

ASCOT: What did the Study show? (1)

An antihypertensive regimen consisting of amlodipine ± perindopril was superior to atenolol ± bendroflumethiazide:

	HR	P
Total coronary events	0.87	0.007
Total CV events + procedures	0.84	0.001
CV mortality	0.76	0.001
Total mortality	0.89	0.02
Strokes	0.77	0.0003
Heart failure	0.84	0.12
Diabetes	0.70	0.0001
Renal impairment	0.85	0.02

ASCOT: Issues in Interpretation (2)

1. Primary outcome of nonfatal MI (including silent MI) + fatal CHD: HR of 0.90 (0.79-1.02); $p=0.10$
2. Premature termination of the trial, although the pre-specified boundary ($Z=3.0$) for the primary outcome was not crossed (Z around 1.85)

Reason: “patients on atenolol/thiazide would be disadvantaged”

Premature termination means that observed magnitude of benefits of aml ± peri may be “upwardly biased”, direction of benefit is likely real

3. Early large (6/2 mm/Hg) differences in BP in favour of Aml + Peri, but smaller differences (3/2) later.

?Some (perhaps about half) of the difference is BP independent.

ASCOT: Consistency with External Data (3)

Direct evidence:

1. In ALLHAT, no sig diff in CHD or mortality but apparent superiority of diuretic over amlodipine or lisinopril on several secondary outcomes (heart failure, strokes, etc)
BUT BP differences (lower with diuretics) between the groups could explain most observed differences
2. LIFE and ANZ-BP2 trials blockade of the RAAS was superior to BB/diuretic

Indirect evidence:

1. BPLTC meta-analysis indicates that ACE-I has a direct benefit in reducing CHD beyond BP lowering. At zero BP lowering, there is a 10% decrease in CHD.
2. In several trials of ACE-inhibitors in “normotensive” populations, there is a reduction in CHD (SOLVD, SAVE, HOPE, EUROPA) and diabetes

OVERALL: The newer drugs (especially blockers of the RAAS) have a modest benefit beyond BP lowering compared to older drugs

ASCOT and OTHER TRIALS: Clinical & Public Health Implications (4)

1. Given the large population burden of hypertension, even modest incremental benefits of specific agents over others, can translate into important public health impact.
2. Most patients with hypertension require 2+ drugs and so the question of the best combo is important. In most patient categories a blocker of the RAAS with either CCB (amlodipine) or a diuretic may be the optimal initial regimen (??value of 2 or more BP lowering drugs)
3. Cost of drugs will be an issue for most societies, but some of the higher costs of newer drugs may be offset by fewer clinical events and better tolerability.
4. BP lowering should be combined with other approaches to reduce risk (lipid lowering, decreasing weight, smoking cessation, healthy lifestyles) and can prevent 80 to 90% of premature CVD events