (0.81-0.99)
- 0.76 (0.65-0.90)
- 0.77 (0.66-0.89)
- 0.70 (0.63-.078)
- 0.85 (0.75-0.97)
- 0.86 (0.77-0.96)
- 0.84 (0.76-0.92)

Why?

- Synergy at clinical level
- Synergy at experimental level
- Different mechanisms and molecular site of action
ACEi reduce risk of CHD
CCBs reduce risk of stroke

Coronary artery disease

Stroke

28 trials > 175.000P

Verdecchia P et Al., Hypertension 2005;46:386-392
Two different sites of action

ACE inhibition Perindopril

Bradykinin

eNOs

NO

Increase in cyclic GMP

Induction of relaxation Vasodilatation

CCB Amlodipine

Angiotensin II

Ca^{2+}

Reduction in cytosolic calcium

Prevention of contraction Vasodilatation
Endothelium – ACEi

- Weight: 1.5 kg, surface: >800 m²
- Produces >250 active substances
- Undergoes the life and death cycle

Smooth muscle - CCBs
Atheroma formation and progression: a struggle between death and regeneration

- Endothelial cells undergo suicide (apoptosis) and regenerate, every 3 months.
- When a mismatch occurs and apoptosis exceed regeneration, the endothelium loses its continuity.

Atherosclerosis ACS
Endothelial function

Biologic end-points:
- eNOS activity
- % of apoptosis

Clinical end-points:
- Vasomotion to endothelial dependent stimulation (Ach, Bradykinine, etc)
- von Willebrand factor
Isolation of human endothelium $\rightarrow$ Incubated (72 h) with serum from Healthy subjects $\rightarrow$ EUOPA pts $\rightarrow$ ecNOS Apoptosis

To mimic the effects of circulating blood on endothelial function
### Apoptosis

**Effects of HUVEC incubation with serum from:**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>CAD PERTINENT patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=45</td>
<td>n=44</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Controls vs baseline
- Perindopril vs placebo

Pancreas

Endothelial apoptosis and atherosclerosis

Normal rate of apoptosis: 3%
- Maintenance of endothelial layer
- Protection against atherosclerosis

Excess rate of apoptosis
- Endothelium continuity
- Onset of atherosclerotic plaque erosion and rupture
ACEi and apoptosis: a class effect?
(after 1 week’s treatment)

How does perindopril reduce endothelial apoptosis?

- By reducing angiotensin-II and TNF-α (pro-apoptotic)
- By enhancing bradykinin (anti-apoptotic)
What about endothelial regeneration?

Bone marrow produces endothelial progenitor cell (EPC) to be incorporated into vessels.
Stable Angina Patients

- **Perindopril**
- **Placebo**

EPC cells (u/mm³)

- Baseline
- 10 days
- 1 month
- 3 months
- 6 months

<table>
<thead>
<tr>
<th>Time</th>
<th>Perindopril</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>10 days</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>1 month</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3 months</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>6 months</td>
<td>4.5</td>
<td>*</td>
</tr>
</tbody>
</table>
ACE inhibition (with perindopril) reduces death and improves life of the endothelium.

Protection against ACS
But... endothelium is not all...

- Smooth muscle cells are also important to
  - maintain vascular tone
  - avoid vasoconstriction
  - avoid remodelling
Amlodipine inhibits the calcium channel from the inside and prevents potassium induced smooth muscle contraction.
Antihypertensive mode of action of ACE inhibition and calcium channel blockade.

ACE inhibition Perindopril

- Bradykinin
  - eNOS
    - NO
    - Increase in cyclic GMP
    - Induction of relaxation
      - Vasodilatation

CCB Amlodipine

- Angiotensin II
  - Reduction in cytosolic calcium
  - Prevention of contraction
    - Vasodilatation
Evidence of efficacy

- ASCOT
- STRONG
- EUROPA
- Other trials
Blood pressure reduction in ASCOT

- Atenolol ± thiazide
- Amlodipine ± perindopril

Mean difference:
- SBP: 2.7 mm Hg
- DBP: 1.9 mm Hg
Coveram allows BP control VS. BP decrease

- ASCOT CAFE: optimal central BP control
- Ambulatory BP: optimal control of nocturnal BP
- Optimal control of over expressed BP variability
- Simple and better tolerated regime
STRONG Trial

Safety & efficacy analysis of coverRsyl amlodipine in unControlled & Newly diaGnosed hypertension

- Out-patient clinic based prospective study
- 1250 hypertensive patients
- Aged 40 – 70yrs (av = 55yrs)
- Newly diagnosed or uncontrolled hypertensives (mono or combo therapy)
- Av BP = 167/101 mmHg

FAST & STRONG BP reductions

The STRONGEST BP reduction in newly diagnosed patients

STRONG BP efficacy in pts uncontrolled on monotherapy

GIRISH MP, V BAHL, U JADHAV, H THACKER, S KUMAR. Blood pressure control of fixed dose, perindopril/amlodipine combination treatment in hypertensive patients uncontrolled on monotherapy or on two drug combination therapy

82% normalisation
Perindopril / Amlodipine: an effective combination provides the strongest BP reductions

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Dose, mg</th>
<th>Δ BP, mm Hg</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan/Am</td>
<td>160/5-10</td>
<td>-26</td>
<td>1250</td>
</tr>
<tr>
<td></td>
<td>80/10</td>
<td>-21</td>
<td>64</td>
</tr>
<tr>
<td>Telmisartan/Am</td>
<td>20/5</td>
<td>-15</td>
<td>1078</td>
</tr>
<tr>
<td>Olmesartan/Am</td>
<td>40/10</td>
<td>-19</td>
<td>162</td>
</tr>
<tr>
<td>Ramipril/Am</td>
<td>2.5-10/2.5-10</td>
<td>-20</td>
<td>117</td>
</tr>
<tr>
<td>Benazepril/Am</td>
<td>2.5-5/5-10</td>
<td>-9</td>
<td>111</td>
</tr>
</tbody>
</table>


SBP > 180 mm Hg

-42

-63

-43
Reduction in total mortality and major cardiac events with perindopril/CCB

Primary end point
(CV death, MI, resuscitated cardiac arrest)

Placebo/CCB
Perindopril/CCB

35% \( P=0.0147 \)

Total mortality

Placebo/CCB
Perindopril/CCB

46% \( P<0.01 \)

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>PI/CCB</th>
<th>Per/CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/CCB</td>
<td>1100</td>
<td>1022</td>
</tr>
<tr>
<td>Perindopril/CCB</td>
<td>1076</td>
<td>1005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Perindopril + amlo</th>
<th>Valsartan + amlo</th>
<th>Olmesartan + amlo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication Hypertension</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Indication CAD</strong></td>
<td>Yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>BP-independent effects</strong></td>
<td>Yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>CV protection evidence</strong></td>
<td>Yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>CABP decrease</strong></td>
<td>CAFE</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
ACE inhibitors vs ARB
Unique Differences

Data from meta-regression analyses

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACE inhibitors</th>
<th>BP-independent effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td>RRR = -2% (8% to -13%)</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td>RRR = 5% (15% to -5%)</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td>RRR = 9% (14% to 3%)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>RRR = 1% (18% to -20%)</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td>RRR = 17% (38% to -12%)</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td>RRR = -8% (17% to -39%)</td>
</tr>
</tbody>
</table>

Why?

- ARBS have little (or no) effect on bradykinin
- Do not reduce endothelial apoptosis
- Do not improve endothelial regeneration
Myocardial Infarction Patients

![Graph showing EPC levels over time for Perindopril and ARB treatments.](image)

- EPC (u/mm³)
- Time: baseline, 3 days, 5 days, 7 days, 10 days
- Perindopril
- ARB

*Significance indicated by asterisks.*
Conclusion

Perindopril is an optimal RAS inhibitor for the combination with amlodipine:

• Synergistic efficacy

• Proven efficacy in CV prevention in hypertension and CAD (ASCOT and EUROPA)

• The only RAS inhibitor/CCB with a double indication: hypertension and CAD
“The combination Amlodipine–Perindopril was widely used in the ASCOT study, being more effective in lowering BP and cardiovascular events…”

Journal of Hypertension 2009, 27:2121–2158
Perindopril has:

- Highest affinity for tissue ACE
- Preservation of bradykinin/angiotensin II balance
- Greatest antiapoptotic effect
- Optimal endothelial protection
• Perindopril exerts a specific well-documented CV protection, in addition to BP reduction

• These effects are not necessarily shared by, or documented for, other ACE inhibitors or ARBs
End
An ACEi/CCB combination: The Verdeccia meta-analysis

- 28 outcome trials, including > 175,000 patients, comparing either ACEis or CCBs with diuretics, beta-blockers or placebo
- High-lights the efficacy of ACEi’s in reducing the risk of CHD
- High-lights the efficacy of CCBs in reducing the risk of stroke

Therefore a combination of ACEi + CCB offers a broad spectrum of CV protection

## Clinical trials of combined ACE-I and CCB

<table>
<thead>
<tr>
<th></th>
<th>ASCOT</th>
<th>ACCOMPLISH</th>
<th>INVEST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>PROBE</td>
<td>RCT DB</td>
<td>PROBE</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>High risk No MI</td>
<td>High risk + MI</td>
<td>High risk + CHD</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>19,257</td>
<td>11,506</td>
<td>22,576</td>
</tr>
<tr>
<td><strong>Age (M)</strong></td>
<td>62 yrs</td>
<td>68 yrs</td>
<td>66 yrs</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>ITT</td>
<td>ITT</td>
<td>ITT</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Amlodipine perindopril free combination</td>
<td>Amlodipine Benazepril Fixed dose</td>
<td>Verapamil Trandolapril free combination</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Atenolol / Bendroflumethiazide</td>
<td>Benazepril HCTZ fixed dose</td>
<td>Atenolol Trandolapril free combination</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Non-fatal MI + fatal CHD</td>
<td>CV death, NFMI/S, Hosp, SCD, Resus</td>
<td>Total death, NFMI/Stroke</td>
</tr>
<tr>
<td><strong>Event reduction driven by</strong></td>
<td>STROKE / MI</td>
<td>MI</td>
<td>NS</td>
</tr>
</tbody>
</table>

Coveram allows BP control VS. BP decrease

- ASCOT CAFE: optimal central BP control
- Ambulatory BP: optimal control of nocturnal BP
- Optimal control of over expressed BP variability
- Simple and better tolerated regime
Coveram for hypertensive patients uncontrolled on an ACEI, ARB or a CCB

PERINDOPRIL 24-h efficacy in:
- ↓ BP
- ↑ Endothelium integrity
- ↓ Remodelling

AMLODIPINE 24-h efficacy in:
- ↓ BP
- ↑ Smooth muscle relaxation
- ↓ Remodelling