The HYpertension in the Very Elderly Trial

N. Beckett, R. Peters, A. Fletcher, C. Bulpitt on behalf of the HYVET committees and investigators

ClinicalTrials.gov: NCT00122811
Disclosure Information

The Hypertension in the Very Elderly Trial – main results

Disclosure Information...
The following relationships exist related to this presentation.

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- Dr. Ruth Peters PhD: No Support
- Prof Astrid Fletcher PhD: No Support
- Prof Christopher Bulpitt MD: Imperial College Consultancy fees supported by Servier
Blood Pressure & The Very Elderly (aged 80 or more)

• Epidemiologic population studies suggest better survival with higher levels of blood pressure

• Clinical trials recruited too few.

• Meta-analysis (n=1670) (Gueyffier et al. 1997)
  - 36% reduction in the risk of stroke (BENEFIT)
  - 14% (p=0.05) increase in total mortality (RISK)

• Hypertension in the Very Elderly Trial (HYVET) pilot results (n=1273) similar to meta-analysis (Bulpitt et al. 2003)
The Trial:
International, multi-centre, randomised double-blind placebo controlled

Inclusion Criteria:
Aged 80 or more,
Systolic BP: 160 - 199mmHg
+ diastolic BP: <110 mmHg,
Informed consent

Exclusion Criteria:
Standing SBP < 140mmHg
Stroke in last 6 months
Dementia
Need daily nursing care

Primary Endpoint:
All strokes (fatal and non-fatal)

Target blood pressure
150/80 mmHg
Statistical Analysis

• Numbers based on a 35% reduction in all strokes
  – $\alpha = 0.01 \ \beta = 0.1$
  – Stroke event rate of 40/1000
  – 10,500 patient-years of follow-up required

• 3 interim analyses planned
  – Stopped at 2nd as decrease in stroke and all-cause mortality

• Independent Steering, Ethics and Data Monitoring Committees
• Independent Endpoints Committee (blinded evaluation)

• ITT and PP analyses

• Other main trial endpoints: total mortality, cardiovascular mortality, cardiac mortality, stroke mortality, heart failure
4761 Entered into Placebo Run-in

916 not randomised

Placebo
1912

Active
1933

- 3845 randomised; Western Europe (86) Eastern Europe (2144), China (1526), Australasia (19), Tunisia (70)

- At end of trial; 1882 still in double blind, 17 vital status not known, 220 in open follow-up
## Baseline data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n= 1912)</th>
<th>Active (n= 1933)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>83.5</td>
<td>83.6</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>60.3%</td>
<td>60.7%</td>
</tr>
<tr>
<td><strong>Blood Pressure:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting SBP (mmHg)</td>
<td>173.0</td>
<td>173.0</td>
</tr>
<tr>
<td>Sitting DBP (mmHg)</td>
<td>90.8</td>
<td>90.8</td>
</tr>
<tr>
<td>Orthostatic Hypotension‡</td>
<td>8.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Isolated Systolic Hypertension</td>
<td>32.6%</td>
<td>32.3%</td>
</tr>
</tbody>
</table>

‡ Fall in SBP ≥ 20mmHg and/or fall in DBP ≥ 10mmHg
## Baseline Data
(Previous Cardiovascular History)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>Active (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>12.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Known Hypertension</td>
<td>89.9</td>
<td>89.9</td>
</tr>
<tr>
<td>Anti-hypertensive treatment</td>
<td>65.1</td>
<td>64.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>
# Baseline data

## Cardiovascular Risk factors

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>6.6%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.9%</td>
<td>6.8%</td>
</tr>
<tr>
<td>(Known DM/DM treatment/glucose&gt;11.1mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>HDL Cholesterol (mmol/l)</td>
<td>1.35</td>
<td>1.35</td>
</tr>
<tr>
<td>Serum Creatinine (μmol/l)</td>
<td>89.2</td>
<td>88.6</td>
</tr>
<tr>
<td>Uric acid (μmol/l)</td>
<td>279</td>
<td>280</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.7</td>
<td>24.7</td>
</tr>
</tbody>
</table>
Blood pressure separation

Placebo
Indapamide SR +/- perindopril

Median follow-up 1.8 years

15 mmHg

6 mmHg

Follow-up (years)

Blood Pressure (mmHg)
All stroke
(30% reduction)

P=0.055
Total Mortality
(21% reduction)

No. at Risk
Placebo group 1912  1492  814  379  202
Active-treatment group 1933  1565  877  420  231

P=0.019
Fatal Stroke
(39% reduction)

P=0.046
Heart Failure
(64% reduction)

No. of Events per 100 Patients

Follow-up (yr)

No. at Risk
Placebo group  1912  1480  794  367  188
Active-treatment group  1933  1559  872  416  228

P<0.0001
## ITT - Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Stroke</td>
<td>0.70</td>
<td>(0.49, 1.01)</td>
</tr>
<tr>
<td>Stroke Death</td>
<td>0.61</td>
<td>(0.38, 0.99)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.79</td>
<td>(0.65, 0.95)</td>
</tr>
<tr>
<td>NCV/Unknown death</td>
<td>0.81</td>
<td>(0.62, 1.06)</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.77</td>
<td>(0.60, 1.01)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.71</td>
<td>(0.42, 1.19)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>0.36</td>
<td>(0.22, 0.58)</td>
</tr>
<tr>
<td>CV events</td>
<td>0.66</td>
<td>(0.53, 0.82)</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>All stroke</td>
<td>-34%</td>
<td>0.46 - 0.95</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-28%</td>
<td>0.59 - 0.88</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>-45%</td>
<td>0.33 - 0.93</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>-27%</td>
<td>0.55-0.97</td>
</tr>
<tr>
<td>Heart failure</td>
<td>-72%</td>
<td>0.17-0.48</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>-37%</td>
<td>0.51-0.71</td>
</tr>
</tbody>
</table>
Biochemical Changes from Baseline (2 year cohort)

• In 2 year cohort there were no significant differences between the groups with regard to change in serum. . .
  • Potassium
  • Uric acid
  • Glucose
  • Creatinine

• At 2 years 73.4% on combination treatment in active group (85.2% placebo)
Safety

Reported serious adverse events (after randomisation)

- 448 in the placebo group vs 358 in active (p=0.001)

- Only 5 categorised by the local investigator possible SADRs (3 in placebo group, 2 being in active)
Conclusions

• Antihypertensive treatment based on indapamide (SR) 1.5mg (± perindopril) reduced stroke mortality and total mortality in a very elderly cohort.

• NNT (2 years) = 94 for stroke and 40 for mortality

• Large and significant benefit in reduction of heart failure events and for combined endpoint of cardiovascular events

• Benefits seen early

• Treatment regime employed was safe
Cautions

• Subjects recruited generally healthier than those within a general population

• Benefit from treating systolic pressures less than 160mmHg requires further research

• Target blood pressure was 150/80 mmHg
  – Benefit from lower targets still needs to be established
• Professor C. Bulpitt (Principal investigator) & Professor A.E. Fletcher (Co-investigator)
• The HYVET co-ordinating office
• The members of the HYVET Committees
  – **Steering Committee** (Dr. T. McCormack, Prof. J. Potter, Prof. B.G. Extremera, Prof. P. Sever, Prof. F. Forette, Assoc. Prof. D. Dumitrascu, Prof. C. Swift, Prof. J. Tuomilehto)
  – **End-points Committee** (Dr. J. Duggan, Prof. G. Leonetti, Dr. N. Gainsborough, Prof. MC. de Vernejoul, Prof. J. Wang, Dr. V. Stoyanovsky)
  – **Data-monitoring Committee** (Dr. J. Staessen, Ms. L. Thijs, Dr R. Clarke, Dr K Narkiewicz)
  – **Ethics Committee** (Prof. R. Fagard, Prof. J. Grimley Evans, Dr. B. Williams)
  – **Dementia Diagnosis Committee** (Prof. J. Tuomilehto, Dr R. Clarke, Dr I. Walton, Dr C. Ritchie, Dr A. Waldman)
• All the HYVET investigators
• All the HYVET national co-ordinators
  – R. Warne/I. Puddey (Australia), H. Celis (Belgium) V. Stoyanovsky (Bulgaria), L. Liu (China), R Antikainen (Finland), F. Forette (France), J. Duggan (Ireland), C.Anderson (New Zealand), T. Grodzicki (Poland), A. Belhani (Tunisia) C. Clara (Portugal), D. Dumitrascu (Romania), Y. Nikitin (Russia), C. Rajkumar (UK)
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