Implications of ASCOT Results for ALLHAT Conclusions
Overall Implications

- ASCOT was not a comparison of initial treatment with newer drugs versus thiazide diuretic-based treatment—therefore, no change in ALLHAT conclusions.

- Differences in fatal/non-fatal events largely due to lesser BP reduction with β-blocker-based regimen.
ASCOT Aim

• To compare a treatment regimen of newer antihypertensive drugs (CCB ± ACEI) with a traditional regimen (β-blocker ± diuretic) for primary prevention of CHD.
ASCOT Design

• Prospective, randomized, open-label, blinded endpoint (PROBE)

• Randomization to CCB or β-blocker
  – Add-on drugs ACEI (CCB arm) or diuretic (β-blocker arm)

• Primary endpoint: Nonfatal MI + fatal CHD

• 19,257 participants

• Mean follow-up: 5.4 years

ASCOT Inclusions

- Blood pressure:
  - Screening and baseline SBP ≥160 and/or DBP ≥100 mm Hg untreated, or
  - Baseline SBP ≥140 and/or DBP ≥ 90 mm Hg following treatment with 1 or more drugs
- Age 40-79 years
- No previous MI or current clinical CHD
- 3 or more risk factors for a future CV event
ASCOT Exclusions

• Previous MI
• Currently treated angina
• CVA within 3 months
• Fasting TG >400 mg/dl
• Heart failure
• Uncontrolled arrhythmias
• Clinically important hematological or biochemical abnormality on routine screening
ASCOT Outcomes

• No significant difference in primary CHD outcome.

• Stopped early due to reduction in total mortality in amlodipine-based treatment arm.
  – Final result 11% reduction in total mortality, p=0.02
ASCOT Secondary Outcomes

- CV mortality reduced 24%, p=0.001
- Total coronary events reduced 13%, p=0.007
  - fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure
- Stroke reduced 23%, p=0.0003
- CV events/procedures reduced 16%, p<0.0001
- Fatal & nonfatal HF non-significantly lower by 16% (p=0.13)
Other ASCOT Results

• 2\textsuperscript{nd} step medications:
  – 58\% of amlodipine person-yrs on perindopril
  – 66\% of atenolol person-yrs on bendroflumethiazide

• 2.7 mm Hg mean SBP difference favoring amlodipine
  (5.9 mm Hg at 3 months)

• HDL lower and TG higher in β-blocker arm

• New onset DM reduced 30\% with amlodipine,
  \(p<0.0001\) (absolute difference 5 per 1000 person-years)

• 98.5\% of participants with complete information at
  end of trial
ASCOT Conclusion

• Amlodipine-based therapy confers an advantage over atenolol-based therapy on some major CV end points, all-cause mortality and new-onset diabetes.
### ASCOT vs ALLHAT

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<thead>
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<th>Comparison</th>
<th>ASCOT</th>
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<tr>
<td>Comparison</td>
<td>Aml vs Aten</td>
<td>Aml vs Chlor</td>
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<tr>
<td>Add-on drugs</td>
<td>Different in the 2 arms</td>
<td>The same in the 2 arms</td>
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- In ASCOT, different add-on drugs in the two arms make comparison of initial agent difficult.
ASCOT

• Atenolol-based regimen inferior to amlodipine-based regimen.
  – β-blockers are also inferior to ARBs based on the LIFE study.¹
  – β-blockers are also inferior to diuretics for CHD, especially in this age group.²

ALLHAT Results

• Compared amlodipine vs chlorthalidone
  – Add-on drugs and achieved BP were similar
  – No difference in CHD outcome or stroke
  – 1/3 higher rates of HF with amlodipine
Comments - Design

• PROBE (open-label) design → bias?
  – Even for total mortality, concomitant interventions can introduce confounding, and were not reported.

• Randomization not to newer vs older drugs but to CCB vs β-blocker with ACEI & diuretic as step-up.
Comments - Endpoints

• CV endpoints in ASCOT include soft outcomes (e.g., chronic stable angina, revascularization, PVD, etc.).
  – Reporting was not blinded

• How might have amlodipine’s anti-anginal properties affected the results?
  – No difference in major CHD
  – Difference for total coronary events
• β-blocker should not be used as initial therapy in uncomplicated hypertension.
  – Inferior to ARB in LIFE, inferior to CCB in ASCOT, and inferior to diuretic in MRC in Elderly
Conclusions from new meta-analysis of beta-blocker trials

"Our present results might affect the interpretation of two of the latest large hypertension trials--the LIFE and the ASCOT-BPLA trial--both of which claim the superiority of newer antihypertensive drugs. Our analyses suggest an alternative interpretation is that the beta blocker in these two mega-trials had a less than optimum cardiovascular effect."

Lindholm et al., www.thelancet.com, published online October 18, 2005
• Amlodipine has shown comparable CVD reduction vs diuretic except for HF (ALLHAT, others).

• Amlodipine superior to ACEI in ALLHAT for stroke and combined CVD (especially in Blacks and women), and inferior for HF.

• Amlodipine superior to ARB for fatal and nonfatal MI (VALUE).
Dose of Thiazide-type Diuretic in ASCOT

• Dose of thiazide-type diuretic used (BFMZ 1.25-2.5 mg/day) was lower than that in any positive CVD outcome trial.
  – MRC trial of treatment of mild HTN: BFMZ dosage was 10 mg daily.

• Evidence evaluating benefit of such thiazide-type diuretic doses (equivalent to 12.5 mg/day or less of HCTZ) on clinical outcomes is not available.

BFMZ = bendroflumethiazide; HCTZ = hydrochlorothiazide
Comments - Unknowns

• Because study population mostly white men, application to women and Black patients is unknown.

• Although potassium supplements routinely given with diuretic, adequacy of treatment for hypokalemia not reported.