Lipid Lowering Evidence-Cardiovascular Mortality Reduction

Optimization of cardiac risk factors and lipid abnormalities can contribute to global cardiovascular morbidity and mortality reduction. The evidence and the cost benefit, particularly in 2o prevention, are compelling. Delays and gaps in implementation compromise patient outcomes and represent a huge lost opportunity to reduce hospitalization and health care costs and diminish the burden of cardiovascular disease.

The clinical benefit of lipid lowering was examined in a meta-analysis of 8 double blind placebo controlled secondary prevention trials up to an including HPS (6) in 54,381 subjects treated with simvastatin, pravastatin, lovastatin or fluvastatin (8) Compared to placebo a mean 20% cholesterol reduction was associated with a 30% reduction in CHD events and a 17% reduction in all cause mortality. The principal secondary prevention trials, 4S (3), CARE (4), and LIPID (5) enrolled patients to a maximum age of 75 years. Patients > 65 years old had similar benefits as compared to younger patients.

Major Dyslipidemia Clinical Trials: Age Ranges

Trial	Enrolment Age	Follow-up Years	Maximum Age
Dyslipidemia Trials			
WOSCOP (1)	45-65 M	4.9	70
AF-CAPS/Tex CAPS (2)	45-73 M, 55-73 W	5.2	78
4S (3)	35-70	5.4	75
CARE (4)	21-75	5	80
LIPID (5)	31-75	6	81
HPS (6)	40-80 (1263 pts 75-80)	5	85
PROSPER (7)	70-82	3.2	85
ALLHAT (8)	≥55, mean 66 (age range not given)	4.8	71
ASCOT-LLA (9)	40-79, mean age 63	3.3	82
REVERSAL(10)	30-75	1.5	76.5
PROVE-IT (11)	≥18,Mean 58	1.5-3.0 mean 2	
CARDS (12)	40-75	4	79

1 J, Cobbe, SM, Ford, I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333:1301.

2. Downs, JR, Clearfield, M, Weis, S, et al for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. JAMA 1998; 279:1615.

3. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383.

4. Sacks, FM, Pfeffer, MA, Moye, LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335:1001.

5. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group [see comments]. N Engl J Med 1998; 339:1349.

Major Dyslipidemia and Cardiovascular Prevention Trials: Event Reduction

Trial	Patient Number	Percentage Change in Trial Endpoint of Treatment Groups. All events (fatal and non fatal)			Intervention vs placebo unless otherwise specified
Dyslipidemia Trials					
		CVA	Cardiac	All CV	Placebo vs
WOSCOP (1)	6595	-11	-31	-32	Pravastatin 40 mg
AF-CAPS/Tex CAPS (2)	6605		-25	-25	Lovastatin 20-40 mg
4S (3)	4444	-30	-34	-35	Simvastatin10-40mg
CARE (4)	4159	-31	-25		Pravastatin 40mg
LIPID (5)	9014	-19 p NS	-29	-24	Pravastatin 40mg
HPS (6)	20536	-25	-27	-24	Simvastatin 40mg
PROSPER (7)	5804	-15	-19	+3 p NS	Pravastatin 40mg
ALLHAT (8)	10,355 5707≥65	No significant difference in any endpoint vs usual care (which included @ 30% use of lipid-lowering therapy)			Usual care vs Pravastatin 40mg
ASCOT-LLA (9)	19342	-23	-29	-21	Atorvastatin 10mg
REVERSAL(10)	654	Primary endpoint: Progression of coronary atherosclerosis Pravastatin 2.7 % vs. Atorvastatin -0.4%			Atorvastatin 80 mg vs. Pravastatin 40 mg
PROVE-IT (11)	4162	Primary endpoint: Death, MI, ACS, revascularization or CVA - Pravastatin 26.3 vs. Atorvastatin 22.4 P=0.005 ARR 3.9 RRR 16% NNT 26			Atorvastatin 80 mg vs. Pravastatin 40 mg
CARDS (12)	2841	-48	-32	-37	Atorvastatin 10mg

6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360: 7–22.

7. Shepherd J, J Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, Ford I,Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RGJ, on behalf of the PROSPER study group*.Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. THE LANCET • published online November 19, 2002

8. 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). JAMA 2002;288: 2998-3007.

9. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M,Collins R, Kjeldsen SE,Kristinsson A, McInnes GT, Mehlsen J, Nieminen M,O'Brien E, Östergren J for the ASCOT investigators* 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: 1140-1158.

10. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAN, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, on behalf of the CARDS investigators*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multirandomised placebo-controlled trial. Lancet 2004; 364: 685-96.