Calcium Channel Blockers in Management of Hypertension

Yong-Jin Kim, MD
Seoul National University Hospital
Contents

• Clinical significance of hypertension
• CCB: Brief introduction
• Evidences of CCB’s in HT and CAD
• Review on ‘beyond BP lowering effect’
• Practical usefulness of CCB’s
Headlines of the *St. Louis Post-Dispatch*, April 13, 1945

‘CAME OUT OF CLEAR SKY,’
SAYS PRESIDENT’S PHYSICIAN

Adm. Ross T. McIntire
Asserts There Was No
Indication of Immi-

DEATH DUE TO CEREBRAL
HEMORRHAGE --- BLOOD
VESSEL IN BRAIN BROKE

WASHINGTON, April 13 (AP).
President Roosevelt
died from what doctors call
a cerebral hemorrhage,
which means a sudden exten-

By CHARLES G. ROSS
Editor of the Post-Dispatch
FDR’s BP recorded April 1944
## Global Burden of CHD

<table>
<thead>
<tr>
<th>Cause</th>
<th>1990 Millions</th>
<th>1990 (%)</th>
<th>2020 Millions</th>
<th>2020 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>6.2</td>
<td>12.4</td>
<td>11.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.3</td>
<td>8.5</td>
<td>7.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Other CVD</td>
<td>2.6</td>
<td>5.1</td>
<td>6.0</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>TOTAL CVD</strong></td>
<td><strong>13.1</strong></td>
<td><strong>26.0</strong></td>
<td><strong>24.8</strong></td>
<td><strong>36.3</strong></td>
</tr>
<tr>
<td>All Cause Death</td>
<td>50.4</td>
<td>100</td>
<td>68.3</td>
<td>100</td>
</tr>
</tbody>
</table>
1. Acute lower respiratory infections
2. HIV/AIDS
3. Perinatal conditions
4. Diarrhoeal diseases
5. Unipolar major depression
6. **Coronary heart disease**
7. **Cerebrovascular disease**
8. Malaria
9. Traffic accidents
10. COPD

1. **Coronary heart disease**
2. Unipolar major depression
3. Road traffic accidents
4. **Cerebrovascular disease**
5. COPD
6. Lower respiratory infections
7. Tuberculosis
8. War
9. Diarrhoeal diseases
10. HIV
HT: A Risk Factor for CV Disease

CV Mortality Risk with BP Increment

*Individuals aged 40 to 69 years, starting at blood pressure 115/75 mm Hg

Small Difference Produces Big Impact

- Meta-analysis of 61 observational studies
- 1 million adults

For every 2 mm Hg decrease in mean SBP:
- 7% reduction in CHD mortality
- 10% reduction in stroke mortality

Individual Risk vs Proportional Attributable Risk

- 5% People with low risk level
- 70% People with average risk level
- 25% People with high risk level

Individual risk of CHD

Distribution of cases
Treatment of Hypertension

- 1957: Chlorothiazide
- 1962: β-blocker
- 1970: α-blocker (CCB)
- 1976: JNC 1
- 1980: ACEI
- 1990: ARB
- 2003: JNC 7
Contents

• Clinical significance of hypertension
• **CCB: Brief introduction**
• Evidences of CCB’s in HT and CAD
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• Practical usefulness of CCB’s
Ion Channels and Ion Gradients

- **Ion channel**
- **Electrical Gradient**
- **Concentration Gradient**

**Ion Exchangers**
- **Na**
- **Ca**
- **Cl**
- **OH**
- **HCO₃⁻**

**Ion pump**
- **ATP**
- **[Cl⁻]** 15 mM
- **[Ca^{++}]** 1 µM
- **[Na^{+}]** 140 mM
- **[K^{+}]** 4 mM
- **[Ca^{++}]** 2 mM

**Concentrations**
- **[K^{+}]** 140 mM
- **[Na^{+}]** 10 mM
- **[Ca^{++}]** 1 µM
- **[Cl⁻]** 15 mM

**Potential Differences**
- **-90 mV**
- **0 mV**
Voltage-Dependent Ca\textsuperscript{++} Channels

- Calcium Binding Sites
- Extracellular
- Intracellular
- Phosphorylation Site
- Selectivity filter
- Activation Gate
- Inactivation Gate

Ca\textsuperscript{++}

Ca\textsuperscript{++}

Ca\textsuperscript{++}

Ca\textsuperscript{++}

Ca\textsuperscript{++}

Ca\textsuperscript{++}

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Ca\textsuperscript{++}

Ca\textsuperscript{++}

Ca\textsuperscript{++}
L-type Ca\(^{++}\) channels open at a level of depol. of ~60 mV.

The entry of small Ca\(^{++}\) triggers Ca\(^{++}\) release from SR.
Excitation-Contraction Coupling

- Myosin complex
- Actin Helix
- Tropomyosin
- ATP
- Pi
- Ca^{2+}
- Mg^{2+}
- ADP
<table>
<thead>
<tr>
<th>Channel</th>
<th>Blockers</th>
<th>Properties</th>
<th>Location/Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>L type</td>
<td>Calcium antagonists</td>
<td>Large, long-lasting current with slow activation</td>
<td>Cardiac &amp; smooth m. neurons; excitation-contraction, excitation-secretion coupling</td>
</tr>
<tr>
<td>T type</td>
<td>Amiloride</td>
<td>Tiny, transient current</td>
<td>SA &amp; Purkinje cell; pacemaker activity</td>
</tr>
<tr>
<td>N type</td>
<td>Conotoxin</td>
<td>Neither L or T</td>
<td>Neurons; neurotransmitter release</td>
</tr>
</tbody>
</table>
First Observation about CCB in 1964

- Developed Tension (g)

- Developed Tension (g)

- [Ca^{++}] = 2.4 mM
- [Ca^{++}] = 0 mM
- [Ca^{++}] = 2.4 mM

- Verapamil 1 µM
- Isoproterenol 1 µM
## Classes of L-Type CCB

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Verapamil, Isoptin™</td>
</tr>
<tr>
<td>Class V</td>
<td>Mibefradil (withdrawn)</td>
</tr>
<tr>
<td>Class II</td>
<td>Amlodipine, Norvasc™, Lotrel™, Felodipine, Plendil™, Lexxel™, Isradipine, Dynacirc™, Nicardipine, Cardene™</td>
</tr>
<tr>
<td>Class III</td>
<td>Nifedipine, Adalat™, Procardia™, Nimodipine, Nimotop ™, Nisoldipine, Sular™</td>
</tr>
<tr>
<td>Class IV</td>
<td>Bepridil, Vascor™</td>
</tr>
<tr>
<td>Class V</td>
<td>Mibefradil (withdrawn)</td>
</tr>
</tbody>
</table>
### Pharmacodynamic Effects of CCBs

<table>
<thead>
<tr>
<th></th>
<th>Phenylalkylamine (Verapamil)</th>
<th>Dihydropyridines (Nifedipine)(Nimodipine)</th>
<th>Benzothiazepine (Diltiazem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peripheral</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>coronary</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>cerebral</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↑</td>
<td>--</td>
</tr>
<tr>
<td>SA node</td>
<td>↓</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AV node</td>
<td>↓↓</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Contractility</td>
<td>↓↓</td>
<td>↑</td>
<td>--</td>
</tr>
</tbody>
</table>
## Classification of CCB’s

<table>
<thead>
<tr>
<th>Group (specificity)</th>
<th>First generation</th>
<th>Second generation</th>
<th>New active principles and/or novel formulations</th>
<th>Third generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridine (artery &gt; cardiac)</td>
<td>Nifedipine</td>
<td>Nifedipine</td>
<td>Benidipine</td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>SR/GITS</td>
<td>Isradipine</td>
<td>Lacidipine</td>
</tr>
<tr>
<td></td>
<td>Felodipine ER</td>
<td></td>
<td>Manidipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine SR</td>
<td></td>
<td>Nilvadipine</td>
<td></td>
</tr>
<tr>
<td>Benzothiazepine (artery = cardiac)</td>
<td>Diltiazem</td>
<td>Diltiazem SR</td>
<td>Nitrendipine</td>
<td></td>
</tr>
<tr>
<td>Phenylalkylamine (artery &lt; cardiac)</td>
<td>Verapamil</td>
<td>Verapamil SR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gallopamil</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ER = extended release; GITS = gastrointestinal therapeutic system; SR = sustained release

Zanchetti, 1997
Contents

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CCB Controversy in 1990’s

Circulation 1995
Evidences of CCB’s in HT, CAD

- CCB vs Placebo
  - PREVENT amlodipine, *Circulation* 2000
  - ACTION nifedipine GITS, *Lancet* 2004
Nitrendipine reduces CV events

- Stroke: -42%
- MI: -30%
- HF: -29%
- All CV events: -31%

4695 Elderly (> 60yr) pts with ISH: SBP>160, DBP<95)

PREVENT: Primary QCA Endpoint

825 symptomatic CAD with 3yr f/u

Change in Minimum Lumen Diameter (MLD)

Mean Change (mm)

Primary QCA Endpoint

Amlodipine  Placebo

≤30%  >30% to ≤50%  >50%  All Segments

* Values are mean ± SE, adjusted for segment, clinic, and PTCA during baseline angiogram.

P=NS for all comparisons of amlodipine versus placebo.
PREVENT: Vascular Event or Procedure

Cumulative Event/Procedure Rate (%)

Placebo (n=408)

Amlodipine (n=417)

P = .01

Evidences of CCB’s in HT, CAD

- CCB vs Active control
  - ABCD  nisoldipine vs ACEI, *NEJM*1998
  - STOP-2  felodipine or isradipine vs ACEI or diuretic/BB, *Lancet* 1999
  - ALLHAT  amlodipine vs diuretics vs ACEI, *JAMA* 2002
  - AASK  amlodipine vs BB vs ACEI, *JAMA* 2002
  - CONVINCE  verapamil vs diuretic/BB, *JAMA* 2003
  - CAMELOT  amlodipine vs ACEI, *JAMA* 2004
  - VALUE  amlodipine vs ARB, *Lancet* 2004
Number of Patients

7434 enrolled

6321 randomised, eligible for intention-to-treat analysis

3157
Long-acting calcium antagonist
Nifedipine GITS

3164
Diuretic combination:
Hydrochlorothiazide & Amiloride ("Active control")
Antihypertensive Efficacy
Mean Blood Pressure

Nifedipine GITS
Hydrochlorothiazide & Amiloride

173 mmHg
138 mmHg
99 mmHg
82 mmHg

Systolic
Diastolic
Sympathetic System
Heart Rate

- Red line: Nifedipine GITS
- Blue line: Hydrochlorothiazide & Amiloride

Axis:
- X-axis: Weeks and Years
- Y-axis: Beats per Minute

Graph shows the heart rate over time for different treatment groups.
Main Clinical Outcome
Kaplan Meier Curves

- **Nifedipine GITS**
- **Hydrochlorothiazide & Amiloride**

**Myocardial Infarction, Sudden Death, Stroke, Heart Failure, Other Cardiovascular Death**
*(Primary Endpoints)*

**All Cardiovascular Morbidity and All-Cause Mortality**
*(Sum of Primary and Secondary Endpoints)*
Overview: Individual and Combined Endpoints
Relative Risk and 95% Confidence Interval

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.91</td>
<td>[0.74, 1.11]</td>
<td>0.61</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.27</td>
<td>[1.09, 1.42]</td>
<td>0.17</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>0.74</td>
<td>[0.54, 1.00]</td>
<td>0.43</td>
</tr>
<tr>
<td>Other Cardiovascular Death</td>
<td>1.09</td>
<td>[0.89, 1.31]</td>
<td>0.85</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.11</td>
<td>[0.92, 1.34]</td>
<td>0.023</td>
</tr>
<tr>
<td>All Primary Endpoints</td>
<td>1.11</td>
<td>[0.92, 1.34]</td>
<td>0.34</td>
</tr>
<tr>
<td>All Cardiovascular Morbidity and All-Cause Mortality</td>
<td>0.96</td>
<td>[0.80, 1.16]</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*All Primary and Secondary Endpoints*
Emergence of New Diseases*  

% of Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nifedipine GITS</th>
<th>Hydrochlorothiazide &amp; Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout¹</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Peripheral Vascular Disorder¹</td>
<td>3.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Diabetes²</td>
<td>4.3</td>
<td>5.6</td>
</tr>
</tbody>
</table>

p < 0.01  
p < 0.01  
p = 0.02

*or Recurrence; ¹Reported by investigator; ²WHO definition of random glucose measurement >11.0 mmol/l or use of anti-diabetic drugs
In January 2000, the National Heart, Lung, and Blood Institute decided to discontinue the doxazosin arm of the antihypertensive trial and report results.


Compared with chlorthalidone:
SBP significantly higher in the amlodipine group (0.8 mm Hg) and the lisinopril group (2 mm Hg) at 5 years.

Compared with chlorthalidone:
DBP significantly lower in the amlodipine group (0.8 mm Hg) at 5 years.

ALLHAT: Fatal CHD or Nonfatal MI

<table>
<thead>
<tr>
<th>Years to CHD Event</th>
<th>Chlorthalidone</th>
<th>Amlodipine besylate</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15,255</td>
<td>9048</td>
<td>9054</td>
</tr>
<tr>
<td>1</td>
<td>14,477</td>
<td>8576</td>
<td>8535</td>
</tr>
<tr>
<td>2</td>
<td>13,820</td>
<td>8218</td>
<td>8123</td>
</tr>
<tr>
<td>3</td>
<td>13,102</td>
<td>7843</td>
<td>7711</td>
</tr>
<tr>
<td>4</td>
<td>11,362</td>
<td>6824</td>
<td>6662</td>
</tr>
<tr>
<td>5</td>
<td>6340</td>
<td>3870</td>
<td>3832</td>
</tr>
<tr>
<td>6</td>
<td>2956</td>
<td>1878</td>
<td>1770</td>
</tr>
<tr>
<td>7</td>
<td>209</td>
<td>215</td>
<td>195</td>
</tr>
</tbody>
</table>

Number at Risk:

- **Chlorthalidone**: 15,255, 14,477, 13,820, 13,102, 11,362, 6340, 2956, 209
- **Amlodipine besylate**: 9048, 8576, 8218, 7843, 6824, 3870, 1878, 215
- **Lisinopril**: 9054, 8535, 8123, 7711, 6662, 3832, 1770, 195

**RR (95% CI)**

- **A/C**: 0.98 (0.90-1.07)  
  - *P Value*: .65
- **L/C**: 0.99 (0.91-1.08)  
  - *P Value*: .81

15245 HT pt with elective titration to target BP

**VALUE: Design**

Valsartan-based regimen

- Valsartan 80 mg
- Valsartan 160 mg
- Valsartan 160 mg + HCTZ 12.5 mg
- Valsartan 160 mg + HCTZ 25 mg

Amlodipine-based regimen

- Amlodipine 5 mg
- Amlodipine 10 mg
- Amlodipine 10 mg + HCTZ 12.5 mg
- Amlodipine 10 mg + HCTZ 25 mg
- Amlodipine 10 mg + HCTZ 25 mg + "Free" add-on

**Month**

- 0.5
- 0
- 1
- 2
- 3
- 4
- 6
- *72

**Screening**

**Randomisation**

**End of treatment adjustment period**

*Patient visits every 6 months for months 6-72.
VALUE: Primary Composite Endpoint

Proportion of Patients With First Event (%)

Time (months)

HR=1.03; 95% CI 0.94-1.14: P=0.49

Number at risk

Valsartan  
7649  7459  7407  7250  7085  6906  6732  6536  6349  5911  3764  1474

Amlodipine besylate  
7596  7469  7424  7267  7117  6955  6772  6576  6391  5959  3725  1474

VALUE: Fatal and Non-Fatal MI

Proportion of Patients With First Event (%)

Time (months)

HR=1.19; 95% CI 1.02-1.38; P=0.02

Number at risk

Valsartan 7649 7499 7458 7319 7177 7016 6853 6680 6504 6078 3864 1520
Amlodipine besylate 7596 7497 7458 7332 7205 7065 6905 6727 6562 6141 3840 1532

## VALUE: Fatal and Non-fatal Stroke

### Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valsartan</strong></td>
<td>7649 7494 7448 7312 7170 7022 6877 6692 6515 6093 3859 1516</td>
</tr>
<tr>
<td><strong>Amlodipine besylate</strong></td>
<td>7596 7499 7455 7334 7195 7055 6918 6744 6587 6163 3846 1532</td>
</tr>
</tbody>
</table>

### Proportion of Patients With First Event (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Valsartan-based regimen</th>
<th>Amlodipine besylate-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**HR=1.15; 95% CI 0.98-1.35; P=0.08**

VALUE: Systolic BP in Study

Sitting SBP by Time and Treatment Group

Difference in SBP Between Valsartan and Amlodipine besylate

VALUE: Outcome and SBP Differences

<table>
<thead>
<tr>
<th>Time Interval (months)</th>
<th>ΔSBP mm Hg</th>
<th>PRIMARY ENDPOINT Odds Ratios and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>12–24</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>24–36</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Study end</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Favours valsartan  
Favours amlodipine besylate

VALUE: Outcome and SBP Differences

<table>
<thead>
<tr>
<th>Study End Point</th>
<th>Δ BP (mmHg)</th>
<th>Odds Ratio</th>
<th>Odds Ratios ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>3.8/2.2</td>
<td>1.78 (1.22 – 2.60)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.8/2.2</td>
<td>1.74 (0.94 – 3.22)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3.8/2.2</td>
<td>1.94 (1.10 – 3.42)</td>
<td></td>
</tr>
<tr>
<td>Total Mortality</td>
<td>3.8/2.2</td>
<td>2.84 (1.51 – 5.34)</td>
<td></td>
</tr>
</tbody>
</table>
# New ESC Guideline: Early Treatment

## Blood pressure (mmHg)

<table>
<thead>
<tr>
<th>Other risk factors</th>
<th>Normal SBP 120–129 or DBP 80–84</th>
<th>High normal SBP 130–139 or DBP 85–89</th>
<th>Grade 1 HT SBP 140–159 or DBP 90–99</th>
<th>Grade 2 HT SBP 160–179 or DBP 100–109</th>
<th>Grade 3 HT SBP ≥ 180 or DBP ≥ 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>No BP intervention</td>
<td>No BP intervention</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>1–2 risk factors</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes for several weeks then drug treatment if BP uncontrolled</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>≥3 risk factors, MS or OD</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes and consider drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Lifestyle changes</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
<tr>
<td>Established CV or renal disease</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
<td>Lifestyle changes + Immediate drug treatment</td>
</tr>
</tbody>
</table>
### BP-Lowering Treatment Trialists

Comparisons of Active Treatments and Control

#### BP Difference (mm Hg) vs Relative Risk vs RR (95% CI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comparison</th>
<th>BP Difference</th>
<th>Relative Risk</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.72 (0.64, 0.81)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>0.62 (0.47, 0.82)</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.80 (0.73, 0.88)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>0.78 (0.62, 0.99)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.82 (0.69, 0.98)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>1.21 (0.93, 1.58)</td>
</tr>
<tr>
<td><strong>Major CV events</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.78 (0.73, 0.83)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>0.82 (0.71, 0.95)</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.80 (0.71, 0.89)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>0.78 (0.61, 1.00)</td>
</tr>
<tr>
<td><strong>Total mortality</strong></td>
<td>ACEI vs placebo</td>
<td>-5/-2</td>
<td></td>
<td>0.88 (0.81, 0.96)</td>
</tr>
<tr>
<td></td>
<td>CA vs placebo</td>
<td>-8/-4</td>
<td></td>
<td>0.89 (0.75, 1.05)</td>
</tr>
</tbody>
</table>

BP-Lowering Treatment Trialists
Comparisons of Different Active Treatments

<table>
<thead>
<tr>
<th>BP Difference (mm Hg)</th>
<th>Relative Risk</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitor vs D/BB</td>
<td>2/0</td>
<td>1.09 (1.00, 1.18)</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>0.93 (0.86, 1.01)</td>
</tr>
<tr>
<td>ACE Inhibitor vs CA</td>
<td>1/1</td>
<td>1.12 (1.01, 1.25)</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitor vs D/BB</td>
<td>2/0</td>
<td>0.98 (0.91, 1.05)</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>1.01 (0.94, 1.08)</td>
</tr>
<tr>
<td>ACE Inhibitor vs CA</td>
<td>1/1</td>
<td>0.96 (0.88, 1.05)</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitor vs D/BB</td>
<td>2/0</td>
<td>1.07 (0.96, 1.19)</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>1.33 (1.21, 1.47)</td>
</tr>
<tr>
<td>ACE Inhibitor vs CA</td>
<td>1/1</td>
<td>0.82 (0.73, 0.92)</td>
</tr>
</tbody>
</table>

• Clinical significance of hypertension
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HOPE Trial

9,297 pt with CAD or DM plus 1 RF (no CHF, LV dysfxn)
75% Aspirin, 40% beta-blocker, 30% statin

Ramipril 10mg/day
n=4,645

Placebo
n=4,652

Primary Endpoint
Composite of cardiac death, MI, or stroke
follow-up: 5 years

HOPE: Primary Endpoint

cardiac death, MI, or stroke

RRR = 28%
p < 0.001

**HOPE: Events per Patient Group**

![Bar chart showing the comparison of events per patient group between Placebo and Ramipril]

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo</th>
<th>Ramipril</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>RR=22%</td>
<td>P&lt;.001</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>RR=26%</td>
<td>P&lt;.001</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>RR=20%</td>
<td>P&lt;.001</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>RR=32%</td>
<td>P=NS</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Non-CV Death</td>
<td>RR=0%</td>
<td>P=NS</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Total Mortality</td>
<td>RR=16%</td>
<td>P=.005</td>
<td>12.2</td>
<td></td>
</tr>
</tbody>
</table>

*MI, stroke, or CV death.

Ramipril Group (n=20)

- SBP baseline
- DBP baseline
- SBP year 1
- DBP year 1

Night: \( \Delta = 17/8 \text{ mm Hg} \) \((P < .001)\)

24-h: \( \Delta = 10/4 \text{ mm Hg} \) \((P < .03)\)

EUROPA Trial

12,218 patients with stable angina without CHF
90% Aspirin, 60% beta-blocker, 60% statin

Perindopril 8mg/day
n=6,110

Placebo
n=6,108

Primary Endpoint
Composite of cardiac death, MI, or cardiac arrest
mean follow-up: 4.2 years

Lancet 2003; 362: 782-88
EUROPA: Primary Endpoint

% CV death, MI or cardiac arrest

Placebo annual event rate: 2.4%

Perindopril

RRR: 20%

p = 0.0003

Lancet 2003; 362: 782-88
CAD Mortality and Usual BP by Age

**Systolic BP**

- 40-49 years
- 50-59 years
- 60-69 years
- 70-79 years
- 80-89 years

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Usual Systolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49 years</td>
<td>0 - 120</td>
</tr>
<tr>
<td>50-59 years</td>
<td>120 - 140</td>
</tr>
<tr>
<td>60-69 years</td>
<td>140 - 160</td>
</tr>
<tr>
<td>70-79 years</td>
<td>160 - 180</td>
</tr>
<tr>
<td>80-89 years</td>
<td>180 - 256</td>
</tr>
</tbody>
</table>

**Diastolic BP**

- 40-49 years
- 50-59 years
- 60-69 years
- 70-79 years
- 80-89 years

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Usual Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49 years</td>
<td>0 - 80</td>
</tr>
<tr>
<td>50-59 years</td>
<td>80 - 100</td>
</tr>
<tr>
<td>60-69 years</td>
<td>100 - 120</td>
</tr>
<tr>
<td>70-79 years</td>
<td>120 - 140</td>
</tr>
<tr>
<td>80-89 years</td>
<td>140 - 256</td>
</tr>
</tbody>
</table>

Stroke Mortality and Usual BP by Age

**Systolic BP**

- **50-59 years**
- **60-69 years**
- **70-79 years**
- **80-89 years**

**Diastolic BP**

- **50-59 years**
- **60-69 years**
- **70-79 years**
- **80-89 years**

Odds Ratio for CV Events & SBP Difference

Recent trials
Older trials placebo
Older trials active

Recent
- AASK L vs H
- ABCD/NT L vs H
- ALLHAT/Aml
- ALLHAT/Lis
- ALLHAT/Lis ≥65
- ALLHAT/Lis Blcks
- ANBP2
- CONVENCE
- DIABHYCAR
- ELSA
- IDNT2
- LIFE/ALL
- LIFE/DM
- NICOLE
- PREVENT
- SCOPE

Older
- ALLHAT/Dox
- ATMH
- EWPHE
- HEP
- HOPE
- HOT
- HOT M vs H
- INSIGHT
- MIDAS/NICS/VHAS
- L vs H
- MRC
- MRC2
- PART2/SCAT
- PATS
- PROGRESS/Per
- PROGRESSION/Com
- RCT70-80
- RENAAL
- SHEP
- STONE
- STOP 1
- STOP2/CCBs
- STOP2/ACEIs
- Syst-China
- Syst-Eur
- UKPDS C vs A
- UKPDS L vs H

Odds Ratio for CV Events & SBP Difference

- **Recent trials**
- **Older trials placebo**
- **Older trials active**

**P<.0001**

**EUROPA**

Recent
- AASK L vs H
- ABCD/NT L vs H
- ALLHAT/Aml
- ALLHAT/Lis
- ALLHAT/Lis ≥65
- ALLHAT/Lis Blcks
- ANBP2
- CONVINCE
- DIABHYCAR
- ELSA
- IDNT2
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- SCOPE

Older
- ALLHAT/Dox
- ATMH
- EWPHE
- HEP
- HOPE
- HOT
- HOT M vs H
- INSIGHT
- MIDAS/NICS/VHAS
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- MRC
- MRC2
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- PROGRESS/Per
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- STONE
- STOP 1
- STOP2/CCBs
- STOP2/ACEIs
- Syst-China
- Syst-Eur
- UKPDS C vs A
- UKPDS L vs H

**Difference (reference minus experimental)**

in Systolic BP (mm Hg)

Target BP in HT

- **JNC 7, 2004**
  - 140/90
  - 130/80: DM, renal disease

- **ESC guideline, 2007**
  - 140/90
  - 130/80: DM, established CV ds (stroke, MI, renal ds)
BP-Lowering Treatment Trialists

Heart Failure

A = CA vs placebo; B = ACE inhibitor vs placebo; C = more intensive vs less intensive blood-pressure-lowering; D = ARB vs control; E = ACE inhibitor vs CA; F = CA vs diuretic or β-blocker; G = ACE inhibitor vs diuretic and β-blocker.

“Regimens based on each of the most commonly used drug classes produce reductions in the risk of major cardiovascular events that appear to be roughly proportional to the size of the blood pressure reductions achieved **With the exception of heart failure, the intensity of blood pressure lowering appears to be a more important determinant of outcome than the choice of drug class.”**

Target BP lowering in ALLHAT

Adequate BP Control First!

National Health and Nutrition Examination Survey

- Treatment
  - 1988-1991: 52%
  - 1991-1994: 52%
  - 1999-2000: 58%

- Control
  - All hypertensives*: 25%
  - 1988-1991: 25%
  - 1999-2000: 31%
  - Hypertensive diabetics†: 29%
    - 1988-1991: 17%
    - 1999-2000: 25%

*BP<140/90 mm Hg; †BP<130/85 mm Hg.
Adequate BP Control First!

source: National health and nutrition examination survey, 2005
CVD Survival in Treated HT

- Untreated BP <140/90 mm Hg
- Untreated BP ≥140/90 mm Hg
- Treated BP at goal <140/90 mm Hg
- Treated BP not at goal ≥140/90 mm Hg

Survival (%)

Follow-up (Years)

P = .03
P < .0001
P = .001

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No. of agents to Achieve BP Goal

<table>
<thead>
<tr>
<th>Study</th>
<th>BP Goal</th>
<th>No. of BP Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>(&lt;85 mm Hg, diastolic)</td>
<td>2</td>
</tr>
<tr>
<td>MDRD</td>
<td>(&lt;92 mm Hg, MAP)</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>(&lt;80 mm Hg, diastolic)</td>
<td>4</td>
</tr>
<tr>
<td>AASK</td>
<td>(&lt;92 mm Hg, MAP)</td>
<td>4</td>
</tr>
<tr>
<td>RENAAL</td>
<td>(&lt;140/90 mm Hg)</td>
<td>4</td>
</tr>
<tr>
<td>IDNT</td>
<td>(≤135/85 mm Hg)</td>
<td>4</td>
</tr>
</tbody>
</table>

Combination Therapy in Korea

- >4 drugs
- 3 drugs
- 2 drugs
- Monotherapy

Note: * Consider small base number for implementation especially when n<30
Effect of CCB for Add-on Therapy

No Previous Therapy (n=421)
ACEI/ARB (n=117)  β-Blocker (n=70)  Diuretic (n=119)  ACE/ARB + diuretic (n=165)  β-Blocker + diuretic (n=47)

Δ SBP mm Hg

-15.9†  -15.1†  -18.1†  -19.3†  -17.3†  -13.9†

*The DHP CCB was Norvasc® (amlodipine besylate).
†P<.001 vs baseline.
Guideline on Combination Therapy

ESC guideline 2007
Summary

- CCB: strong evidences in management in HT
- Benefit of HT drugs: mainly from BP lowering effect
- Early initiation of HT drug: high risk patients
- Importance of BP lowering at goal
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Methods

Literature search
We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines. We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The
Thank You for Your Attention!