An Overview of ASCOT-BPLA [1] - Blood Pressure Lowering Arm

ASCOT-BPLA Trial Overview

- a multi-center randomized placebo-controlled trial to determine effects of amlodipine +/- 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 [80% on previous therapy] SBP≥140 or DBP>90 or both)
- two treatment arms:
  - amlodipine (5/10mg) +/- perindopril (4/8mg) daily (n=9639) **vs**
  - 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 (amlodipine arm BP 164.1/94.8→136.1/77.4 mmHg; atenolol arm BP 163.9/94.5→**137.7/79.2** mmHg)
  - total cholesterol (mean 5.9mmol/l), LDL (mean 3.8mmol/l); BMI=29kg/m^2; glucose 6.2 mmol/l; Scr 99umol/L
  - risk factors: **hypertension plus ≥3 additional CHD risk factors:**
    (age ≥ 55 [84%], male [77%], microalbuminuria/proteinuria [62%], smoking [33%], family history of CHD [26%], type 2 diabetes [27%], TC/HDL ≥6 [14%], other ECG abnormalities [23%], LVH [22%], previous stroke/TIA [11%] or peripheral artery disease [6%]).
    age **40-79** (mean **63** years); 77% male (evenly distributed)
- trial **halted early** [Nov 2004] after median of 5.5 years due to all-cause mortality reduction benefits

Table 1: ASCOT-BPLA results:

Endpoints	Amlodipine arm % n=9639	Atenolol arm % n=9618	ARR %	RRR %	NNT	p value
1° fatal CHD & non-fatal MI (incl. silent MI)	4.5 (429 events)	4.9 (474 events)	0.4	9	**NS**	0.1052
2° **total CVD events & procedures**	14.1	16.7	2.6	18	39	<0.0001
2° **total coronary events**	7.8	8.9	1.1	14	91	.0070
2° **non-fatal MI plus fatal CHD***	4	4.6	0.6	15	167	0.0458
2° **mortality-all cause**	7.7	8.5	0.8	10	125	.025
2° **CVD mortality**	2.7	3.6	0.9	33	112	.0010
2° **fatal & non-fatal stroke**	3.4	4.4	1	29	100	.0003
2° **fatal & non-fatal heart failure**	1.4	1.7	0.3	21	NS	0.1257
3° New onset **diabetes**	5.9	8.3	2.4	41	42	<0.0001
3° Development of **renal** impairment	4.2	4.9	0.7	17	143	0.0187

***** not including silent MI **1°**=primary outcome **2°**=secondary outcome **3°**=tertiary outcome **ARR**=absolute risk reduction **BP**=blood pressure **CHD**=coronary heart disease **CVD**=cardiovascular disease **HF**=heart failure **MI**=myocardial infarction **NS**=not significant **NNT**=number needed to treat to benefit 1 patient **RRR**=relative risk reduction

Of Note:

- **lower BP with amlodipine** (differences at 3 months of 5.9/2.4 mm/Hg; and **throughout the trial** of **2.7/1.9** mm/Hg)
- atenolol arm: ↑ of 0.2 mmol/l glucose & ↓ HDL by 0.1mmol/l more than amlodipine 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: amlodipine arm worse for cough, joint swelling & edema; atenolol arm worse for bradycardia, fatigue & peripheral coldness
- only **32%** of diabetic & **60%** nondiabetic achieved **BP goals** (more emphasis needs to be directed at ↓BP in high risk pts)
- percent of pts using different regimens: amlodipine [83%] +/- perindopril [59%] **vs** atenolol [79%] +/- bendroflumethiazide [66%]
- crossover to a drug included in the group to which they were **not** allocated (16% with amlodipine & 26% with atenolol)

What we knew and what these results add to that knowledge: [2-4,9]

- **ASCOT-BPLA** found **amlodipine 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 note, no difference seen in primary endpoint.)
- This trial adds to the evidence for **outcome benefits with amlodipine based regimens**[2,4]; however, one may not get too excited as **atenolol** appears as an inferior agent in this & other trials. Elderly>60yr, LIFE, ASCOT & in a hypertension meta-analysis [5] {Beta-blockers still useful Post-MI & HF}.
- 63% of patients >60yrs [Ascot]; yet Canadian guidelines already recommend against beta-blockers if no cardiac disease & >60yrs
- Other agents with strong outcome evidence: Chlorthalidone -overall equivalent in ALLHAT (but superior vs lisinopril [for stroke & HF] & amlodipine [for HF]); ACEIs [ramipril HOPE, perindopril EUROPA & PROGRESS, trandolapril TRACE; high-dose ARBs [candesartan CHARM, valsartan VALIANT & Val-HeFT]; other beta blockers [bisoprolol CIBIS-II , carvedilol COMET & metoprolol MERT-HF] have performed well in post-MI & HF trials.
- A **BP difference** of 2.7/1.9 mm/Hg favoring amlodipine could account for these results [6] as larger reductions in BP produce larger risk reductions. [7] Others believe amlodipine to have unique benefits. [8] Amlodipine is not beneficial for renal outcomes [AASK & IDNT].

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