APPENDIX B: LIST OF THE SELECTED SECONDARY STUDIES

Main systematic reviews – secondary studies on the general effectiveness of statins in secondary cardiovascular prevention (search date: 2003-2006)

NICE. Statins for the prevention of coronary events - Technology assessment report commissioned to ScHARR by the NICE HTA Programme–2005

Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Int Med* 2004;164:1427-36

Cheung BMY, Lauder IJ, Lau CP, et al. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol 2004*;57:640-51

Briel M, Studer M, Glass TR, et al. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. *American Journal of Medicine* 2004;117:596-606

Amarenco P, Labreuche J, Lavallee P, et al. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902-9

Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423-9

Vrecer M, Turk S, Drinovec J, et al. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke: meta-analysis of randomized trials. *International Journal of Clinical Pharmacology and Therapeutics* 2003;41:557-67

Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Int Med* 2003;163:669-76

Clinical Evidence. Secondary prevention of ischaemic cardiac events. Published on web in December 2005

Clinical Evidence. Stroke prevention. Published on web in July 2006

Systematic review on the effectiveness of statins in secondary cardiovascular prevention in acute settings (search date: 2003-2006)

Briel M, Schwartz GG, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA* 2006;295:2046-56

Systematic review on the effectiveness of statins in secondary cardiovascular prevention in women (search date: 2003-2006)

Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. JAMA 2004;291:2243-52

Systematic review on the effectiveness of statins in secondary cardiovascular prevention in people with diabetes (search date: 2003-2006)

Costa J, Borges M, David C, et al. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;332:1115

Systematic review on the effectiveness of different statins in secondary cardiovascular prevention (search date: 2003-2006)

Zhou Z, Rahme E, Pilote L. Are statins created equal: evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. *American Heart Journal* 2006;151:273-81

Other secondary publications on statins safety

Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74-80

Table B1. Characteristics and results of the main placebo controlled primary prevention statin trials. From Ong HT (2006)

Variable	West of Scotland Coronary Prevention Study [2]	AFCAPS/TexCAPS [5]	Pravastatin in Elderly Individuals at Risk of Vascular Disease [9]	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [10]	Anglo-Scandinavian Cardiac Outcomes Trial [11]	Collaborative Atorvastatin Diabetes Study (12]
Number of patients	6,595	6,605	5,804	10,355	10,305	2,838
Duration follow-up (years)	4.9	5.2	3.2	4.8	3.3	3.9
Statin used	Pra, 40 mg	Lovastatin, 20 to 40 mg	Pra, 40 mg	Pra, 40 mg	Ator, 10 mg	Ator, 10 mg
Reduction from baseline, total cholesterol	20%	18%		10%[a]	24%	26%
Reduction from baseline, LDL-C	26%	25%	34%	17%[a]	35%	40%
Primary end point	Nonfatal MI, coronary mortality	MI, unstable angina, sudden cardiac death	Coronary mortality, nonfatal MI, stroke	Total mortality	Fatal coronary heart disease, nonfatal MI	Acute coronary event, Revascularisation, stroke
Relative risk with statin treatment (95% confidence interval)	0.69 (0.57–0.83)	0.63 (0.50–0.79)	0.85 (0.74–0.97)	0.99 (0.89–1.11)	0.64	0.63
Significance (*p* value)	$p < 0.001$	$p < 0.001$	$p = 0.014$	$p = 0.88$	$p = 0.0005$	$p = 0.001$
NNT	42	49	48	250	91	31

References:

2. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR et al. for the West of Scotland Coronary Prevention Study Group. 1995. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333:1301–1307

5. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR et al. for the AFCAPS/TexCAPS Research Group 1998. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA* 279:1615–1622.

9. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM et al., on behalf of the PROSPER study group. 2002. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet* 360:1623–1630

10. The ALLHAT Officers and Coordinators for the ALLHAT Cooperative Research Group. 2002. 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* 288:2998–3007.

11. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, et al. (2003) 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 randomized controlled. trial. *Lancet* 361:1149–1158.

12. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA et al. on behalf of the CARDS investigators (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomized placebo-controlled trial. *Lancet* 364:685–696.

Table B2. Characteristics and results of the main placebo controlled secondary prevention statin trials (RCTs published until 2003). From Ong HT (2006)

Variable	Scandinavian Simvastatin Survival Study Group [1]	Cholesterol and Recurrent Events Trial [3]	Long-Term Intervention with Pravastatin in Ischemic Disease Study [4]	Heart Protection Study Collaborative Group [6]	Lescol Intervention Prevention Study [8]
Number of patients	4,444	4,159	9,014	20,536	1,677
Duration follow-up (years)	5.4	5	6.1	5	3.9
Statin used	Simvastatin, 5 to 40 mg	Pra, 40 mg	Pra, 40 mg	Simvastatin, 40 mg	Fluvastatin, 80 mg
Reduction from baseline, total cholesterol	25%	20%	18%	20%	
Reduction from baseline, LDL-C	35%	28%	25%	29%	22%
Primary end point	Total mortality	Coronary mortality, nonfatal MI	Coronary mortality	Total mortality	Major adverse cardiac events
Relative risk with statin treatment (95% confidence interval)	0.7 (0.58–0.85)	0.76 (0.64–0.91)	0.76 (0.65–0.88)	0.87 (0.81–0.94)	0.78 (0.69–0.95)
Significance (*p* value)	$p = 0.0003$	$p = 0.003$	$p = 0.0001$	$p = 0.0003$	$p = 0.01$
NNT	25	33	53	56	19

References:

1. Scandinavian Simvastatin Survival Study Group. 1994 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383–1389

3. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD et al. for the Cholesterol and Recurrent Events Trial Investigatore. 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New Engl J Med* 355:1001–1009

4. Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. 1998. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349–1357.

6. Heart Protection Study Collaborative Group. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high risk individuals: A randomized placebo controlled trial. *Lancet* 360:7–22

8. Seruys PW, de Feyter P, Macaya C, Kokott N, Puel J et al. for the Lescol Intervention Prevention Study (LIPS) Investigators 2002. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: A randomized controlled trial. *JAMA* 287:3215–322

Table B3. Summary of secondary prevention statin trials, main characteristics and results (RCTs published after 2003, > 1000 pz per study arm, with at least 6 months of follow-up) considering clinical outcomes

Study title (reference)	objective	main inclusion criteria	# of patients per study arm	intervention (and doses)	control (and doses)	main outcome	median follow-up period	statistically significant benefits (absolute diff)	risks
High dose atorvastatin after stroke or transient ischemic attack. NEJM 2006;355:549-59	Prevention of recurrent **stroke** or TIA in people with no CHD	stroke or tia within 6 months; LDL between 100 and 190 mg/dl; no CHD	2365/2366	atorvastatin 80 mg	placebo	first nonfatal or fatal stroke	4,9 years	3.5% in five years	+1.7% elevate liver enzymes no difference in adverse and serious adverse events, myopathy and rhabdomyolysis
Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes. Diabetes Care 2006;29:1478-85	CVD prevention in subjects with Type 2 **diabetes** and LDL below the target currently suggested by cpg	LDL < 140-160 mg/dl (depending on present/absent previous mi). Excluded if blood pressure > 160/100, bmi > 35 and mi, angina or revascularization in the previous 3 months	1211/1199	atorvastatin 10 mg	placebo	cv death + nonfatal mi + nonfatal stroke + revascularization + worsened angina	4 years	no difference	+2.3% serious adverse events + 1.4% myalgia
High dose atorvastatin vs usual dose simvastatin for secondary prevention after myocardial infarction. JAMA 2005;294:2437-45	coronary prevention with **more aggressive LDL reduction** than is actually recommended in people with mi	80 years or younger with previous mi	4449/4449	atorvastatin 80 mg	simvastatin 20 mg	major coronary event	4.8 years	no difference in the primary outcome. -1.2% in nonfatal mi -3.6% in any chd	+1.3% elevate liver enzymes with aggressive treatment (1.40% vs 0.15%) 2.2% vs 1.1% myalgia

Table 4B (cont)

Study title (reference)	objective	main inclusion criteria	# of patients per study arm	intervention (and doses)	control (and doses)	main outcome	median follow-up period	statistically significant benefits (absolute differences)	risks
Intensive lipid lowering with atorvastatin in patients with stable coronary disease. NEJM 2005;352:1425-35	coronary prevention with **more aggressive LDL reduction** than is actually recommended in people with mi	35-75 years with previous mi or revascularization or objective evidence of atherosclerotic chd	5006/4995	atorvastatin 80 mg	atorvastatin 10 mg	major cv event	4.9 years	-2.2% major cvd -1.3% nonfatal mi -0.8% fatal/nonfatal stroke -1.6% major coronary event -1.1% fatal/nonfatal stroke + tia	+2.3% adverse events with aggressive treatment. Overall, 5 cases of rhabdomyolysis (3 with 10 mg vs 2 with 80 mg)
Intensive vs moderate lipid lowering with statins after acute coronary syndromes. NEJM 2004; 350:1495-1504	coronary prevention with **more aggressive LDL reduction** than is actually recommended in people hospitalised for an acute coronary syndrome	> 18 years old, hospitalised for an acute coronary syndrome (mi or unstable angina) in the preceding 10 days	2063/2099	80 mg atorvastatin	40 mg pravastatin	death from any cause + mi + unstable angina requiring rehospitalization + revascularization + stroke	2 years	- 3.9% primary end point	+ 2.2% elevation of alanine aminotransferase (with more intense treatment)