An Overview of ASCOT-LLA [1,7] - Atorvastatin in Primary Prevention

ASCOT-LLA Trial Overview

- a multi-center randomized placebo-controlled trial to determine effects of atorvastatin on 'non-fatal MI and fatal CHD' in high risk (eg. diabetes 24%), hypertensive patients without previous heart disease and a total cholesterol ≤6.5 mmol/l
- two treatment arms:
  - **atorvastatin** (**LIPITOR**) 10mg daily plus antihypertensive medications (n=5,168)
  - **placebo** plus antihypertensive medications (n=5,137)
- 10,305 patients with the following characteristics:
  - hypertension (mean BP 164.2/95 mmHg)
  - total cholesterol (mean 5.5mmol/l→4.2 mmol/L), LDL (mean 3.4mmol/l→ 2.3mmol/l)
  - risk factors: **hypertension plus ≥3 additional CHD risk factors** (Average **3.7** additional risk factors/patient) (age ≥ 55 [84%], male [81%], microalbuminuria/proteinuria [62%], smoking [33%], family history of CHD [26%], type 2 diabetes [24%], TC/HDL ≥6 [14%], other ECG abnormalities [14%], LVH [14%], previous stroke/TIA [10%] or peripheral artery disease [5%]). age **40-79** (mean 63 years); 81% male (evenly distributed)
- trial **halted** after 3.3 years due to morbidity benefits (e.g. significant reduction in 'non-fatal MI & fatal CHD' & stroke)

Table 1: ASCOT-LLA results (atorvastatin 10mg daily vs placebo)

Endpoints	atorvastatin %	placebo %	ARR %	RRR %	NNT	p value
1° fatal CHD & non-fatal MI	1.9 (100 events)	3.0 (154 events)	1.1	36	**91**	0.0005
2° total CVD events & procedures	7.5	9.5	2.0	21	50	0.0005
2° total coronary events	3.4	4.8	1.4	29	72	0.0005
2° non-fatal MI plus fatal CHD*	1.7	2.7	1.0	37	100	0.0005
2° mortality-all cause	3.6	4.1	0.5	12	NS	0.1649
2° CVD mortality	1.4	1.6	0.2	13	NS	0.5066
2° fatal & non-fatal stroke	1.7	2.4	0.7	29	143	0.0236
2° fatal & non-fatal heart failure	0.8	0.7	-	-	-	0.5794
3° chronic stable angina	0.6	1.1	0.5	45	200	0.0135

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

Of Note:

- study did not provide risk/benefit data for higher atorvastatin doses or for more aggressive treatment to target
- short trial; lack data on long term effects; reduction in all-cause death did not reach statistical significance
- adverse event data lacking in the publication (1 case of non-fatal rhabdomyolysis in atorvastatin arm reported)
- benefits only in **men** (no benefit seen in women **n=1942**; rate of 1° outcome non-fatal MI & fatal CHD 1.9% atorvastatin vs 1.8% placebo **p>0.7**)
- lack of significant risk reduction in diabetes; may relate to study design; 14% of diabetes-placebo arm received a statin (similar limitation seen in ALLHAT-LLT [2] trial with pravastatin 40mg daily where 26% of control group received a statin)

Comparison to WOSCOPS [3]

- a primary prevention study of pravastatin 40mg od vs placebo in Scottish males age 45-64 with cholesterol ≥7 mmol/l
- both had relative reductions in the primary outcome of non-fatal MI and fatal CHD (RRR= ASCOT: 36% at 3.3yrs; WOSCOPS: 31% at 4.9yrs)
- both had favorable all-cause mortality trends (ASCOT 4.1% ⇨ 3.6% at 3.3yrs; WOSCOPS 4.1% ⇨ 3.2 % at 4.9 yrs)
- LDL reduction (ASCOT 3.4 mmol/l ⇨ 2.3 mmol/l at 3.3yrs; WOSCOPS 5.0 mmol/l ⇨ 4.1 mmol/l at 4.9 yrs)

What we knew and what these results add to that knowledge:

- **1° prevention**: previous evidence supported benefit of statins (pravastatin [3] & lovastatin [4]) in primary prevention of CHD in moderate to high risk male patients with dyslipidemia. **1° & 2° prevention**: in PROSPER [5], pravastatin 40mg daily reduced fatal MI & non-fatal CHD in elderly male patients (age 70-82yrs) with or at high risk of CVD; in HPS [6], simvastatin 40mg daily reduced morbidity & mortality in **male and female** patients (age 40-80yrs) with or at high risk of CVD.
- **ASCOT-LLA supports** the use of **atorvastatin 10mg daily** for primary prevention of CHD & stroke in hypertensive **male** patients (especially >60years of age) with multiple risk factors for CHD and total cholesterol levels ≤6.5 mmol/L. **Magnitude of benefit** was "**one less** fatal CHD event or non-fatal MI for every **91 patients** treated over **3.3 years**"; additional reductions seen in other endpoints such as stroke.

References:
1) Peter S Sever, Björn Dahlöf et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the **Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm** (**ASCOT-LLA**): a multicentre randomised controlled trial Lancet 2003; **361:** 1149-58. Online April 2, 2003.
2) Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT-LLT**). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2998-3007.
3) Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia (**WOSCOPS**). N Engl J Med 1995;333:1383-9.
4) Downs JR, Clearfield M et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of (**AFCAPS/TexCAPS**). JAMA 1998;279:1615-22.
5) Shepherd J, Blauw G et al. Pravastatin in elderly individuals at risk of vascular disease (**PROSPER**): a randomised controlled trial. Lancet 2002 Nov 23;360(9346):1623-30.
6) Heart Protection Study Group.MRC/BHF **HPS** study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22.
7) http://www.ascotstudy.co.uk

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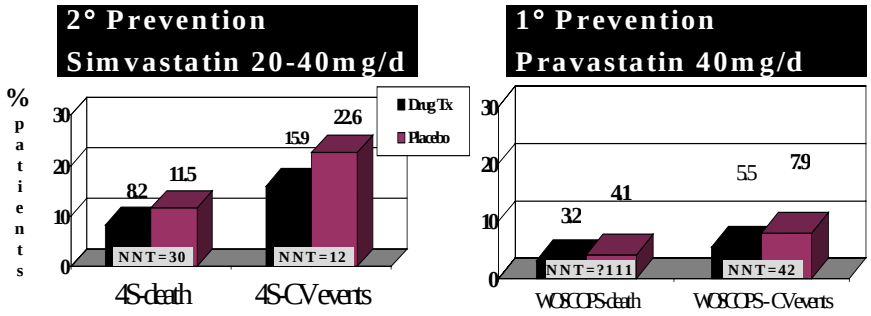
Statins *(the only group with all-cause mortality evidence)*

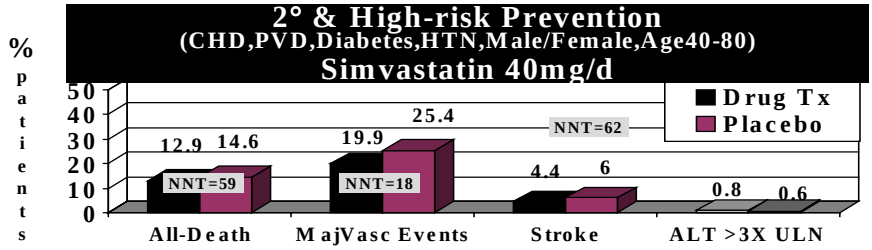
- Who benefits most?
- Differences: Evidence? DI's? Potency?

Watch for toxicity: hepatic/myopathy.



HPS *Lancet, July 2002*

- **No benefit for Vitamins** E 600mg, C 250mg, or beta-carotene
- **Evidence for simvastatin 40mg in 2° & very high risk 1° prevention in diabetes, stroke, age<80, women, LDL<3**
- **Questions remaining:** safety/efficacy of aggressive pursuit of targets, combination therapies, low-risk patients with ↑ LDL.



ASCOT *Lancet, April 2003*

- Trial provided evidence for primary prevention of CHD and stroke in hypertensive male patients with multiple CHD risk factors with total cholesterol ≤6.5mmol/L
- **Questions remaining**: women, adverse effects, long term effects, safety and efficacy of titrating dose to attain targets, magnitude/$