In addition to their BP lowering potential all antihypertensive agents have other important mechanisms of action, indications, and side effects. These actions may convey benefits or risks independent of BP lowering. By having a common BP goal for all treatment arms, ALLHAT aimed to evaluate the health effects of these non-BP actions.
Overall Purpose

To determine whether the newer, more costly antihypertensive drugs - CCBs, ACE inhibitors and alpha-blockers - are superior to the older, less expensive diuretics in preventing CV complications of hypertension.
Health Effects of Diuretics

Low-dose thiazide-type diuretic-based treatment in large clinical trials has been shown to reduce the risks of:

<table>
<thead>
<tr>
<th>Event</th>
<th>Reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>34</td>
</tr>
<tr>
<td>Heart failure</td>
<td>42</td>
</tr>
<tr>
<td>CHD</td>
<td>28</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>24</td>
</tr>
<tr>
<td>Total mortality</td>
<td>10</td>
</tr>
</tbody>
</table>

Psaty et al., JAMA 1997;277:739-45
ALLHAT

Strengths

• Largest hypertension trial ever (n=42,418); practice-based
• Diverse study population
• High methodologic standards
• Independent sponsorship and conduct
• Conclusions based on 10,834 cardiovascular events
Implications

1. Selection of first-line drug
2. Selecting treatments for particular patients
3. Drug cost and health benefit
   • To patients
   • To society
4. Design of future hypertension trials
5. Impact on treatment guidelines
Selection of 1st-line Drug - Conclusions

Among antihypertensive drugs, thiazide-like diuretics were unsurpassed in:

- long-term drug adherence
- controlling elevated blood pressure

and were superior to other therapies in:

- preventing one or more forms of cardiovascular events
- having lower drug cost
Selection of 2nd-line Drug(s) - Type of Add-on

- Large proportion of hypertensive patients require additional drug(s) for BP control
- No direct comparison of 2nd-line drugs in ALLHAT
- Optimal type of add-on agent unknown
- Need for large trials comparing different classes of agents added to diuretics
2002 Use of Antihypertensive Medications, Proportion of Drug-Treated Patients by Drug Class

- **37%** for ACE-Inhibitors
- **27%** for Calcium Channel Blockers
- **20%** for Diuretics
- **20%** for Beta-Blockers
- **19%** for ARBs

Source: NDTI -- IMS HEALTH
Benefits of diuretics generalizable to:

- Men and women
- Age group <65 and ≥ 65 yrs
- Blacks and non-blacks
- Diabetics and non-diabetics
- Presence and absence of other co-morbidity
Diuretics are better than:

- ACEIs (lisinopril) for patients at high risk of CVD events, especially heart failure, as well as for African-Americans at risk of stroke
- Alpha-blockers (doxazosin) for patients at high risk of heart failure, stroke, angina and coronary revascularizations
- CCBs (amlodipine) for patients at high risk of developing heart failure
Thiazide-type diuretics should be considered for nearly all patients with hypertension:

- Untreated patients
- Inadequately controlled patients on non-diuretic agent(s)
- Controlled patients on non-diuretic agent(s) unless compelling indication exists for another agent
ALLHAT

Drug Cost to Patient (U.S. 2002)

Annual

Chlorthalidone $36
Amlodipine $679
Lisinopril - branded $533
- generic** $280

*Drugstore.com (exclusive of dispensing fee) **available 3rd quarter 2002
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Average Annual Drug Cost/Pt*</th>
<th>No. of Annual Users**</th>
<th>Total Drug Cost**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>$280-533</td>
<td>12.7</td>
<td>$3,556-6,769</td>
</tr>
<tr>
<td>CCBs</td>
<td>$679</td>
<td>9.3</td>
<td>$6,315</td>
</tr>
<tr>
<td>Diuretics</td>
<td>$36</td>
<td>6.9</td>
<td>$248</td>
</tr>
</tbody>
</table>

*price of largest selling drug/class (2002) **in million

Implications

ALLHAT Drug Cost to Society
### Excess CV Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>6-yr Excess</th>
<th>Total Users*</th>
<th>Excess events/yr**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs Comb CV Events</td>
<td>2.3%</td>
<td>12.7</td>
<td>48,700</td>
</tr>
<tr>
<td>CCBs CHF</td>
<td>2.5%</td>
<td>9.3</td>
<td>38,800</td>
</tr>
</tbody>
</table>

*in million  **concomitant use of diuretics may reduce these numbers by up to 20%
Design of Hypertension Trials

Thiazide-like diuretics, in low to moderate dose, should be the treatment control group of future comparative trials in patients with hypertension.
Thiazide-like diuretics, in low to moderate dose, should be the guideline-recommended first-line drug treatment for nearly all patients with hypertension.
Conclusions

- The benefit of diuretics as first-line therapy applies to nearly all patients with hypertension.
- Diuretics are superior or unsurpassed in reducing the risks of cardiovascular complications.
- Diuretics are the least expensive agents for treating hypertension.
Conclusions II

- Translating the ALLHAT findings into practice will reduce the financial cost of antihypertensive drugs and reduce the societal burden of CV complications.
- Future comparative hypertension trials should use diuretics as the control group or base therapy.
- Treatment guidelines are being revised to reflect the ALLHAT findings.