ACCOMPLISH 1,2: ACEI + Amlodipine vs ACEI + Hydrochlorothiazide in High Risk Hypertensives

- **Trial:** n=11,506; 36months (mean follow-up); an international multi-center, Novartis funded RCT to evaluate two combination antihypertensive approaches on CV outcomes in high risk patients (mostly white overweight Americans with CHD &or DM but not HF). Trial halted early after mean of 3 yrs.
- **Treatment studied:** benazepril + HCT (HCT) vs. amlodipine + norvasc (HCT).

{Following max doses of studied drugs, add on therapy could include β-blockers, α-blockers, clonidine, spironolactone & loop diuretics. Lack of info on 3rd drug limits interpretation.)

- **Population:** 50-80 yrs, any ethnicity. White 64%, African 71%. Age mean: 68. Target BP: <140/90. Mean 180/108 yrs if diabetes/renal disease
- **Inclusion criteria:** A) age ≥60 with hypertension (HTN): SBP≥160mmHg or currently on antihypertensive therapy and evidence of cardiovascular or renal disease or target end organ damage and 1 of the following: previous MI, stroke/TIA, previous hospitalization for unstable angina, coronary revascularization, peripheral arterial occlusive disease, diabetes (DM), left ventricular hypertrophy, or renal events (SCr>133μmol/L, <150μmol/L, or macroalbuminuria OR B) age 55-59 if evidence of ≥2 or more CV diseases or target organ damage (Demographics: prior MI 25% & stroke/TIA 19%, previous hospitalization for unstable angina 11% & coronary revascularization 14%, smoking 10% CCI <60, race A1% & renal disease 11%, DM 99%, LVH 15%, Dyslipidemia 1%, AFib 6%, BP change: (amlodipine arm BP=145/80 – 131.67±4mm HCT arm BP=145/80 – 122.57±4mm HCT); amlodipine 0.9±1.1mg/more than HCT. [97% on previous BP meds & 75% on ≥2 antihypertensives, but only 37% controlled BP <140/90].

- **Baseline drugs:** on ASA ~65%, lipid agents ~68%, β-blockers ~48%. Cholesterol total (mean 4.8±1.1), HDL (mean 1.3±1.0), BMI=31. Wt=89kg; glucose 7±1.9; Scr 88±1.9.
- **Exclusion criteria:** angina prior 3 months, HF or left ventricular EF <40%, MI/ACS/coronary revascularization in prior month, stroke/ischemic event, severe/refractory HTN, or other illnesses, physical impairments or mental condition that may interfere with study.

**Table 1: ACCOMPLISH results:**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>ACEI + Amlodipine</th>
<th>ACEI + HCT</th>
<th>ARR %</th>
<th>RRR %</th>
<th>NNT/3yrs</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, non fatal MI &amp; stroke</td>
<td>9.6 (552 events)</td>
<td>11.8 (679 events)</td>
<td>2.2</td>
<td>18.4</td>
<td>46</td>
<td>95% CI: 30-96</td>
</tr>
<tr>
<td>CV death, non fatal MI &amp; stroke (Hope1=Endpoints)</td>
<td>5.0 (288 events)</td>
<td>6.3 (364 events)</td>
<td>1.3</td>
<td>21</td>
<td>77</td>
<td>95% CI: 47-218</td>
</tr>
<tr>
<td>coronary revascularization</td>
<td>5.8</td>
<td>6.7</td>
<td>0.9</td>
<td>14</td>
<td>113</td>
<td>0.04</td>
</tr>
<tr>
<td>fatal &amp; non-fatal MI</td>
<td>2.2</td>
<td>2.8</td>
<td>0.6</td>
<td>21</td>
<td>171</td>
<td>0.04</td>
</tr>
<tr>
<td>fatal &amp; non-fatal stroke</td>
<td>1.9</td>
<td>2.3</td>
<td>0.4</td>
<td>17</td>
<td>NS</td>
<td>0.17</td>
</tr>
<tr>
<td>hospitalizations for heart failure</td>
<td>1.7</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>0.77</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>1.9</td>
<td>2.3</td>
<td>0.4</td>
<td>17</td>
<td>NS</td>
<td>0.28</td>
</tr>
<tr>
<td>mortality-all cause</td>
<td>4.1</td>
<td>4.5</td>
<td>0.4</td>
<td>9</td>
<td>NS</td>
<td>0.24</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>13.4</td>
<td>14.3</td>
<td>0.9</td>
<td>6.3</td>
<td>0.6</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Both arms: (ACEI) in 20%, hyperkalemia in 0.6%; Amlodipine arm: T edema 31.2% ± 31.7%, T dizziness 27.5% ± 25.4%, hypotension 15.2% ± 8.3% & hypokalemia 5.1% ± 4.9%.

**Of Note:**

- Adverse Events: amlodipine arm worse for edema; HCT arm worse for dizziness & hypokalemia. [Angioedema 0.9% in amlodipine arm]
- BP control - achievement of target BP: ACEI + amlodipine arm 75%; ACEI + HCT arm 72%.
- BP control - achievement of target BP: difference in BP reduction may partly explain the result, and actual differences may have been greater due to timing of HCT and BP measurement (further ABPM analysis awaited). Choice of antihypertensive therapy should not be based on compelling indications (comorbidities e.g. HF, post-MI, asthma, diabetes, nephropathy), contraindications & patient factors (race, side effects, cost). Combination antihypertensive regimens can dramatically achieve BP targets & offer benefit in a high percentage of patients.

**Cut to the Chase:** Where does this trial LEAVE Thiazide Diuretics?

- This trial suggests that an ACEI+amlodipine combination may be preferred to an ACEI+HCT combination in ACCOMPLISH type patients.
  - Magnitude of benefit: 1% endpoint (including the softer endpoints): 1 person benefited for every 46 patients treated over 3 years.
  - For typical major CV endpoints: 1 less non-fatal MI/stroke or CV death for every 77 patients treated over 3 yrs

- HOWEVER, there are some important qualifiers given the ACCOMPLISH trial design:
  - HF patients were excluded, and HF outcomes were worse with amlodipine compared to the thiazide & ACEI in ALLHAT 3
  - The ACEI+amlodipine arm had greater BP reduction leading to question of whether BP control or specific drugs had a greater role in outcome.
  - Amlodipine benefit similar to thiazide or ACEI in ALLHAT; better than thiazide in ASCOT-BPLA4; not beneficial for renal outcomes AASK & IDNT (5, 6).
  - Best thiazides evidence currently lies with chlorthalidone & indapamide (ALLHAT, Elderly ≥60yr HYVET, ISH SHEF, Stroke/TIA PROGRESS) 7,8,9
  - Potential differences between HCT and chlorthalidone: 10,11,12
  - Cost considerations: Thiazides have cost-effective role for both initial & add-on therapy

- Practically, physicians may sometimes use an ACEI/low-dose thiazide combination in addition to a CCB (amlodipine) rather than automatically maximizing dosages of just two agents. The trial does not offer any insight on this common management alternative.

**Take Home:** An ACEI (benazepril) + amlodipine is a reasonable combination option in some patients with HTN & additional risk factors. In ACCOMPLISH type patients it appeared to be better than an ACEI + HCT combination; magnitude of benefit on major CV outcomes non-fatal MI/stroke, CV death, was an absolute risk reduction of 1.3% (NNT=77 / 3 years). There was no difference in CV or all-cause mortality. This result should be interpreted in context of design limitations and previous trial experiences where thiazides have done well.

*Difference in BP reduction may partly explain the result, and actual differences may have been greater due to timing of HCT and BP measurement (further ABPM analysis awaited). Choice of antihypertensive should be based on compelling indications (comorbidities e.g. HF, post-MI, asthma, diabetes, nephropathy), contraindications & patient factors (race, side effects, cost). Combination antihypertensive regimens can dramatically achieve BP targets & offer benefit in a high percentage of patients.*

**References** (for full reference list, see next page):


T. Jameson K et al. Randomisation & the avoiding CV events through combination therapy in patients living with systolic hypertension (ACCOMPLISH): that the first RCT to compare the clinical outcomes effects of first-line combination therapies in hypertension. AJH 2009(79);B901

**Essential Evidence Plus:** This study of patients with coronary disease or coronary disease equivalents, the combination of benazepril and amlodipine provided a small benefit in terms of the composite cardiovascular outcome. However, it did not reduce all-cause mortality or cardiovascular mortality. These findings should not prompt a change in our usual management of hypertension, since this was a very-high-risk group of older patients. We should not change our practice to adopt this much more expensive alternative for high-risk patients unless another study confirms these findings, which run somewhat counter to those of ALLHAT. (LOE 1b)

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RxFiles – Trial Summary www.RxFiles.ca - Dec 2008


Additional References


Davis BR, Kostis JB, Simpson LM, et al. for the ALLHAT Collaborative Research Group. Heart Failure With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation. 2008 Nov 10. [Epub ahead of print] in ALLHAT ANTihypertensive outcomes, chlorthalidone significantly reduced the occurrence of new-onset hospitalised HFREF and HFREF compared with atenolol and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFREF compared with doxazosin. Among high-risk hypertensive men and women, HFREF has a better prognosis than HFREF.


Staessen JA, Birkhager KH. Evidence that new antihypertensives are superior to older drugs. Lancet 2005 Sep 10;366(9469):899-71.