Second Australian National Blood Pressure Study

ANBP2

Conducted by the High Blood Pressure Research Council of Australia in conjunction with Australia’s General Practitioners

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High Blood Pressure Research Council of Australia
Today’s Plan….

• Review the main study results
• Examine consistency with other data
  – Design
  – Study population
  – Results
• Discuss causes of greater benefit in ACE treated patients?
  – New data on LVH regression
  – Diabetes patients
The Question

• Diuretics and/or beta blockers lower BP and improve outcomes
  but
• Is there additional benefit beyond blood pressure reduction with agents inhibiting the renin-angiotensin system?

Main Study Aim

• To determine in hypertensive patients aged 65-84 years whether there is a difference in total cardiovascular events (fatal and non-fatal) over 5 years when treatment is initiated with either a diuretic or an ACE inhibitor
Study Drug Treatments – Stepwise to Target

• **ACE Inhibitor Group**
  - Step 1. ACE Inhibitor
  - Step 2. Beta or alpha blocker or calcium antagonist
  - Step 3. Drug from class not used in Step 2 or diuretic
  - Step 4. Drug from class not used in step 2 or 3

• **Diuretic Group**
  - Step 1. Thiazide type diuretic at low dose
  - Step 2. Beta or alpha blocker or calcium antagonist
  - Step 3. Drug from class not used in Step 2
  - Step 4. Drug from class not used in step 2 or 3

i.e. commonly used drugs and combinations
In-Study Blood Pressure was Identical

Blood Pressure (mmHg)

Years Since Randomization

ACE
Diuretic

-26 mmHg

-12 mmHg

Blood Pressure (mmHg)

Systolic

Diastolic
A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly

Cumulative Events

Cumulative Event Rate (per 1000 person-years)
Including Non-vascular Deaths

Years Since Randomization

Number at Risk
ACE 3044 3015 2961 2890 1652 302
DIURETIC 3039 3010 2937 2849 1664 288
## Primary Result

<table>
<thead>
<tr>
<th>Event</th>
<th>ACE</th>
<th>Diuretic</th>
<th>HR</th>
<th>(95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular events or any death</td>
<td>n = 692, Rate = 55.8</td>
<td>n = 732, Rate = 59.5</td>
<td>0.89</td>
<td>(0.79, 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>First cardiovascular event or death</td>
<td>n = 490, Rate = 41.9</td>
<td>n = 529, Rate = 45.7</td>
<td>0.89</td>
<td>(0.79, 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death</td>
<td>n = 195, Rate = 15.7</td>
<td>n = 210, Rate = 17.1</td>
<td>0.90</td>
<td>(0.75, 1.09)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Rate per 1000 patient years
Adjusted for age, gender
Summary

• 11% reduction in total cardiovascular events (or death from any cause) with ACE inhibitor treatment

• 11% reduction in first events with ACE inhibitor treatment

• 17% reduction in total events in males and no effect evident in females
Summary

- **No difference between treatments**
  - total or cardiovascular mortality
  - all cerebrovascular events
  - all coronary events
- **With ACE inhibitor treatment**
  - reduction in first non-fatal cardiovascular events (HR 0.86)
  - reduction in non-fatal myocardial infarctions (HR 0.68)
  - increase in fatal strokes (HR 1.91) but not strokes in total
  - cause-specific effects only in males
ANBP2 and ALLHAT were very different populations
Differences between ALLHAT and ANBP2

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Fatal/ non fatal CHD</th>
<th>All CV events &amp; deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>146/84</td>
<td>168/92</td>
</tr>
<tr>
<td>achieved</td>
<td>134/75</td>
<td>142/80</td>
</tr>
<tr>
<td>groups</td>
<td>differ 2-4 mmHg</td>
<td>identical</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>chlorthalidone</td>
<td>hydrochlorothiazide</td>
</tr>
<tr>
<td>lisinopril</td>
<td>enalapril (ACEi)</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>β blocker</td>
<td>CCB</td>
<td></td>
</tr>
<tr>
<td>clonidine, reserpine</td>
<td>β blocker</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

ANBP2 and ALLHAT are complementary

- BP control is the most important issue
- No one class of drug is markedly superior (ACE may be slightly better at a given level of BP)
- Individual characteristics (eg ethnicity) and concomitant disease (diabetes) are discriminators of appropriate drug selection
Let’s assume that ACE really is slightly better overall:

Then why?
A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly


Some new and unpublished results
1288 Patients Had Echo Study At Baseline and After 3 Year Treatment

• Powered to detect a 5% difference in LV mass between treatments
Baseline Predictors of CVD and Death

Echo variables
- Structure
- Function

BP
- CHD
- Cholesterol
- Age
- Sex

Hazard Ratio
Confidence Intervals
Changes in LV Wall Thickness at 3 Years Between Drug Treatment Groups

- ** - p<0.00001

** ns

IVS

PWT
Changes in LV Mass at 3 Years Between Drug Treatment Groups

-14  -12  -10  -8  -6  -4  -2  0

ACE  Diuretic

ns  **  ns  **

** - p<0.0001

LV Mass  LVMI
Changes in Echocardiographic Measures of Diastolic Filing at 3 Years Between Drug Treatment Groups

-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0

ACE
Diuretic

EA Ratio  Deceleration Time

* - p<0.01
** - p<0.0001
ns
Although LVH was a strong predictor of outcome differences in LVH regression do not account for better outcome in ACE group

What about metabolic changes?
Diabetic subjects had similar Blood Pressure to the overall cohort in ANBP2

<table>
<thead>
<tr>
<th></th>
<th>Non Diabetic n=5,642</th>
<th>Diabetic n=441</th>
<th>Diabetic ACEi n = 229</th>
<th>Diuretic n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline mmHg</strong></td>
<td>168/91</td>
<td>170/89</td>
<td>170/89</td>
<td>172/88</td>
</tr>
<tr>
<td><strong>Last visit mmHg</strong></td>
<td>142/79</td>
<td>142/77</td>
<td>143/78</td>
<td>142/78</td>
</tr>
<tr>
<td><strong>Average fall mmHg</strong></td>
<td>26/12</td>
<td>28/12</td>
<td>27/11</td>
<td>30/10</td>
</tr>
</tbody>
</table>
Comparison of ACE inhibitor to Diuretic Therapy in Diabetic Cohort

<table>
<thead>
<tr>
<th>Event</th>
<th>ACE (n=229) Rate/1000 person yrs</th>
<th>Diuretic (n=212) Rate/1000 person yrs</th>
<th>HR* (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CVS events and deaths</td>
<td>73.7</td>
<td>107.0</td>
<td>0.74 (0.51-1.09)</td>
<td>0.13</td>
</tr>
<tr>
<td>First CVS event or deaths</td>
<td>55.7</td>
<td>71.2</td>
<td>0.74 (0.50-1.59)</td>
<td>0.12</td>
</tr>
<tr>
<td>First CVS event</td>
<td>44.1</td>
<td>64.6</td>
<td>0.66 (0.44-0.99)</td>
<td>0.05</td>
</tr>
<tr>
<td>First non-fatal CVS event</td>
<td>37.1</td>
<td>60.6</td>
<td>0.59 (0.38-0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>8.7</td>
<td>21.8</td>
<td>0.40 (0.17-0.95)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*adjusted for age and gender
Comparison of ACE inhibitor to Diuretic Therapy in Diabetic Cohort

ACE inhibitor therapy (n=229) compared to diuretic treated group (n=212) was associated with:

- 26% in Primary endpoint \( p = 0.13 \)
- 34% in First CVS event \( p = 0.05 \)
- 60% in Heart Failure \( p = 0.04 \)

No difference in mortality
New cases of diabetes

\[ n=3039 \quad n=3044 \]

Adjusted Hazard Ratio 0.67
95% Confidence Interval 0.55 - 0.83

6.58% 4.54%
P=0.0002
<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANBP-2</td>
<td>ACEi v D</td>
<td>33%</td>
</tr>
<tr>
<td>HOPE</td>
<td>Ramipril V Rx</td>
<td>34%</td>
</tr>
<tr>
<td>CAPPP</td>
<td>Captopril v BB</td>
<td>24%</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan v BB</td>
<td>25%</td>
</tr>
</tbody>
</table>
Conclusions

• ACE initiation showed a slight advantage over low dose thiazide on 10 combined end point in an elderly HT population
• Diabetics and males benefited more from ACE than thiazide
• Design and population differences probably account for apparent discrepancy with ALLHAT
• Metabolic advantages seen with ACE but similar effects on LVH to thiazide
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