ASCOT-BPLA Trial Overview

- A multi-center randomized placebo-controlled trial to determine effects of amlopidine +/- perindopril vs atenolol +/- bendroflumethiazide on ‘non-fatal MI and fatal CHD’ in moderate risk (eg. diabetes 27%) hypertensive patients without previous heart disease. (Untreated SBP≥160 or DBP≥100 or both; Treated 10% or previous therapy SBP≥140 or DBP≥90 or both)
- Two treatment arms:
  - Amlodipine (5/10mg) +/- perindopril (4/8mg) daily (n=9639)
  - Atenolol (50/100mg) +/- bendroflumethiazide (1.25-2.5mg) (n=9618)
- 19,257 patients with the following characteristics (At baseline: aspirin use 19%, lipid agents 10%)
  - Hypertension: (amlopidine arm BP 164.1/94.8 vs 136.1/77.4; Atenolol arm BP 163.9/94.5 vs 137.7/79.2)
  - Total cholesterol (mean 5.9mmol/l, LDL (mean 3.8mmol/l); BMI=29kg/m²; glucose 6.2 mmol/l; Scr 99umol/l)
  - Risk factors: hypertension plus ≥3 additional CHD risk factors:
    - Age ≥ 55%: male 77%, microalbuminuria/proteinuria 62%; smoking 33%; family history of CHD 26%; type 2 diabetes 27%;
    - TC/HDL ≥ 14%; other ECG abnormalities 23%; LHV 22% previous stroke/TIA 11% or peripheral artery disease 6%.
- Age 40-79 (mean 63 years); 77% male (evenly distributed)
- Trial halted early after median of 5.5 years due to all-cause mortality reduction benefits

Table 1: ASCOT-BPLA results:

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Amlodipine arm % =9639</th>
<th>Atenolol arm % =9618</th>
<th>ARR %</th>
<th>RRR %</th>
<th>NNT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal CHD &amp; non-fatal MI (incl. silent MI)</td>
<td>4.5 (429 events)</td>
<td>4.9 (474 events)</td>
<td>0.4</td>
<td>9</td>
<td>NS</td>
<td>0.1052</td>
</tr>
<tr>
<td>Total CVD events &amp; procedures</td>
<td>14.1</td>
<td>16.7</td>
<td>2.6</td>
<td>18</td>
<td>39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>7.8</td>
<td>8.9</td>
<td>1.1</td>
<td>14</td>
<td>91</td>
<td>0.0070</td>
</tr>
<tr>
<td>Non-fatal MI plus fatal CHD *</td>
<td>4</td>
<td>4.6</td>
<td>0.6</td>
<td>15</td>
<td>167</td>
<td>0.0458</td>
</tr>
<tr>
<td>Mortality-all cause</td>
<td>7.7</td>
<td>8.5</td>
<td>0.8</td>
<td>10</td>
<td>125</td>
<td>0.25</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>2.7</td>
<td>3.6</td>
<td>0.9</td>
<td>33</td>
<td>112</td>
<td>0.0010</td>
</tr>
<tr>
<td>Fatal &amp; non-fatal stroke</td>
<td>3.4</td>
<td>4.4</td>
<td>1</td>
<td>29</td>
<td>100</td>
<td>0.0003</td>
</tr>
<tr>
<td>Fatal &amp; non-fatal heart failure</td>
<td>1.4</td>
<td>1.7</td>
<td>0.3</td>
<td>21</td>
<td>NS</td>
<td>0.1257</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>5.9</td>
<td>8.3</td>
<td>2.4</td>
<td>41</td>
<td>42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Development of renal impairment</td>
<td>4.2</td>
<td>4.9</td>
<td>0.7</td>
<td>17</td>
<td>143</td>
<td>0.0187</td>
</tr>
</tbody>
</table>

*Not including silent MI

Of Note:

- Lower BP with amlopidine (differences at 3 months of 5.9/2.4 mmHg and throughout the trial of 2.7/1.9 mmHg)
- Atenolol arm: ↑ of 0.2 mmol/l glucose & ↓ HDL by 0.1mmol/l more than amlopidine arm (baseline glucose was 6.2mmol/l)
- Reduction in PRIMARY endpoint NOT statistically significant but significant for 6 of the 7 secondary endpoints (halted early)
- Adverse effects: amlopidine arm worse for cough, joint swelling & edema; atenolol arm worse for bradycardia, fatigue & peripheral coldness
- Only 32% of diabetic & 60% of nondiabetic achieved BP goals (more emphasis needs to be directed at BP in high risk pts)
- Percent of pts using different regimens: amlopidine 83% +/- perindopril 59% vs atenolol 79% +/- bendroflumethiazide 66%
- Crossover to a drug included in the group to which they were not allocated (16% with amlopidine & 26% with atenolol)

What we know and what these results add to that knowledge:

- ASCOT-BPLA found amlopidine 10mg +/- perindopril to be better than atenolol 100mg +/- bendroflumethiazide for those with hypertension and additional risk factors. Those who are using “atenolol +/- bendroflumethiazide” first line may strongly consider alternatives. It has not provided evidence to change practice for those who were using more common combination of an “ACEI + thiazide”.
- Magnitude of benefit was “one less death for every 125 patients treated over 5.5 years”; plus additional reductions seen in other endpoints such as coronary events, stroke & new onset diabetes. (Of no note, difference seen in primary endpoint).
- This trial adds to the evidence for outcome benefits with amlopidine based regimens; however, one may not get too excited as atenolol appears as an inferior agent in this & other trials.
- 63% of patients ≥60yrs older, LIFE, ASCOT & in a hypertension meta-analysis Beta-blockers still useful Post-MI & HF.
- Other agents with strong outcome evidence: Chlorthalidone overall equivalent in ALLHAT (but superior vs lisinopril for stroke & HF & amlopidine for HF), AACEs rampol HOPE, perindopril EUROPA & PROGRESS, randopril TRACe, high-dose ARBs candesartan CHARM, valsartan VALLANTI & Val-HeFT; other beta blockers bisoprolol CIBIS II, carvedilol COMET & metoprolol MERIT-HF; have performed well in post-MI & HF trials.
- A BP difference of 2.7/1.9 mmHg favoring amlopidine could account for these results as larger reductions in BP produce larger
- Others amlopidine have unique benefits. 8 Amlopidine is not beneficial for renal outcomes.

References: