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Appendices

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A systematic review and economic evaluation of statins for the prevention of coronary events

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Appendix 1

MEDLINE search strategy

Clinical effectiveness

1 randomized controlled trial.pt. (187081)
2 randomized controlled trials/ (31619)
3 random allocation/ (50342)
4 double blind method/ (77461)
5 single blind method/ (7962)
6 clinical trial.pt. (378915)
7 exp clinical trials/ (152599)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (485131)
9 (clinic$ adj1 trial$).tw. (77257)
10 ((singl$ or doubl$ or treb$ or trip$) adj3 (blind$ or mask$)).tw. (74642)
11 PLACEBOS/ (22859)
12 placebo$.tw. (83145)
13 randomly allocated.tw. (7575)
14 (allocated adj2 random).tw. (602)
15 or/9-14 (194563)
16 8 or 15 (534732)
17 case report.tw. (97812)
18 letter.pt. (501492)
19 historical article.pt. (207878)
20 review of reported cases.pt. (49218)
21 review, multicase.pt. (8081)
22 or/17-21 (847807)
23 16 not 22 (518130)
24 statin$.tw. (4866)
25 simvastatin.tw. (2023)
26 pravastatin.tw. (1550)
27 fluvastatin.tw. (621)
28 atorvastatin.tw. (907)
29 rosuvastatin.tw. (125)
30 hmg$.tw. (9052)
31 co-A reductase inhibitor$.tw. (25)
32 Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (4855)
33 Anticholesteremic Agents/ or Pravastatin/ or Simvastatin/ or Lovastatin/ (10480)
34 lipid lowering.tw. (4073)
35 or/24-34 (23939)
36 23 and 35 (4990)

Cost-effectiveness

1. statin$.tw.
2. simvastatin.tw.
3. pravastatin.tw.
4. lovastatin.tw.
5. fluvastatin.tw.
6. atorvastatin.tw.
7. rosuvastatin.tw.
8. hmg$.tw.
9. co-reductase inhibitor$.tw.
10. Hydroxymethylglutaryl-CoA Reductase Inhibitors/
11. Anticholesteremic Agents/ or Pravastatin/ or Simvastatin/ or Lovastatin/
12. lipid lowering.tw.
13. or/1-12
14. Coronary Disease/
15. (coronary or heart or arter$).tw.
16. Cerebrovascular Disorders/
17. stroke.tw.
18. or/14-17
19. 13 and 18
20. ECONOMICS/
21. "Costs and Cost Analysis"/
22. Cost Allocation/
23. Cost-Benefit Analysis/
24. Cost Control/
25. Cost Savings/
26. Cost of Illness/
27. Health Care Costs/
28. Drug Costs/
29. Health Expenditures/
30. exp Economics, Medical/
31. exp Economics, Pharmaceutical/
32. exp "Fees and Charges"/
33. exp BUDGETS/
34. (high adj cost).tw.
35. (low adj cost).tw.
36. cost utility.tw.
37. (fiscal or funding or financial or finance).tw.
38. (health?care adj cost).tw.
39. (cost adj estimate).tw.
40. (cost adj variable).tw.
41. (unit adj cost).tw.
42. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
43. or/20-42
44. 19 and 43

Appendix 2

Trials meeting the inclusion criteria for review

The major publication for each study is marked with an asterisk.

3T

*Olsson AG, Eriksson M, Johnson O, Kjellstrom T, Lanke J, Larsen ML, *et al*. A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the Treat-to-Target (3T) study. *Clin Ther* 2003;**25**:119–38.

45221L-0026

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45221L-0028

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4D

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4S

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Appendix 3

Ongoing studies, and studies for which data are unavailable

TABLE 93 *Ongoing studies, and studies for which data are unavailable*

Study	No. randomised	Population (subgroups)	Comparison	% with CHD at baseline	% with CVD at baseline	Mean total cholesterol at baseline (mmol l^{-1})	Main outcome measures	Comment
AIDA[282]	600	Patients with type 2 diabetes and albuminuria	Atorvastatin 20 mg per day vs placebo	No data	No data	No data	Cardiovascular events	Published results not found, although study completion was expected by 2001
ASPEN[283]	Aim 2250	Patients with type 2 diabetes with or without a previous MI	Atorvastatin 10 mg per day vs placebo	No data	No data	No data	Mortality, morbidity	Ongoing study
AURORA[284]	Aim 2700	Male and female haemodialysis patients aged 50–80 years, irrespective of previous history of CVD	Rosuvastatin 10 mg per day vs placebo	No data	No data	No data	All-cause mortality, cardiovascular mortality, major cardiovascular events (death, MI, stroke), cardiovascular interventions, cost per LYS	Study not likely to report until 2007 at the earliest
CORONA[285]	4950	Men and women aged ≥60 years with chronic symptomatic systolic heart failure	Rosuvastatin 10 mg per day vs placebo	100%			Cardiovascular death, non-fatal MI, non-fatal stroke	
GISSI-HF[285]		Patients with chronic heart failure	Rosuvastatin 10 mg per day vs placebo					
HYRIM[286]	567	Men aged 40–74 years with hypertension	Fluvastatin 40 mg per day vs placebo				Major cardiac events, CVD events	Publication expected January 2005

continued

TABLE 93 *Ongoing studies, and studies for which data are unavailable (cont'd)*

Study	No. randomised	Population (subgroups)	Comparison	% with CHD at baseline	% with CVD at baseline	Mean total cholesterol at baseline (mmol l^{-1})	Main outcome measures	Comment
IDEAL[286]	Aim 7600 (achieved 8888)[66]	Patients aged ≤80 years with definite AMI	Atorvastatin 80 mg per day vs simvastatin 20–40 mg per day	MI 100%	No data	No data	CHD mortality, non-fatal MI	Ongoing study
Japanese Mega Study[287]	8009	Patients aged 40–70 years without pre-existing vascular disease with TC 220–270 mg dl^{-1}	Pravastatin 10–20 mg per day vs dietary therapy	No data	0%	No data	CHD mortality, non-fatal MI, fatal stroke, non-fatal stroke	Ongoing study
JUPITER[288]	Aim 15,000	Men aged ≥55 and women aged ≥65 years with low LDL-C (<3.36 mmol l^{-1}) and elevated high-sensitivity CRP	Rosuvastatin 20 mg per day vs placebo	No MI	No stroke or arterial revascularisation	No data	All-cause mortality, cardiovascular mortality, non-cardiovascular mortality, MI, stroke, hospitalisation for unstable angina, arterial revascularisation, type 2 diabetes, fractures, venous thromboembolic events, adverse events	Ongoing study
SEARCH[289]	12,000	Patients with prior MI	Simvastatin 20 vs 80 mg per day	100%			Coronary events	Ongoing study

continued

TABLE 93 *Ongoing studies, and studies for which data are unavailable (cont'd)*

Study	No. randomised	Population (subgroups)	Comparison	% with CHD at baseline	% with CVD at baseline	Mean total cholesterol at baseline (mmol l^{-1})	Main outcome measures	Comment
SPARCL[290]	4732	Patients with prior stroke or TIA but without known CHD	Atorvastatin 80 mg per day vs placebo	0%	Stroke 69%, TIA 31%	5.5	All-cause mortality, fatal or non-fatal stroke, cardiac mortality, non-fatal MI, resuscitated cardiac arrest, unstable angina, TIA, clinically significant PVD, any revascularisation (cardiac or peripheral), stroke disability	Ongoing study: data collection anticipated to end by October 2004
Stegmayr 2001[291]	40+	Patients with severe renal dysfunction	Atorvastatin 10 mg per day vs no treatment	No data	No data	No data	Mortality, MI, CABG, PTCA	Study completed but manuscript submitted to journal so author currently unwilling to provide full data. Duration of intervention >5 years; study not industry supported (Stegmayr BG: personal communication)
TNT[292]	10,003	Men and women aged 35–75 years with clinically evident CHD (previous MI, previous or present angina with objective evidence of atherosclerotic CHD) who had undergone a coronary revascularisation procedure	Atorvastatin 80 vs 10 mg per day	100% (MI 42%)	Cerebrovascular disease 5.2%, PVD 11.0%	4.5	All-cause mortality Fatal or non-fatal stroke CHD death Non-fatal MI Resuscitated cardiac arrest, angina, TIA, PVD, revascularisation	Ongoing study

Appendix 4

Excluded studies

TABLE 94 *RCTs identified by the electronic searches and excluded at the full paper stage, for reasons not immediately apparent from the full text*

Study	Reason for exclusion
LCAS[293]	Monotherapy subgroups not truly randomised as randomisation not stratified taking into account the need for cholestyramine
FAST[294]	Not clear whether the same dietary intervention was used in both arms or only in the control arm

TABLE 95 *RCTs referred to in the manufacturers' submissions which did not meet the study inclusion criteria, with reasons*

Manufacturer/study	Reason for exclusion
AstraZeneca (rosuvastatin)	
ANDROMEDA[295]	Too short (16 weeks)
CORALL[296]	Too short (12 weeks)
MERCURY I[297]	Too short (16 weeks)
RADAR[298]	Too short (18 weeks)
STELLAR[208]	Too short (6 weeks)
Study 24[299]	Too short (12 weeks)
Study 25[300]	Too short (24 weeks)
Study 27[301]	Too short (12 weeks)
Study 30[302]	Too short (18 weeks)
Study 33[303]	Too short (6 weeks)
URANUS[304]	Too short (16 weeks)
Bristol-Myers Squibb (pravastatin)	
Wiegman, 2004[305]	Wrong patient group (children)
MSD (simvastatin)	
None	
Novartis (fluvastatin)	
Baggio, 1994[306]	Too short (6 weeks)
Ballantyne, 2000[307]	Too short (6 weeks)
Bruckert, 2004[308]	Does not report clinical outcomes
Buzzi, 1997[309]	Not RCT
Farnier, 2000[310]	Too short (16 weeks)
Farnier, 2003[311]	Combination therapy
FLUENT[312]	Not RCT
Fluvastatin titrate-to-goal study[313]	Too short (12 weeks)
Hunninghake, 2002[314]	Too short (24 weeks)
Insull, 1994[315]	Too short (6 weeks)
Insull, 2004[316]	Too short (24 weeks)
Isaacsohn, 2003[317]	Too short (12 weeks)
Jacotot, 1994[318]	Too short (6 weeks)
LCAS,[293]	Monotherapy subgroups not truly randomised as randomisation not stratified taking into account the need for cholestyramine
Leitersdorf, 1995[319]	Combination therapy
Lye, 1998[320]	Too short (24 weeks)
Olsson, 2001[321]	Too short (24 weeks)
Pauciullo, 2000[322]	Combination therapy
Peters, 1994[323]	Not RCT
Teramoto, 1995[324]	Not RCT
Tomlinson, 1995[325]	Too short (8 weeks)
Winkler, 2002[326]	Too short (8 weeks)

continued

TABLE 95 *RCTs referred to in the manufacturers' submissions which did not meet the study inclusion criteria, with reasons (cont'd)*

Manufacturer/study	Reason for exclusion
Pfizer (atorvastatin)	
ACCESS[327]	Does not report clinical outcomes
ADVOCATE[328]	Too short (16 weeks)
ARBITER[329]	Does not report clinical outcomes
ASSETT[330]	Too short (6 weeks)
Assmann, 1999[331]	Does not report clinical outcomes
Athyros, 1998[332]	Does not report clinical outcomes
ATROCAP[333]	Too short (19 weeks)
Bakker-Arkema, 1996[334]	Too short (4 weeks)
Ballantyne, 2003[335]	Too short (12 weeks)
BELLES[336]	Unfinished; not clinical end-points
Bertolami, 2002[337]	Too short (12 weeks)
Bertolini, 1997[338]	No clinical outcomes
Best, 1996[339]	Too short (4 weeks)
Bo, 2001[340]	Too short (24 weeks)
Boquist, 2002[341]	Too short (8 weeks)
Branchi, 2001[342]	Too short (2 months)
CARDS II[343]	Does not report clinical outcomes
CAVEAT[344]	Too short (8 weeks)
Chan, 2002[345]	Too short (6 weeks)
CURVES[346]	Too short (8 weeks)
Dalla Nora, 2003[347]	Does not report clinical outcomes
Dallongeville, 1998[348]	Too short (16 weeks)
Dart, 1997[349]	Does not report clinical outcomes
Davidson, 1997[350]	Inappropriate comparator
Davidson, 2002[299]	Too short (12 weeks)
Farnier, 2000[351]	Too short (6 weeks)
Ferrier, 2002[352]	Cross-over study; does not report clinical outcomes
Gentile, 2000[353]	Does not report clinical outcomes
Harris, 2002[354]	Too short (16 weeks)
Heinonen, 1996[355]	Does not report clinical outcomes
Hunninghake, 2001[356]	Combination therapy
Hunninghake, 2001[357]	Inappropriate comparator
Illingworth, 2001[358]	Does not report clinical outcomes
J-CLAS[359]	Too short (8 weeks)
Jialal, 2001[360]	Too short (6 weeks); cross-over trial
Jilma, 2003[361]	Too short (12 weeks)
Joukhadar, 2001[362]	Too short (13 weeks)
Kadikoylu, 2003[363]	Too short (24 weeks)
Karalis, 2002[364]	Too short (6 weeks)
Kastelein, 2000[134]	Too short (12 weeks)
Kinlay, 2002[365]	Inappropriate comparator
McCrindle, 2003[366]	Irrelevant patient group (children and adolescents)
Magnani, 2000[367]	Too short (4 months)
MIRACL,[368]	Too short (16 weeks)
Mullen, 2000[369]	Too short (6 weeks)
Muscari, 2001[370]	Too short (13 weeks)
Nawawi, 2003[371]	Too short (13 weeks)
Nawrocki, 1995[372]	Too short (6 weeks)
Olsson, 2001[373]	Too short (6 weeks)
Oranje, 2001[374]	Too short (13 weeks)
Paiva, 2003[375]	Too short (8 weeks)
Pontrelli, 2002[376]	Too short (8 weeks)
Raison, 2002[377]	Too short (12 weeks)
Recto, 2000[378]	Too short (6 weeks)
Renders, 2001[379]	Too short (3 months)
Sardo, 2002[380]	Too short (12 weeks)
Schneck, 2003[303]	Too short (6 weeks)
Schrott, 1998[381]	Too short (6 weeks)

continued

TABLE 95 *RCTs referred to in the manufacturers' submissions which did not meet the study inclusion criteria, with reasons (cont'd)*

Manufacturer/study	Reason for exclusion
Schuster, 1998[382]	Does not report clinical outcomes
Sposito, 2003[383]	Too short (6 weeks)
Stein, 2001[384]	Too short (6 weeks)
Stein, 2001[385]	Inappropriate comparator; too short (18 weeks)
STELLAR[208]	Too short (6 weeks)
Tan, 2002[386]	Does not report clinical outcomes
Tanaka, 2001[387]	Too short (12 weeks)
Tannous, 1999[388]	Too short (4 weeks)
Target Tangible,[389]	Too short (14 weeks)
Van den Akker, 2003[390]	Too short (18 weeks)
Vansant, 2000[391]	Too short (4 weeks)
Wang, 2001[392]	Too short (8 weeks)
Watts, 2003[393]	Too short (6 weeks)
Wierzbicki, 1999[394]	Too short (12 weeks); cross-over trial
Wolffenbuttel, 1998[395]	Too short (16 weeks)
Wu, 2002[396]	Too short (16 weeks)

Appendix 5

Tabulation of study quality

TABLE 96 *Atorvastatin: placebo-controlled trials*

	4D[84]	ASCOT-LLA[102]	CARDS[103]	DALI[86]	Mohler 2003[21]
Was the method used to assign participants to the treatment groups really random?	Y	Y	Y	?	?
What method of assignment was used?	Centrally determined code	Computer	Computer	?	?
Was the allocation of treatment concealed?	Y	Y	Y	?	?
What method was used to conceal treatment allocation?	Allocation by statistical coordinating centre	Allocation by local coordinating centre	Prepackaged medication	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	N	Y	Y	Y	Y
Was baseline comparability achieved?	?	Y	Y	N (placebo group younger, with shorter mean duration of diabetes and higher mean BMI)	N (disparity re smoking, no information re lipid levels)
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	?	Y	Y	N	? (possible disparities in the doses of aspirin)
Were the outcome assessors blinded to the treatment allocations?	?	Y	Y	?	Y for peripheral vascular outcomes
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	Y presumably	Y	Y	Y presumably
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y	Y	Y	Y
Was the success of the blinding procedure assessed?	N	N	N	N	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	?	Y	Y	Y	Y
Were the reasons for withdrawal stated?	N	N	Y	Y	Y
Was an ITT analysis included?	?	Y	Y	Y	Y

N, no; Y, yes; ?, not enough information or not clear.

TABLE 97 *Atorvastatin: comparisons with 'usual care' and 'no statin'*

	ALLIANCE[88]	Colivicchi 2002[129]	ESTABLISH[89]	GREACE[128]
Was the method used to assign participants to the treatment groups really random?	Y	Y	Y	Y
What method of assignment was used?	By central laboratory	Computer	Minimisation	Computer-generated list
Was the allocation of treatment concealed?	Y	?	?	?
What method was used to conceal treatment allocation?	Allocation by central laboratory	?	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	Y	Y	Y	Y
Were the outcome assessors blinded to the treatment allocations?	?	Y	Y	?
Were the individuals who administered the intervention blinded to the treatment allocation?	N	N	N	N
Were the participants who received the intervention blinded to the treatment allocation?	N	N	N	N
Was the success of the blinding procedure assessed?	NA	NA	NA	NA
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y for clinical end-points, N for lipid results in control arm	Y	Y for clinical end-points, N for the primary end-point	Y
Were the reasons for withdrawal stated?	Y	Y	Y	Y
Was an ITT analysis included?	Y	Y	Y for clinical events	Y

TABLE 98 *Fluvastatin: placebo-controlled studies*

	ALERT[142]	FLARE[108]	FLORIDA[109]	LIPS[110]	LiSA[93]	O'Rourke 2004[139]
Was the method used to assign participants to the treatment groups really random?	Y	?	?	Y	?	?
What method of assignment was used?	Fixed block randomisation	?	?	Block randomisation	?	?
Was the allocation of treatment concealed?	Y	?	?	Y	?	?
What method was used to conceal treatment allocation?	Prepackaged medication	?	?	Medication pack numbers	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y	Y generally, but higher percentage of patients with diabetes in the fluvastatin group	Y	Y, largely
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	Y	N	Y	Y	N	Y
Were the outcome assessors blinded to the treatment allocations?	Y	?	Y	Y	Y	?
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	Y	Y presumably	Y in theory	Y presumably (matching placebo)	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y	Y	Y in theory but many got to know their TC levels, thus effectively breaking the blind	Y presumably (matching placebo)	Y
Was the success of the blinding procedure assessed?	N	N	N	Informally	N	N

continued

TABLE 98 *Fluvastatin: placebo-controlled studies (cont'd)*

	ALERT[142]	FLARE[108]	FLORIDA[109]	LIPS[110]	LiSA[93]	O'Rourke 2004[139]
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	No, mainly because of the requirement for uncomplicated PTCA	Y	Y	Y for clinical events	Y for safety
Were the reasons for withdrawal stated?	Y	Y	?	Y	Y	Y
Was an ITT analysis included?	Y	Yes by the authors' terms, not perhaps in the generally accepted sense	Y	Y	Y	Y for safety

TABLE 99 *Pravastatin: placebo-controlled studies*

	CAIUS[107]	CARE[111]	KAPS[133]	LIPID[112]	PLAC I[113]	PLAC II[95]	PMSG[96]	PREDICT[114]	PROSPER[81]	REGRESS[115]	WOSCOPS[82]
Was the method used to assign participants to the treatment groups really random?	Y	Y	Y	Y	?	?	?	?	Y	Y	Y
What method of assignment was used?	Allocation by independent coordinating and analysis centre	Computer	Allocation by biostatistician	Block randomisation	?	?	?	?	Computerised pseudorandom number generator	Block randomisation	Permuted block
Was the allocation of treatment concealed?	Y	Y	Y	?	?	?	?	?	Y	?	?
What method was used to conceal treatment allocation?	Allocation by independent coordinating and analysis centre	Telephone allocation by data coordinating centre	Allocation by biostatistician	?	?	?	?	?	Telephone call or through fax exchange with study data centres	?	?

continued

TABLE 99 *Pravastatin: placebo-controlled studies (cont'd)*

	CAIUS[107]	CARE[111]	KAPS[133]	LIPID[112]	PLAC I[113]	PLAC II[95]	PMSG[96]	PREDICT[114]	PROSPER[81]	REGRESS[115]	WOSCOPS[82]
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	N	Y	N	Y	Y	Y	Y	N	Y	?	N
Were the outcome assessors blinded to the treatment allocations?	?	Y	Y	Y	Y	Y	?	Y	Y	Y	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	Y presumably	Y	?	Y	Y	Y presumably	Y presumably	Y	Y	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y	Y	Y	Y	Y	Y presumably	Y presumably	Y	Y	Y presumably
Was the success of the blinding procedure assessed?	N	N	N	N	N	N	N	N	N	N	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y for clinical outcomes	Y	Y	Y for clinical outcomes	Y for clinical outcomes	Y	Y	Y	Y	N
Were the reasons for withdrawal stated?	N	N	Y	Y	Y	N	Y	Y	Y	Y	N
Was an ITT analysis included?	Y	Y	Y	Y	Y	Y	Y	Y (for secondary clinical outcomes only)	Y	Y	Y

TABLE 100 *Pravastatin: comparisons with 'usual care' and 'no statin'*

	ALLHAT-LLT[127]	GISSI-P[130]	Kobashigawa 1995[140]	Sato 2001[87]
Was the method used to assign participants to the treatment groups really random?	Y	Y	?	?
What method of assignment was used?	Computer generated	Block randomisation	?	?
Was the allocation of treatment concealed?	Y	?	?	?
What method was used to conceal treatment allocation?	Concealed randomisation scheme	?	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	N	Y
Were any cointerventions identified that may influence the outcomes for each group?	Y	Y	N	N
Were the outcome assessors blinded to the treatment allocations?	For some outcomes	Y	N	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	N	N	N	?
Were the participants who received the intervention blinded to the treatment allocation?	N	N	N	?
Was the success of the blinding procedure assessed?	NA	NA	NA	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y for clinical outcomes	Y for mortality data	Y for lipids and clinical events
Were the reasons for withdrawal stated?	Y	N	N	N
Was an ITT analysis included?	Y	Y	N	Y

TABLE 101 *Simvastatin: placebo-controlled studies*

	4S[97]	Aronow 2003[118]	CIS[98]	HPS[74]	MAAS[100]	Mondillo 2003[105]	Oxford Cholesterol Study[101]	SCAT[116]
Was the method used to assign participants to the treatment groups really random?	Y	?	?	Y	?	?	Y	Y
What method of assignment was used?	Coded prepackaged medication	?	?	Minimisation	?	?	Computer	Computer
Was the allocation of treatment concealed?	Y	?	?	Y	?	?	Y	Y
What method was used to conceal treatment allocation?	Coded prepackaged medication	?	?	Central telephone randomisation service	?	?	Randomisation at central unit	Coded medication
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Only for patients who survived to study end	Y	Y	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y for patients who survived to study end	Y	Y	Y	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Implicitly	Y	Y	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	Y	N	Y	Y	Y	N	Y	Y
Were the outcome assessors blinded to the treatment allocations?	Y	?	Y	?	Y	?	?	?
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	?	Y	Y	Y	Y	Y	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y	Presumably, since placebo was used	Y	Y in theory, but their family doctors were free to monitor their cholesterol levels	Y	Y	Y	Y

continued

TABLE 101 *Simvastatin: placebo-controlled studies (cont'd)*

	4S[97]	Aronow 2003[118]	CIS[98]	HPS[74]	MAAS[100]	Mondillo 2003[105]	Oxford Cholesterol Study[101]	SCAT[116]
Was the success of the blinding procedure assessed?	Y	N	N	N	N	N	N	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	Y	Y	Y	Y for insomnia	Y
Were the reasons for withdrawal stated?	Y	Y	N	Y	To a degree	NA	Y	Y
Was an ITT analysis included?	Y	Y	Y	Y	Y	Y	Y	Y

TABLE 102 *Simvastatin: comparison with 'no statin'*

	Wenke 1997[141]
Was the method used to assign participants to the treatment groups really random?	?
What method of assignment was used?	?
Was the allocation of treatment concealed?	?
What method was used to conceal treatment allocation?	?
Was the number of participants who were randomised stated?	Y
Were details of baseline comparability presented?	Y
Was baseline comparability achieved?	Y
Were the eligibility criteria for study entry specified?	Y but not very specifically
Were any cointerventions identified that may influence the outcomes for each group?	N
Were the outcome assessors blinded to the treatment allocations?	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Probably not
Were the participants who received the intervention blinded to the treatment allocation?	Probably not
Was the success of the blinding procedure assessed?	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y
Were the reasons for withdrawal stated?	NA
Was an ITT analysis included?	Y

TABLE 103 *Statin–statin comparisons*

	4522II/0026[125]	4522II/0028[126]	3T[83]	ASAP[85]	Mehra 2002[94]	PROVE IT-TIMI[124]	REVERSAL[90]
Was the method used to assign participants to the treatment groups really random?	?	Y	Y	Y	?	Y	Y
What method of assignment was used?	?	Block randomisation	Randomisation code prepared by study statistician	Computer-generated	?	Central randomisation scheme	Permuted block
Was the allocation of treatment concealed?	?	?	Y	Y	?	Y	Y
What method was used to conceal treatment allocation?	?	?	Prepackaged numbered medication	Opaque envelopes kept by hospital pharmacist	?	Allocation by centre	Generated by consulting statistician not otherwise involved in the trial
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	Y	Y	N for full safety population; only for those included in primary analysis
Was baseline comparability achieved? no data re total population	Y	Y	Y	Y	Y	Y	Y for primary analysis;
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	N	N	N	Y	N	N	N
Were the outcome assessors blinded to the treatment allocations?	?	?	Y	Y	?	?	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y presumably	Y presumably	Y	Y	N	Y presumably	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y presumably	Y presumably	Y	Y	N	Y presumably	Y
Was the success of the blinding procedure assessed?	N	N	N	N	NA	N	N

continued

TABLE 103 *Statin–statin comparisons (cont'd)*

	4522II/0026[125]	4522II/0028[126]	3T[83]	ASAP[85]	Mehra 2002[94]	PROVE IT-TIMI[124]	REVERSAL[90]
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	Y	Y	Y	Y for clinical events
Were the reasons for withdrawal stated?	Y	Y	Partially	Y	Y	Y	Y
Was an ITT analysis included?	N (for data at 52 weeks)	N (for data at 52 weeks)	Y	Y	Presumably Y	Y	Y for all patients with evaluable ultrasounds at baseline and 18 months

TABLE 104 *Dose comparisons*

	A-to-Z[131]	PATE[132]
Was the method used to assign participants to the treatment groups really random?	Y	Y
What method of assignment was used?	Central	Minimisation
Was the allocation of treatment concealed?	Y	Y
What method was used to conceal treatment allocation?	Blinded medication	Telephone call or fax
Was the number of participants who were randomised stated?	Y	Y
Were details of baseline comparability presented?	Y	Y
Was baseline comparability achieved?	Y	Largely
Were the eligibility criteria for study entry specified?	Y	Y
Were any cointerventions identified that may influence the outcomes for each group?	Y	N
Were the outcome assessors blinded to the treatment allocations?	Y	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	?
Were the participants who received the intervention blinded to the treatment allocation?	Y	?
Was the success of the blinding procedure assessed?	N	N
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y for clinical outcomes
Were the reasons for withdrawal stated?	Y	N
Was an ITT analysis included?	Y	Y

Appendix 6

Placebo-controlled RCTs: data sheets

TABLE 105 *Placebo-controlled RCTs: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
Atorvastatin											
4D (full report not available)[84]	Type 2 diabetes, haemodialysis for <2 years	NR	NR	Germany	Atorvastatin 20 mg per day	NR	Not clear	Median 4	MF	NR	619/636
ASCOT-LLA[102]	Hypertensive, no CHD	3.4	NR; CVD mortality 0.5%	UK, Republic of Ireland, Norway, Sweden, Denmark, Finland	Atorvastatin 10 mg per day	None reported	Aggressive antihypertensive therapy	Median 3.3	MF	63.2	5168/5137
CARDS[103]	Type 2 diabetes, no clinical CVD	3.0	0.5%	UK, Republic of Ireland	Atorvastatin 10 mg per day	Modified AHA Step I diet	No	Median 4.0	MF	61.7	1428/1410
DALI[86]	Type 2 diabetes and diabetic dyslipidaemia	3.7	0%	The Netherlands	Atorvastatin 10 or 80 mg per day	None reported	No	0.58	MF	59.4	73/72/72
Mohler 2003[21]	CVD (stable intermittent claudication)	No data	0.9%	Canada, USA	Atorvastatin 10 or 80 mg per day	NCEP Step I diet	Aspirin	1.0	MF	68	120/120/114
Fluvastatin											
FLARE[108]	CHD (successful balloon angioplasty)	4.0	1.2%	Belgium, The Netherlands, France, Italy, Spain, UK, Republic of Ireland	Fluvastatin 80 mg per day	None reported	Aspirin ≤325 mg per day	0.78	MF	61	409/425

continued

TABLE 105 *Placebo-controlled RCTs: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
FLORIDA[109]	CHD (acute MI)	3.6	Cardiac mortality 4.0%	The Netherlands	Fluvastatin 80 mg per day	None reported	Standard medication (including aspirin, β-blockers and/or ACE inhibitors) at the attending cardiologist's discretion	1.0	MF	60	265/275
LIPS[110]	CHD (angina or silent ischaemia)	3.4	0.7%	Belgium, France, Germany, Italy, UK, The Netherlands, Spain, Switzerland, Canada, Brazil	Fluvastatin 80 mg per day	Dietary and lifestyle counselling	No	Median 3.9	MF	60	844/833
LiSA[93]	Hyperlipidaemia, stable symptomatic CHD	5.1	2.2%	Germany, Czech Republic	Fluvastatin 40–80 mg per day	European Atherosclerosis Society cholesterol-lowering diet	No	1.0	MF	60	187/178
Pravastatin											
CAIUS[107]	Moderately elevated LDL-C, ultrasono-graphically identified early atherosclerosis, no symptomatic CVD	4.7	0%	Italy	Pravastatin 40 mg per day	AHA Step I diet	No	3.0	MF	55	151/154

continued

TABLE 105 *Placebo-controlled RCTs: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
CARE[111]	MI, average cholesterol	3.6	1.1%	USA, Canada	Pravastatin 40 mg per day	NCEP Step I diet (Step II if LDL-C ≥4.5 mmol l^{-1})	Cholestyramine 8–16 mg per day if LDL-C ≥4.5 mmol l^{-1}	Median 5.0	MF	59	2081/2078
KAPS[133]	Hypercholes-terolaemia, with and without CVD	4.9	0.3%	Finland	Pravastatin 40 mg per day	Dietary advice to lower LDL-C	No	3.0	M	57	224/223
LIPID[112]	CHD (MI or unstable angina)	3.9	1.4%	Australia, New Zealand	Pravastatin 40 mg per day	Lipid-lowering diet (max. cholesterol intake 300 mg per day)	No	6.1	MF	Median 62	4512/4502
PLAC I[113]	CHD	4.2	1.5%	USA	Pravastatin 40 mg per day	AHA Phase I diet or equivalent	Cholestyramine resin in patients with LDL-C ≥4.9 mmol l^{-1} on the AHA Phase II or equivalent diet. If LDL-C remained ≥4.9 on max. dose of 6 packets per day cholestyramine, patients received open-label pravastatin 5–10 mg per day (or placebo, depending on original	3.0	MF	57	206/202

continued

TABLE 105 *Placebo-controlled RCTs: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
							treatment assignment); if these measures were unsuccessful, they were withdrawn from the study				
PLAC II[95]	CHD	4.3	Not clear	USA	Pravastatin 10–40 mg per day	AHA Phase I diet with individual nutritional counselling	No	3.0	MF	62	75/76
PMSG[96]	Primary hypercholes-terolaemia and ≥2 additional CHD risk factors	NR; TC 6.8	1.1%	Australia, Belgium, Finland, Germany, Israel, The Netherlands, Sweden, UK	Pravastatin 20–40 mg per day	Diet modification; advice on smoking	No	0.5	MF	55	530/532
PREDICT[114]	CHD (successful PTCA)	4.0	Not clear	France	Pravastatin 40 mg per day	None reported	Aspirin 100 mg per day	0.5	MF	58	347/348
PROSPER[81]	Elderly, with or at significant risk of CVD	3.8	1.3%	Scotland, Ireland, The Netherlands	Pravastatin 40 mg per day	NCEP Step I diet or local equivalent	No	3.2	MF	75	2891/2913
REGRESS[115]	CHD	4.3	0.6%	The Netherlands	Pravastatin 40 mg per day	Dietary counselling	No	2.0	M	56	450/434

continued

TABLE 105 *Placebo-controlled RCTs: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
WOSCOPS[82]	Moderate hypercholesterolaemia	5.0	0.4%	Scotland	Pravastatin 40 mg per day	Smoking and dietary advice	No	4.9	M	55	3302/3293
Simvastatin											
4S[97]	CHD and moderate hypercholesterolaemia	4.9	1.6%	Scandinavia	Simvastatin 20–40 mg per day	Dietary counselling consistent with European Atherosclerosis Society guidelines	No	Median 5.4	MF	58	2221/2223
Aronow 2003[118]	Intermittent claudication due to PVD	3.3	17%	USA	Simvastatin 40 mg per day	None reported	No	1.0	MF	75	34/35
CIS[98]	CHD and hypercholesterolaemia	4.3	0.7%	Germany	Simvastatin 20–40 mg per day	Lipid-lowering diet (max. cholesterol intake 300 mg per day)	After 12 weeks, an ion-exchange resin was added to patients in the simvastatin group with LDL-C ≥3.11 mmol l^{-1} or ≥6.48 mmol l^{-1} in the placebo group	2.3	M	49	129/125
HPS[74]	Substantial risk of death from CHD	3.4	1.4%	UK	Simvastatin 40 mg per day	None reported	Factorial design (also evaluating antioxidant vitamins)	5.0	MF	NR	10,269/ 10,267

continued

TABLE 105 *Placebo-controlled RCTs: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Duration of intervention (years)	Gender	Mean age (years)	No. treated/ no. controls
MAAS[100]	Moderate hypercholesterolaemia and known CAD	4.4	0.5%	Europe	Simvastatin 20 mg per day	Lipid-lowering diet	No	4.0	MF	55	193/188
Mondillo 2003[105]	PVD and hypercholesterolaemia	4.9	NR	Italy	Simvastatin 40 mg per day	None reported	No. Patients asked to avoid analgesic medication	0.5	MF	67	43/43
Oxford Cholesterol Study[101]	Increased risk of CHD	4.8	NR	England	Simvastatin 20 or 40 mg per day	Dietary advice broadly similar to AHA Step I diet	No	6.0	MF	63	206/208/207
SCAT[116]	CHD	3.4	0.5%	Canada	Simvastatin 20–40 mg per day	NCEP Step I or, if necessary, Step II, diet	2 × 2 factorial design also evaluating an ACE inhibitor (enalapril 2.5–10 mg twice daily)	4.0	MF	61	230/230

[a] In most studies, many patients were, at randomisation, already receiving medications other than statins to treat conditions such as hypertension and diabetes. This column only lists medications that specifically formed a part of the study protocol.

AHA, American Heart Association; F, female; M, male; NCEP, National Cholesterol Education Program.

TABLE 106 *Placebo-controlled RCTs: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Atorvastatin								
4D (full report not available)[84]	NR	NR	NR	NR	NR	NR	NR	NR
ASCOT-LLA[102]	185/5168	212/5137	NR	NR	89/5168	121/5137	100/5168	154/5137
CARDS[103]	61/1428	82/1410	21/1428[397]	25/1410[397]	21/1428	39/1410	NR	NR
DALI[86]	0/145	0/72	0/145	0/72	NR	NR	0/145	1/72
Mohler, 2003[21]	5/240	1/114	2/240	1/114	2/240	0/114	7/240	3/114
Fluvastatin								
FLARE[108]	NR	NR	3/409	7/425	NR	NR	6/409	17/425
FLORIDA[109]	7/265	11/275	2/265	9/275	NR	NR	NR	NR
LIPS[110]	36/844	49/833	13/844	24/833	NR	NR	42/844	60/833
LiSA[93]	NR	NR	2/187	4/178	NR	NR	2/187	5/178
Pravastatin								
CAIUS[107]	NR	NR	1/151	0/154	NR	NR	2/151	2/154
CARE[111]	180/2081	196/2078	96/2081	119/2078	52/2081	76/2078	212/2081	274/2078
KAPS[133]	3/224	4/223	2/224	2/223	2/224	4/223	5/224	8/223
LIPID[112]	498/4512	633/4502	287/4512	373/4502	169/4512	204/4502	557/4512	715/4502
PLAC I[113]	4/206	6/202	3/206	3/202	0/206	2/202	NR	NR
PLAC II[95]	3/75	5/76	NR	NR	NR	NR	NR	NR
PMSG[96]	NR	NR	0/530	3/532	0/530	3/532	0/530	7/532
PREDICT[114]	4/347	1/348	NR	NR	NR	NR	NR	NR
PROSPER[81]	298/2891	306/2913	94/2891	122/2913	135/2891	131/2913	292/2891	356/2913
REGRESS[115]	5/450	8/434	2/450	4/434	3[a]/450	5[a]/434	NR	NR
WOSCOPS[82]	106/3302	135/3293	38/3302	52/3293	46/3302	51/3293	174/3302	248/3293
Simvastatin								
4S[97]	182/2221	256/2223	111/2221	189/2223	75[a]/2221[398]	102[a]/2223[398]	431/2221	622/2223
Aronow, 2003[118]	NR	NR	3/34	6/35	NR	NR	NR	NR
CIS[98]	1/129	4/125	1/129	2/125	NR	NR	2/129	7/125
HPS[74]	1328/10,269	1507/10,267	587/10,269	707/10,267	444/10,269	585/10,267	898/10,269	1212/10,267
MAAS[100]	4/193	11/188	4/193	4/188	NR	NR	NR	NR
Mondillo, 2003[105]	NR	NR	NR	NR	NR	NR	NR	NR
Oxford Cholesterol Study[101]	NR	NR	NR	NR	NR	NR	NR	NR
SCAT[116]	13/230	6/230	7/230	4/230	4/230	7/230	NR	NR

[a] TIA or stroke.

Appendix 7

Placebo-controlled studies: additional forest plots

Review: Statins
Comparison: 79 Placebo-controlled studies: cardiovascular mortality
Outcome: 01 Cardiovascular mortality

Study or subcategory	Treatment *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Atorvastatin					
DALI[86]	0/145	0/72			Not estimable
ASCOT-LLA[102]	74/5168	82/5137		4.32	0.90 (0.66 to 1.23)
Mohler[21]	3/240	1/114		0.08	1.43 (0.15 to 13.55)
CARDS[103]	25/1428	37/1410		1.67	0.67 (0.40 to 1.10)
Subtotal (95% CI)	6981	6733		6.07	0.83 (0.64 to 1.08)
Total events: 102 (treatment), 120 (control)					
Test for heterogeneity: $\chi^2 = 1.19$, df = 2 ($p = 0.55$), $I^2 = 0\%$					
Test for overall effect: $z = 1.37$ ($p = 0.17$)					
02 Fluvastatin					
FLORIDA[109]	6/265	11/275		0.44	0.57 (0.21 to 1.51)
Subtotal (95% CI)	265	275		0.44	0.57 (0.21 to 1.51)
Total events: 6 (treatment), 11 (control)					
Test for heterogeneity: NA					
Test for overall effect: $z = 1.14$ ($p = 0.26$)					
03 Pravastatin					
PMSG[96]	0/530	3/532		0.05	0.14 (0.01 to 2.77)
PLAC I[113]	3/206	3/202		0.17	0.98 (0.20 to 4.80)
WOSCOPS[82]	50/3302	73/3293		3.31	0.68 (0.48 to 0.98)
CARE[111]	112/2081	130/2078		6.99	0.86 (0.67 to 1.10)
LIPID[112]	331/4512	433/4502		22.39	0.76 (0.67 to 0.87)
Subtotal (95% CI)	10,631	10,607		32.90	0.77 (0.69 to 0.87)
Total events: 496 (treatment), 642 (control)					
Test for heterogeneity: $\chi^2 = 2.56$, df = 4 ($p = 0.63$), $I^2 = 0\%$					
Test for overall effect: $z = 4.47$ ($p < 0.00001$)					
04 Simvastatin					
4S[97]	136/2221	207/2223		9.70	0.66 (0.53 to 0.81)
CIS[98]	1/129	2/125		0.07	0.48 (0.04 to 5.28)
HPS[74]	781/10,269	937/10,267		50.82	0.83 (0.76 to 0.91)
Subtotal (95% CI)	12,619	12,615		60.59	0.76 (0.62 to 0.93)
Total events: 918 (treatment), 1146 (control)					
Test for heterogeneity: $\chi^2 = 4.35$, df = 2 ($p = 0.11$), $I^2 = 54.0\%$					
Test for overall effect: $z = 2.71$ ($p = 0.007$)					
Total (95% CI)	30,496	30,230		100.00	0.79 (0.74 to 0.85)
Total events: 1522 (treatment), 1919 (control)					
Test for heterogeneity: $\chi^2 = 8.94$, df = 11 ($p = 0.63$), $I^2 = 0\%$					
Test for overall effect: $z = 7.02$ ($p < 0.00001$)					

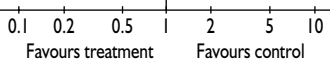

FIGURE 37 *Placebo-controlled studies: cardiovascular mortality*

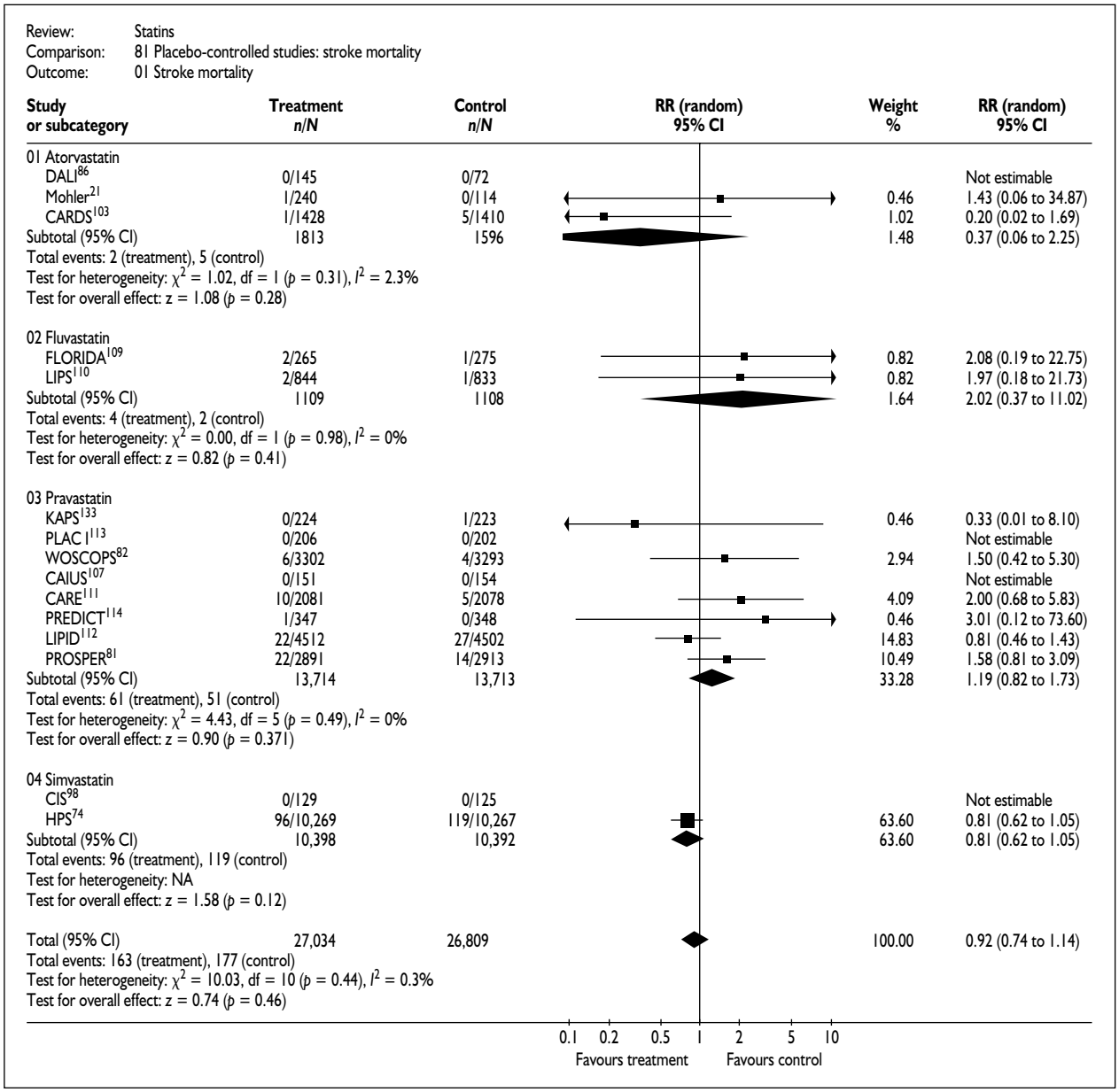

FIGURE 38 *Placebo-controlled studies: stroke mortality*

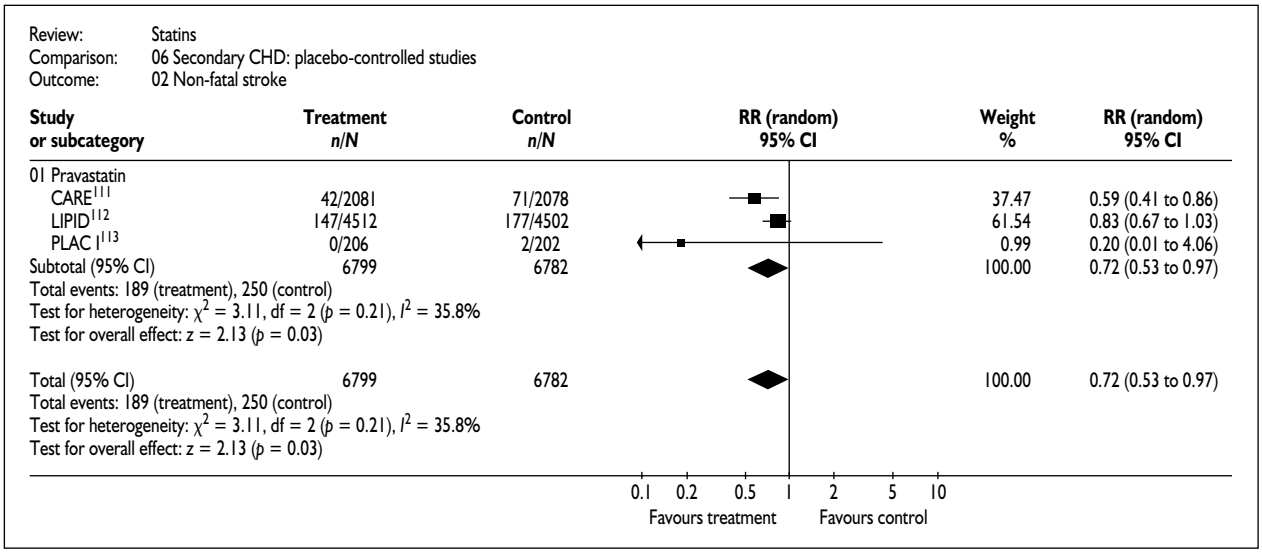

FIGURE 39 *Placebo-controlled studies: non-fatal stroke*

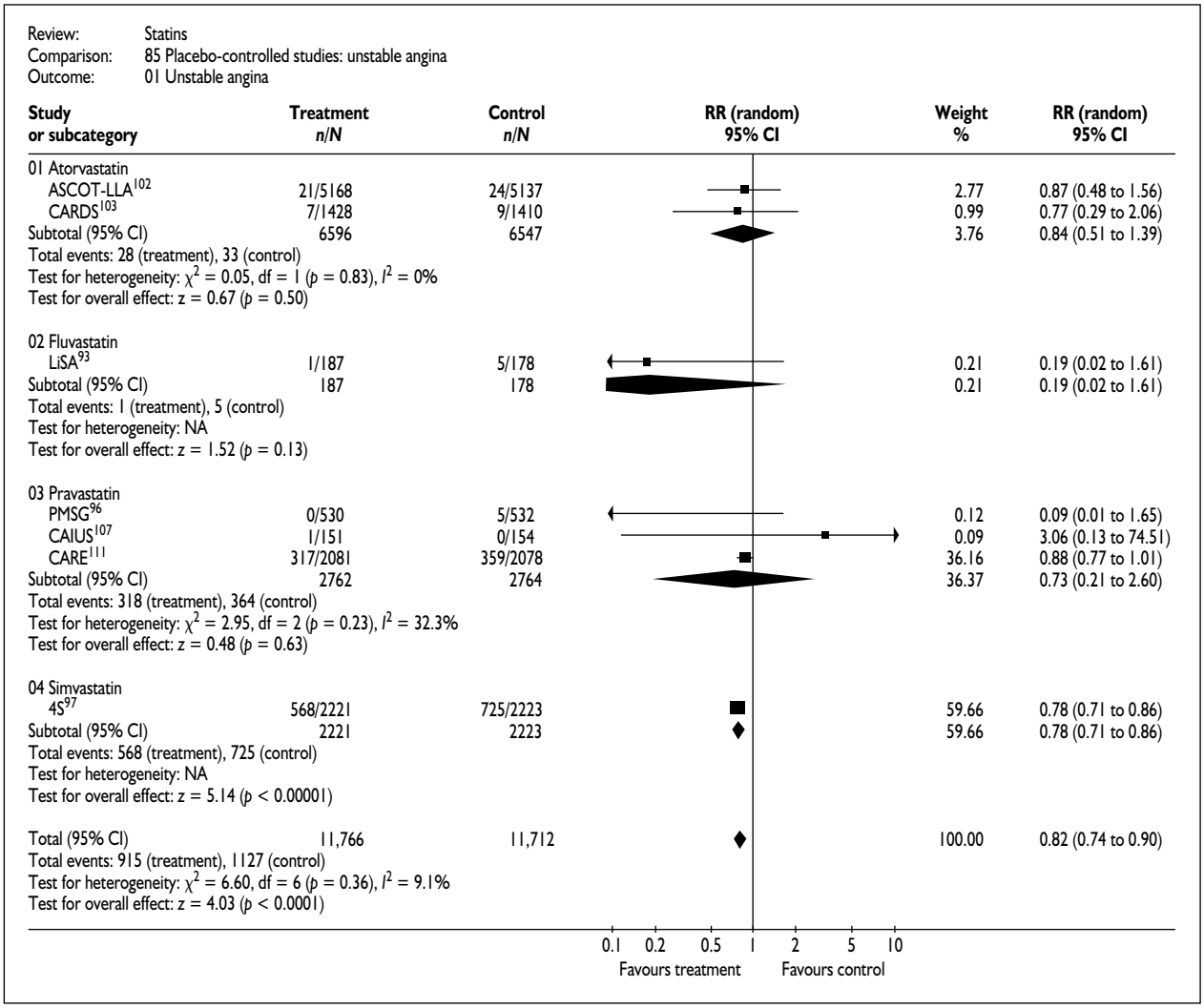

FIGURE 40 *Placebo-controlled studies: unstable angina*

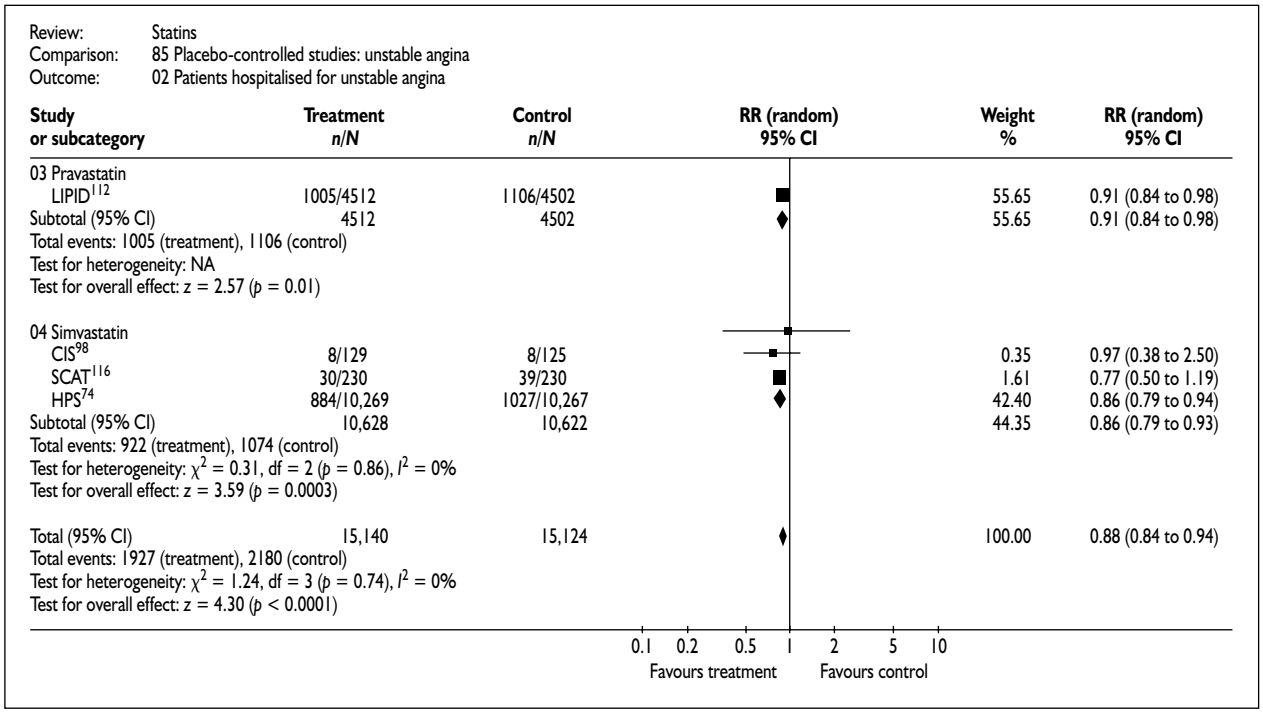

FIGURE 41 *Placebo-controlled studies: hospitalisations for unstable angina*

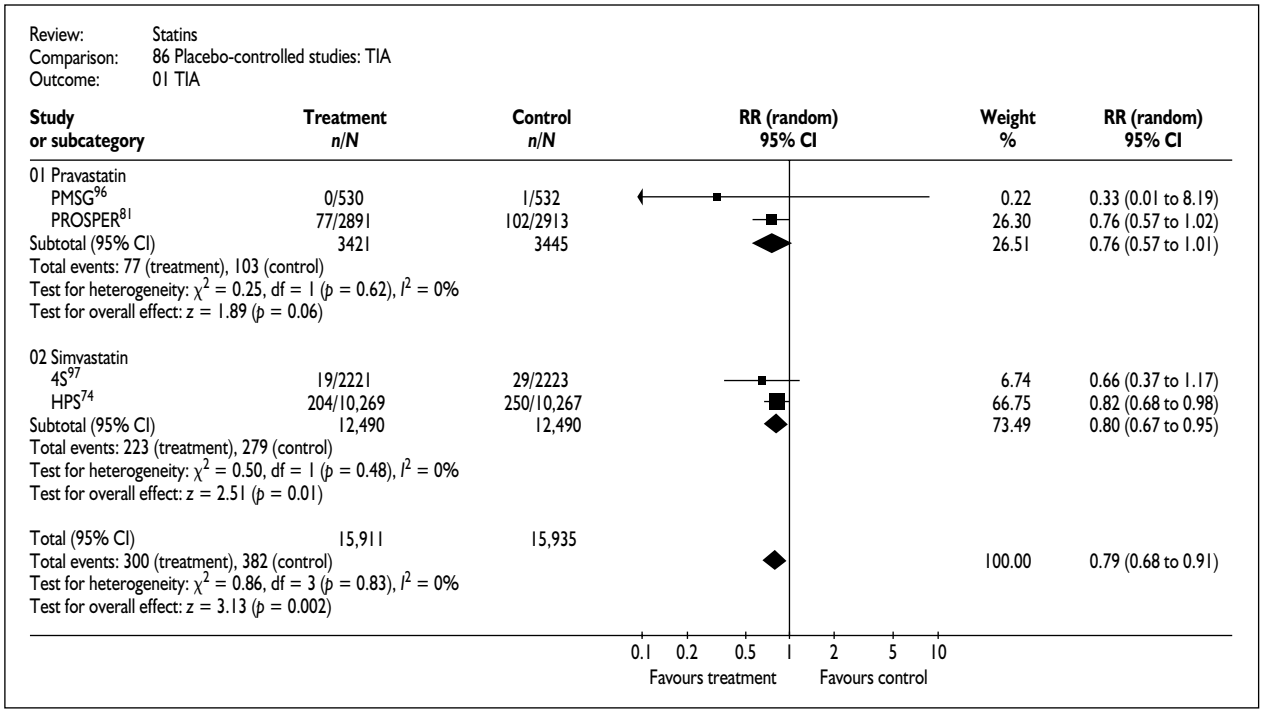

FIGURE 42 *Placebo-controlled studies: TIA*

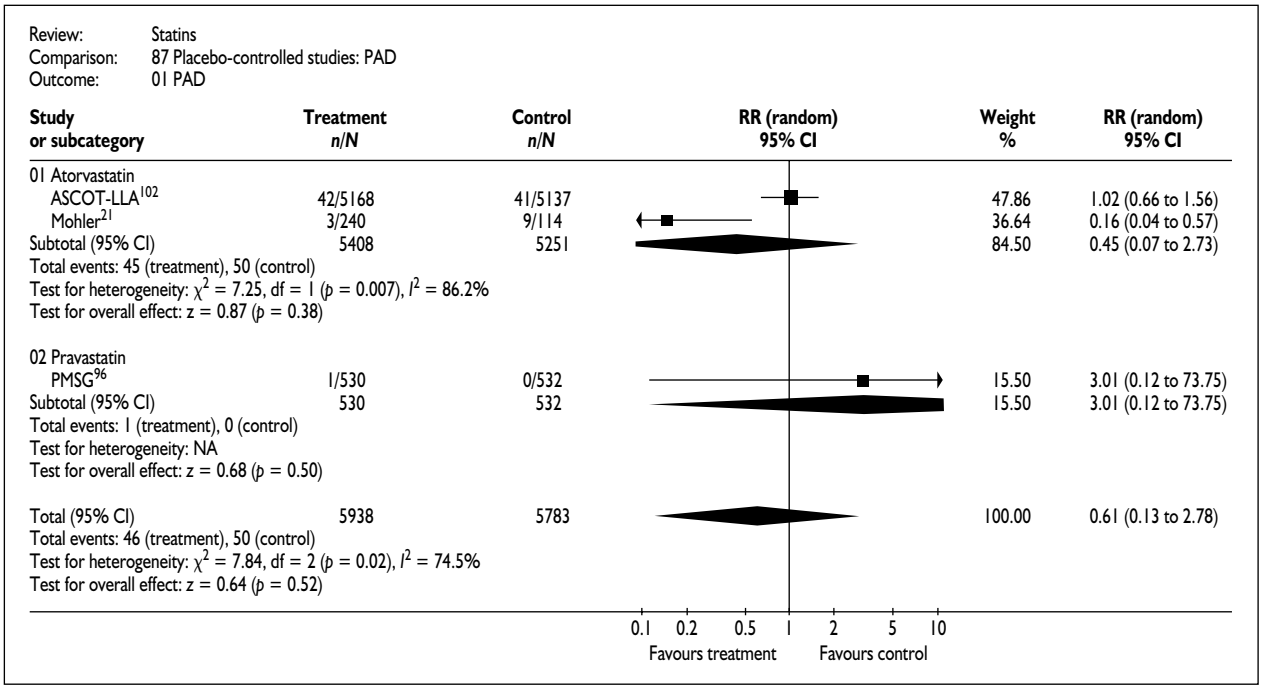

FIGURE 43 *Placebo-controlled studies: PAD*

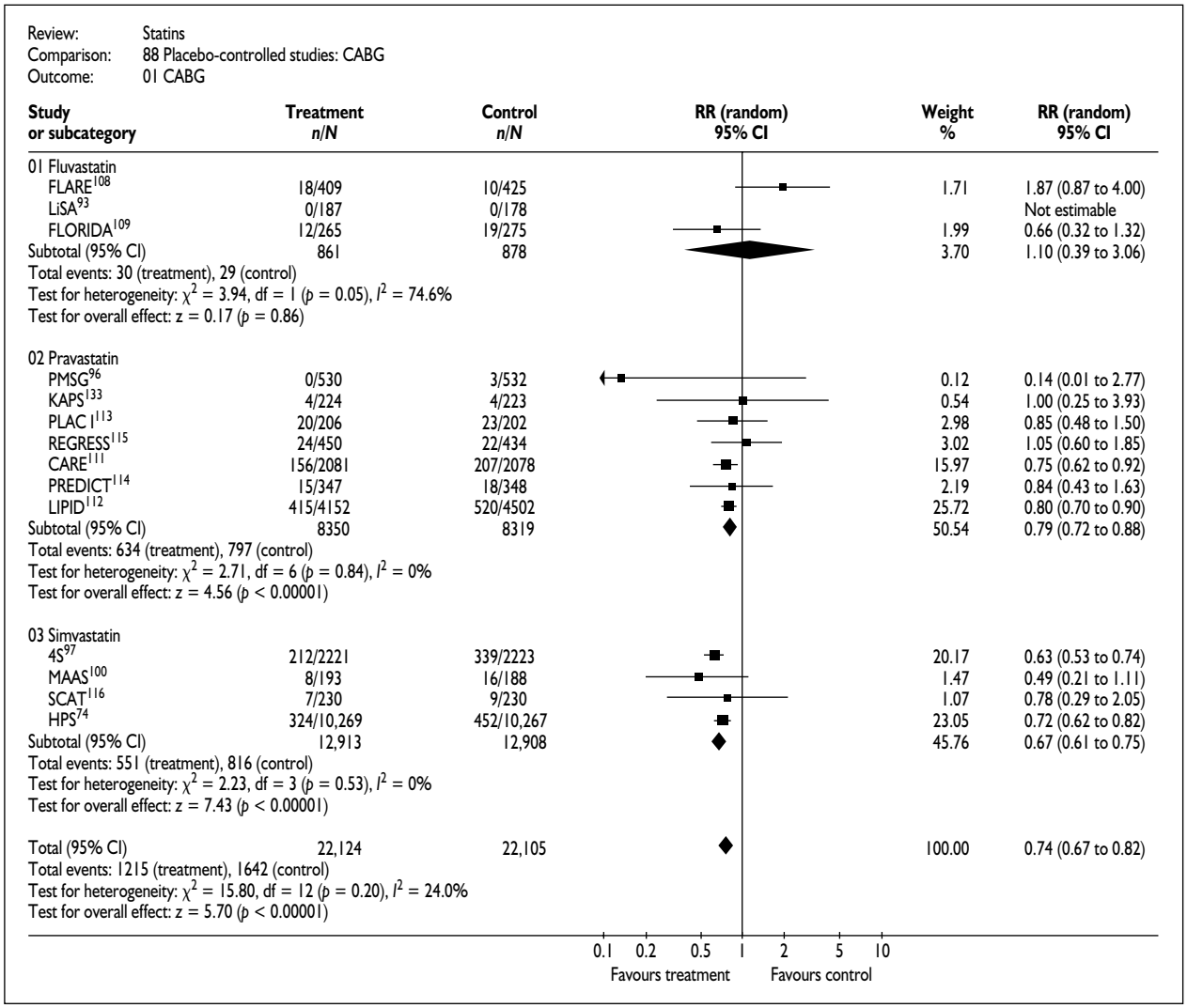

FIGURE 44 *Placebo-controlled studies: CABG*

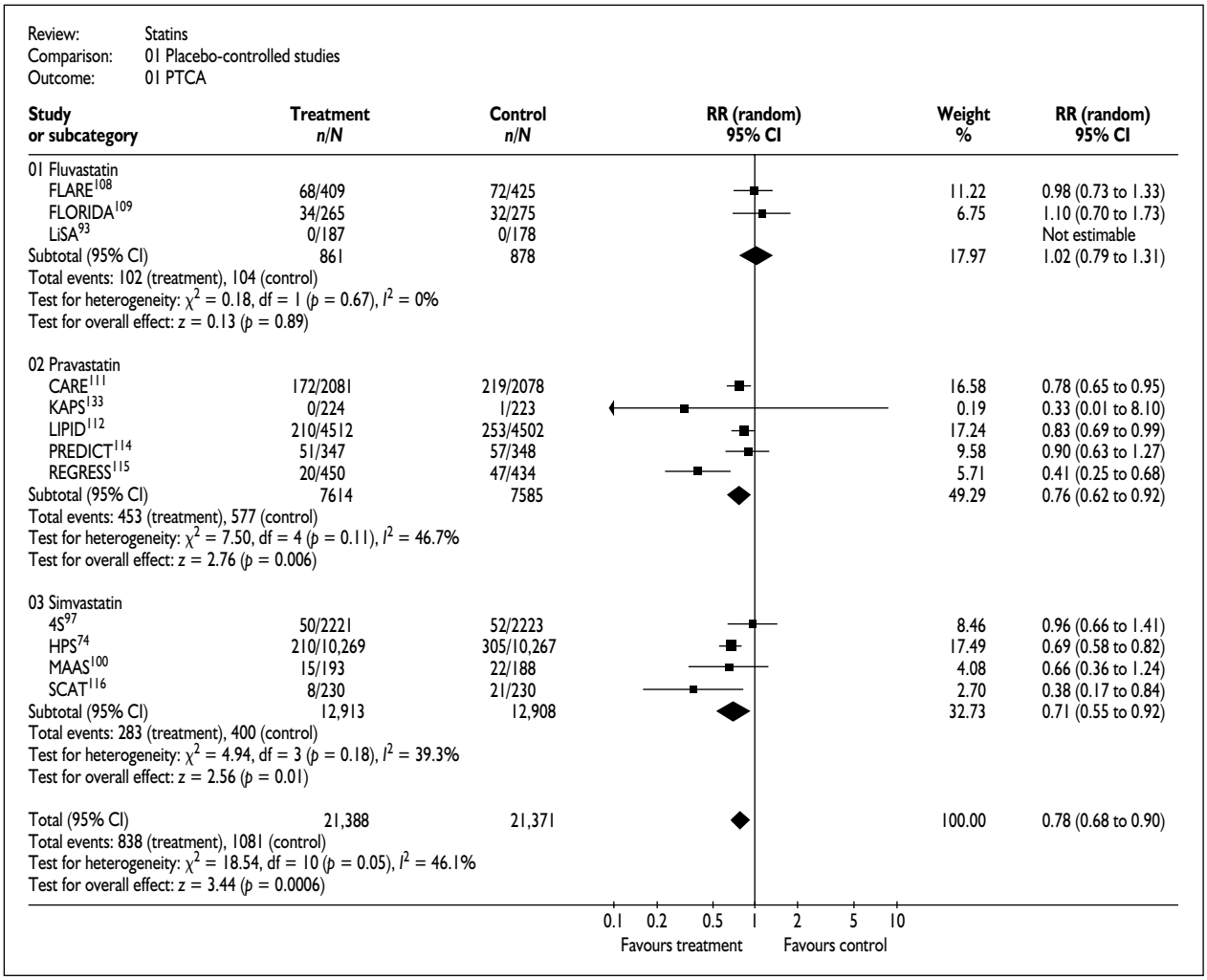

FIGURE 45 *Placebo-controlled studies: PTCA*

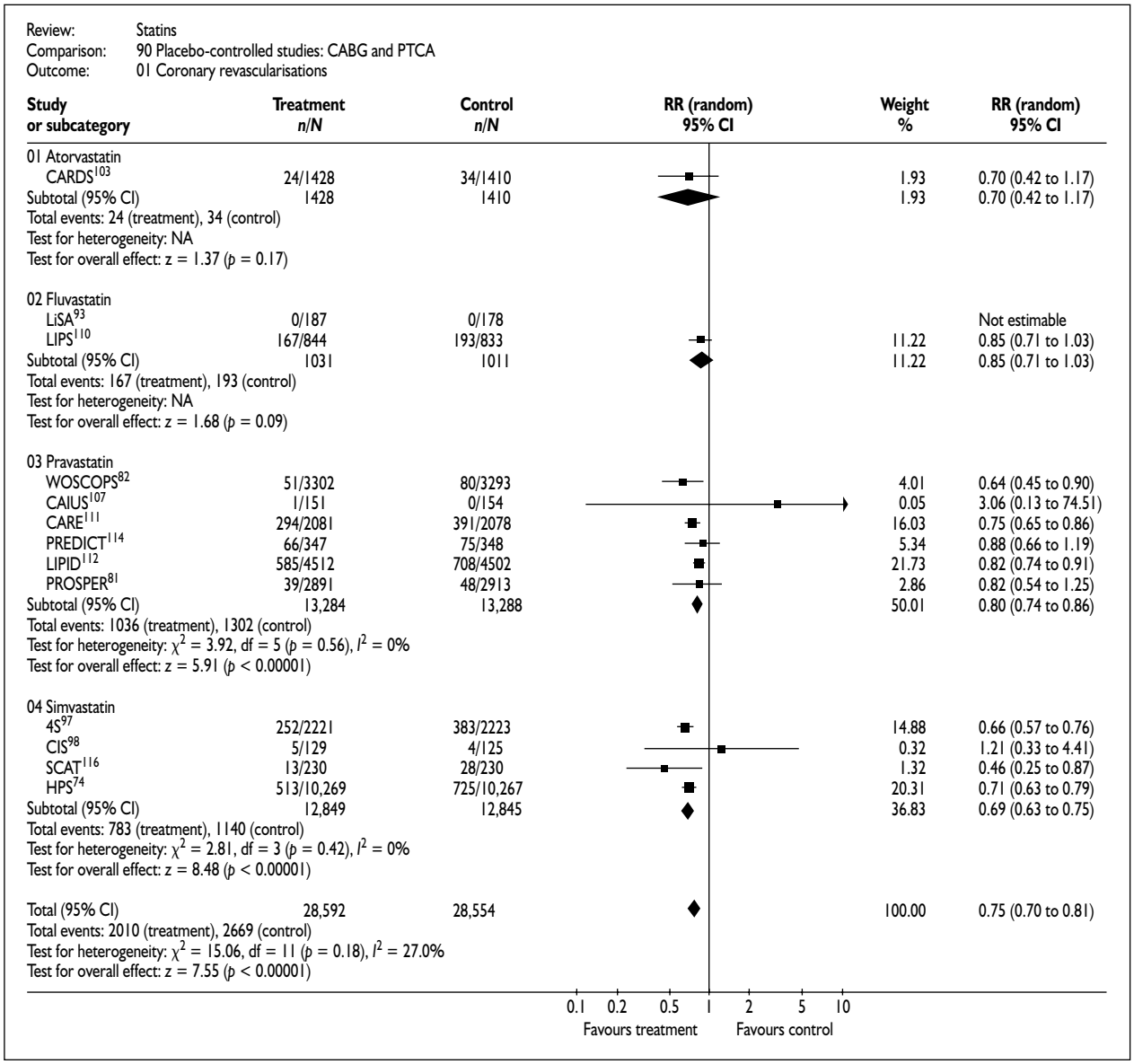

FIGURE 46 *Placebo-controlled studies: CABG + PTCA*

Appendix 8

Placebo-controlled studies: statins in primary CVD prevention

TABLE 107 *Placebo-controlled studies: statins in primary CVD prevention*

Outcome	Studies contributing data	No. with event/total no.: statin	No. with event/total no.: placebo	RR	95% CI
All-cause mortality	CARDS	61/1428	82/1410	0.73	0.53 to 1.01
Cardiovascular mortality	CARDS	25/1428	37/1410	0.67	0.40 to 1.10
CHD mortality	CARDS, CAIUS	22/1579	82/1564	0.86	0.49 to 1.52
Stroke mortality	CARDS	1/1428	5/1410	0.20	0.02 to 1.69
Non-fatal stroke	CARDS	20/1428	30/1410	0.66	0.38 to 1.15
TIA	No data				
PAD	No data				
Fatal MI	CARDS, CAIUS	9/1579	20/1564	0.60	0.12 to 3.04
Non-fatal MI	CARDS, CAIUS	26/1579	43/1564	0.60	0.37 to 0.97
Stable angina	No data				
Unstable angina	CARDS	7/1428	9/1410	0.77	0.29 to 2.06
CABG		No data			
PTCA	No data				
CABG + PTCA	CARDS, CAIUS	25/1579	34/1564	0.72	0.49 to 1.21
CHD death plus non-fatal MI	CARDS, CAIUS	45/1579	67/1564	0.66	0.46 to 0.96
CHD death, non-fatal MI and fatal or non-fatal stroke	CARDS, PROSPER non-CVD subgroup	246/3013	300/3064	0.79	0.53 to 1.17
CHD death, non-fatal MI, fatal or non-fatal stroke and coronary revascularisation	CARDS	76/1428	118/1410	0.64	0.48 to 0.84

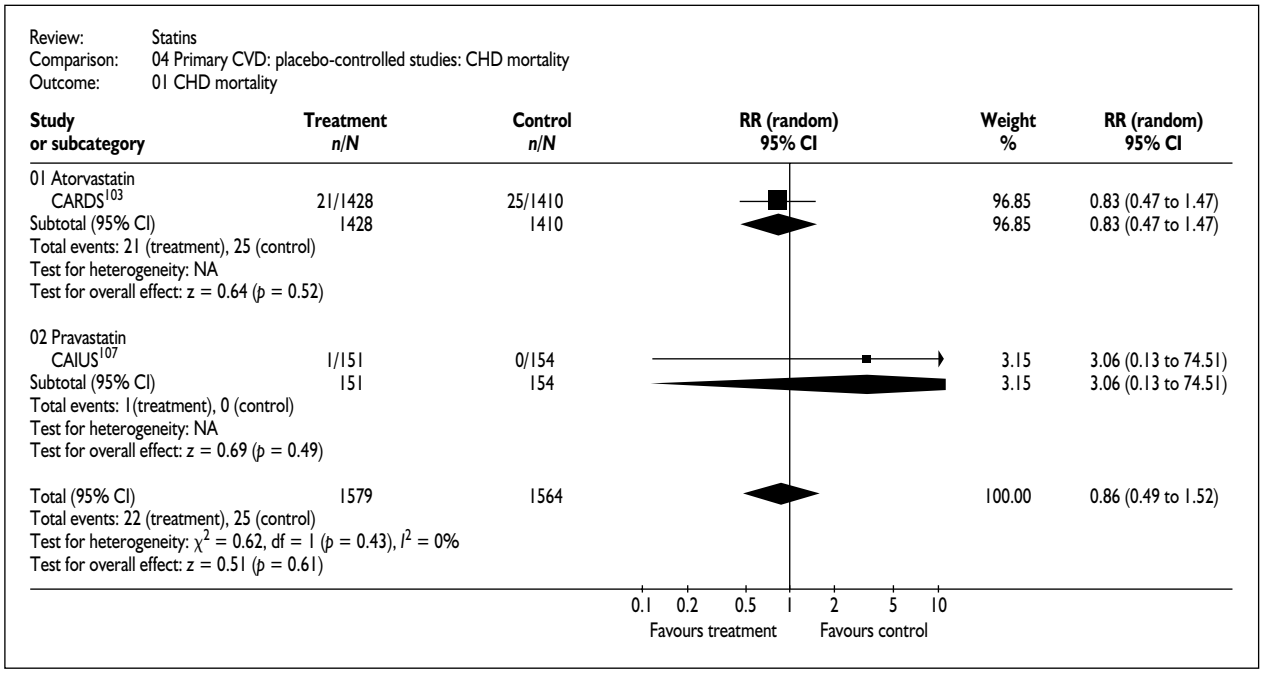

FIGURE 47 *Placebo-controlled studies: statins in primary CVD prevention: CHD mortality*

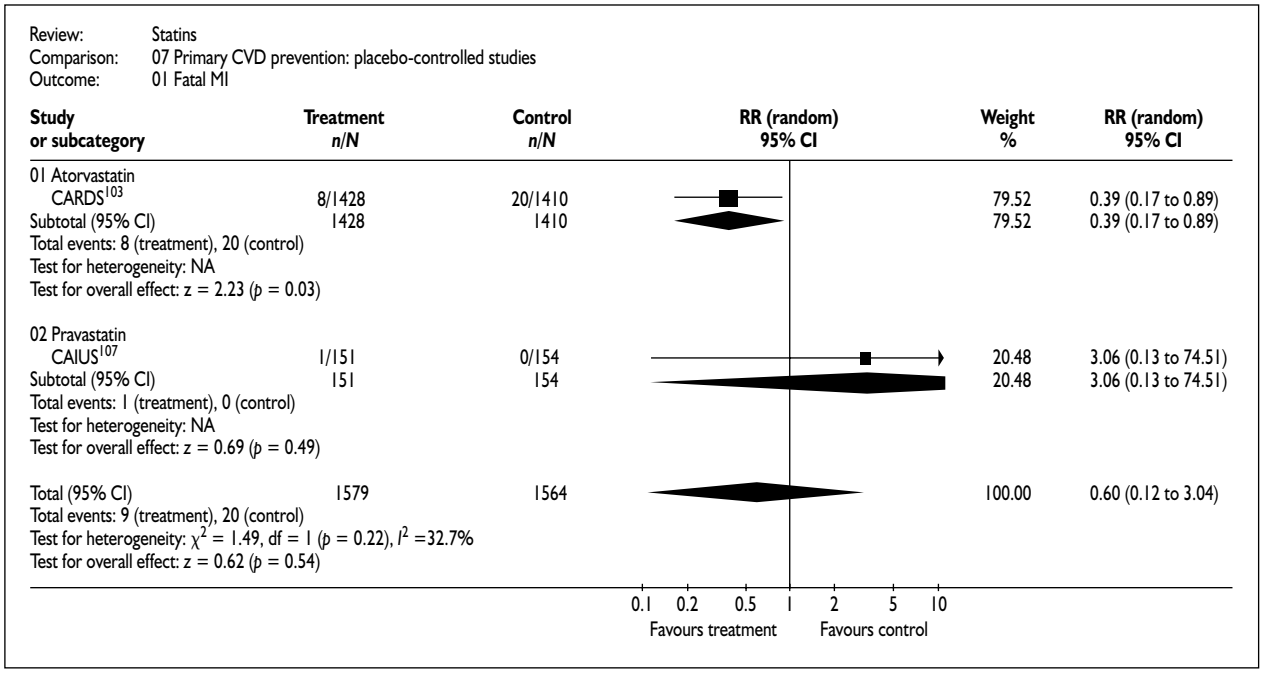

FIGURE 48 *Placebo-controlled studies: statins in primary CVD prevention: fatal MI*

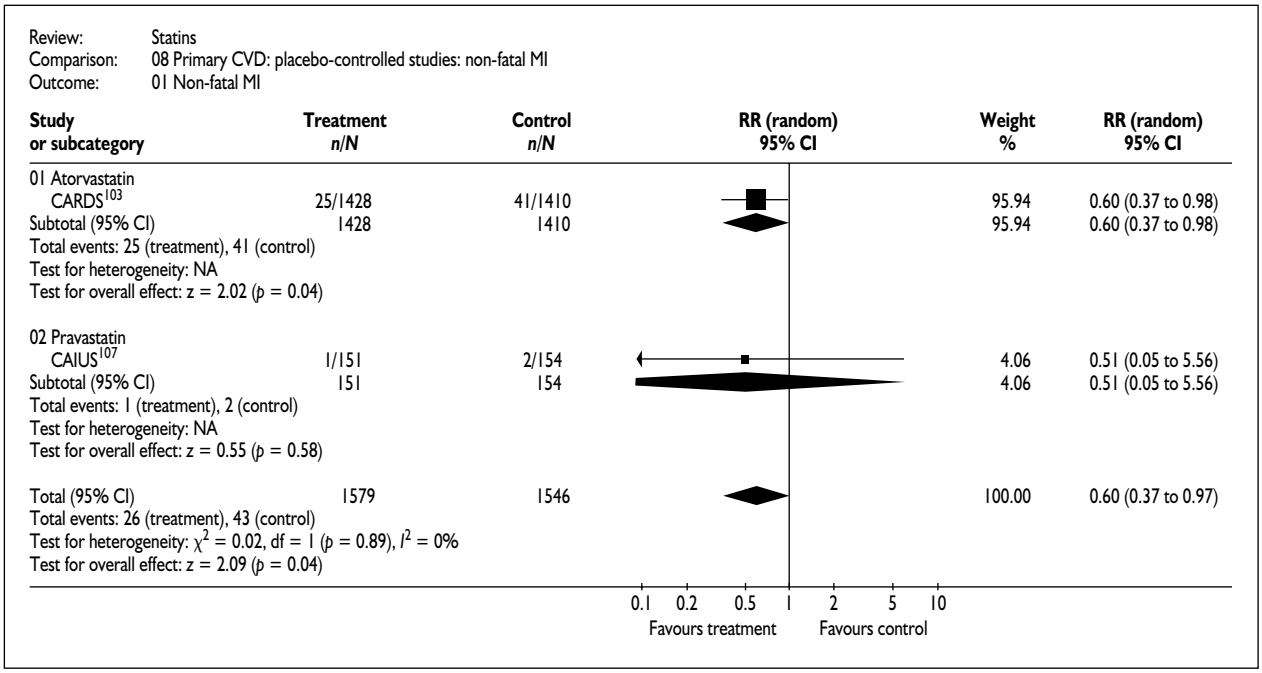

FIGURE 49 *Placebo-controlled studies: statins in primary CVD prevention: non-fatal MI*

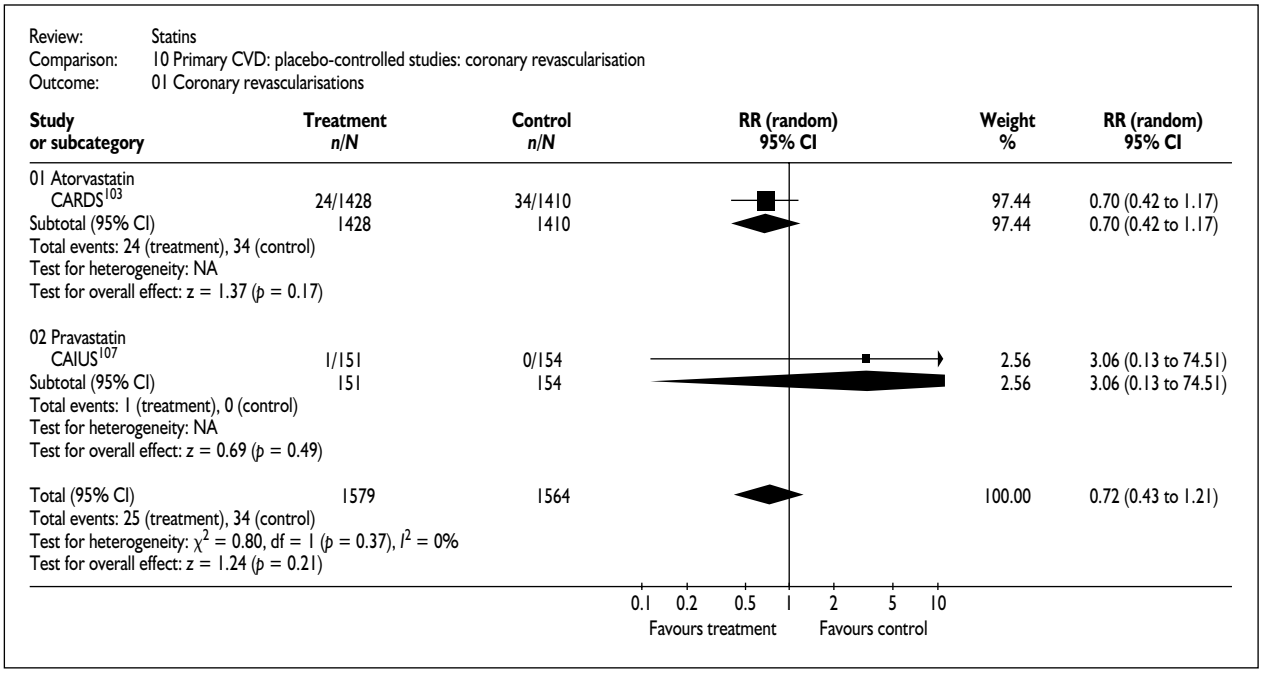

FIGURE 50 *Placebo-controlled studies: statins in primary CVD prevention: coronary revascularisations*

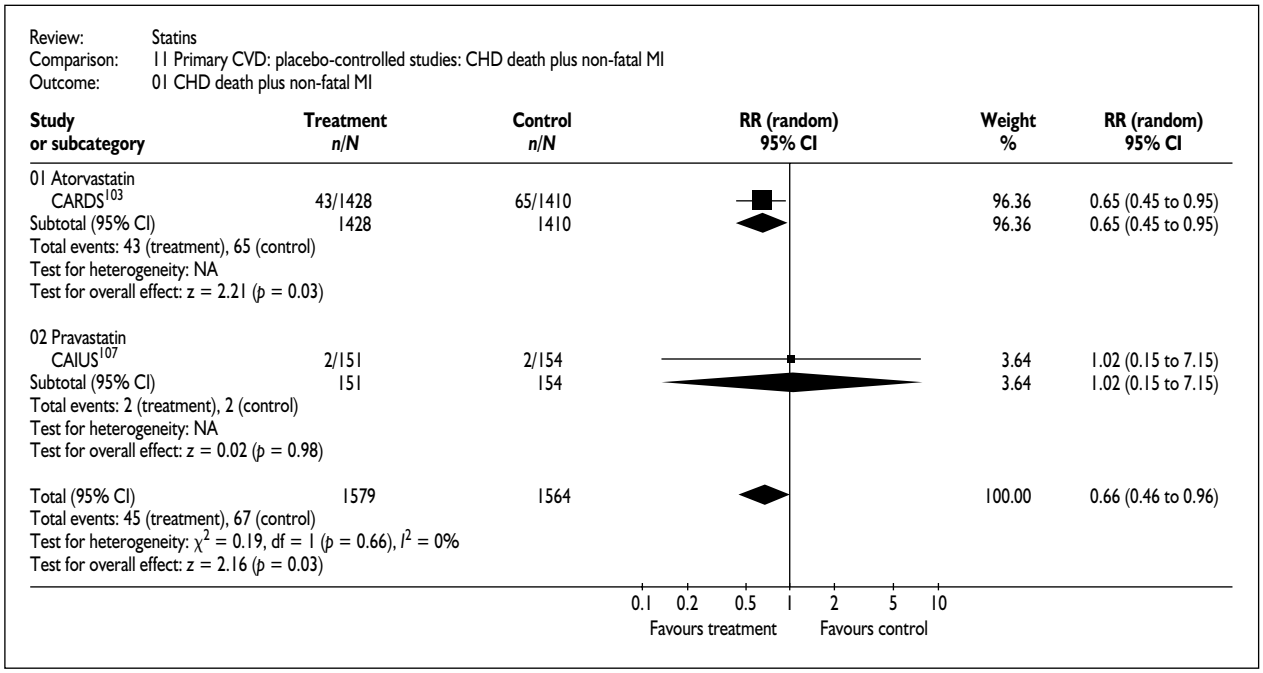

FIGURE 51 *Placebo-controlled studies: statins in primary CVD prevention: CHD death plus non-fatal MI*

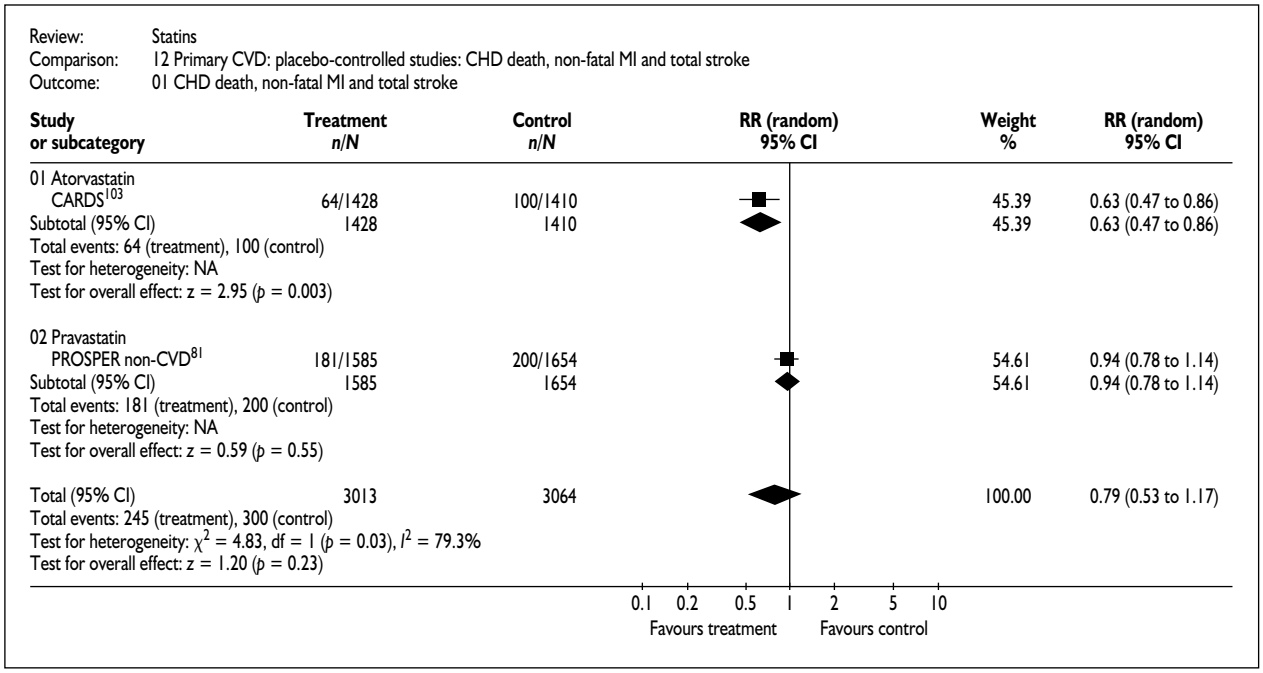

FIGURE 52 *Placebo-controlled studies: statins in primary CVD prevention: CHD death, non-fatal MI and fatal or non-fatal stroke*

Appendix 9

Placebo-controlled studies: statins in primary CHD prevention

TABLE 108 *Placebo-controlled studies: statins in primary CHD prevention*

Outcome	Studies contributing data	No. with event/total no.: statin	No. with event/total no.: placebo	RR	95% CI
All-cause mortality	DALI, ASCOT-LLA, CARDS	246/6741	294/6619	0.83	0.70 to 0.98
Cardiovascular mortality	DALI, ASCOT-LLA, CARDS	99/6741	119/6619	0.83	0.63 to 1.08
CHD mortality	DALI, CARDS, CAIUS	22/1724	25/1636	0.86	0.49 to 1.52
Stroke mortality	DALI, CARDS, CAIUS	1/1724	5/1636	0.20	0.02 to 1.69
Non-fatal stroke	CARDS	20/1428	30/1410	0.66	0.38 to 1.15
TIA	No data				
PAD	ASCOT-LLA	42/5168	41/5137	0.59	0.66 to 1.56
Fatal MI	DALI, CARDS, CAIUS	9/1724	20/1636	0.60	0.12 to 3.04
Non-fatal MI	DALI, CARDS, CAIUS	26/1724	44/1636	0.58	0.36 to 0.94
Stable angina	ASCOT-LLA	33/5168	56/5137	0.59	0.38 to 0.90
Unstable angina	ASCOT-LLA, CARDS, CAIUS	29/6747	33/6701	0.87	0.53 to 1.43
CABG	No data				
PTCA	No data				
CABG + PTCA	CARDS, CAIUS	25/1579	34/1564	0.72	0.43 to 1.21
CHD death plus non-fatal MI	DALI, ASCOT-LLA, CAIUS	102/5464	157/5363	0.64	0.50 to 0.82
CHD death, non-fatal MI and fatal or non-fatal stroke	DALI, CARDS, PROSPER non-CVD subgroup	245/3158	301/3136	0.77	0.52 to 1.13
CHD death, non-fatal MI, fatal or non-fatal stroke and coronary revascularisation	DALI, CARDS, HPS non-CHD subgroup	650/5184	863/5057	0.73	0.63 to 0.86

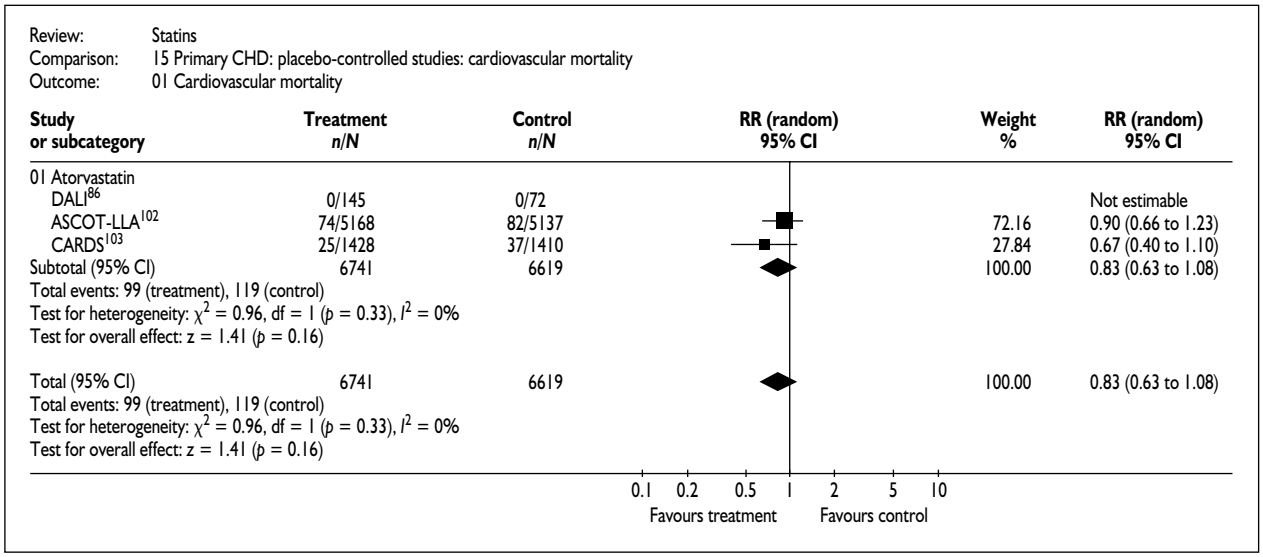

FIGURE 53 *Placebo-controlled studies: statins in primary CHD prevention: CVD mortality*

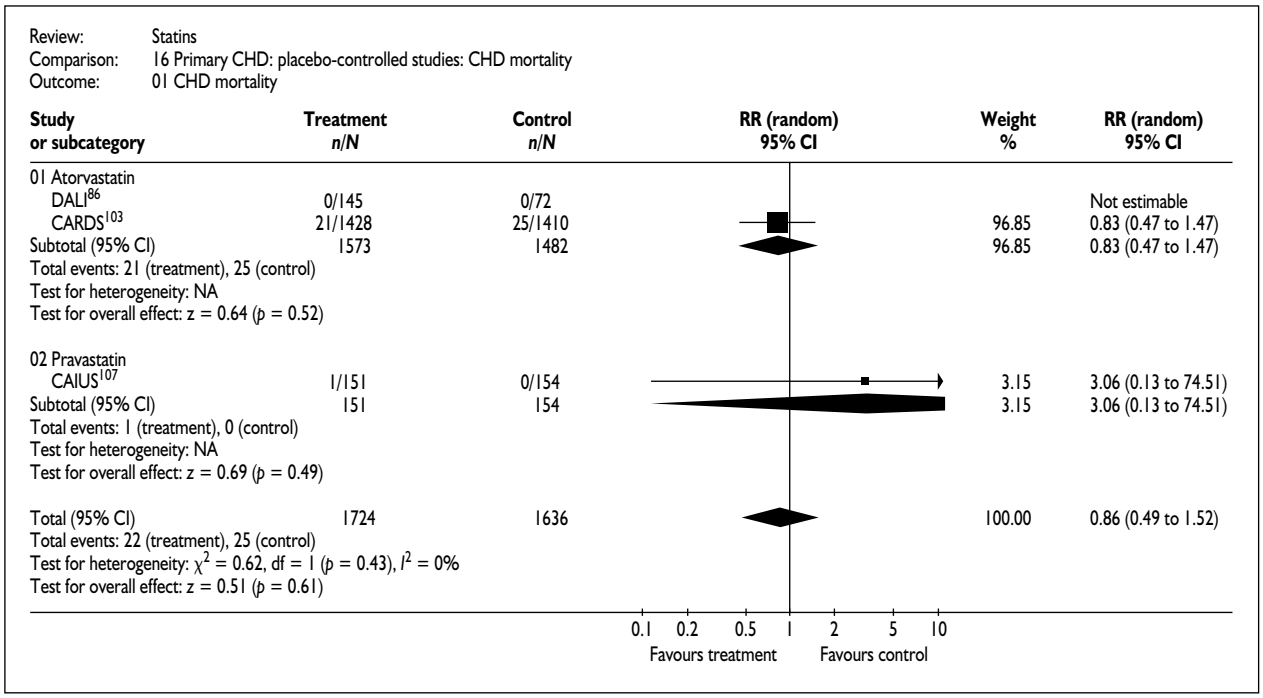

FIGURE 54 *Placebo-controlled studies: statins in primary CHD prevention: CHD mortality*

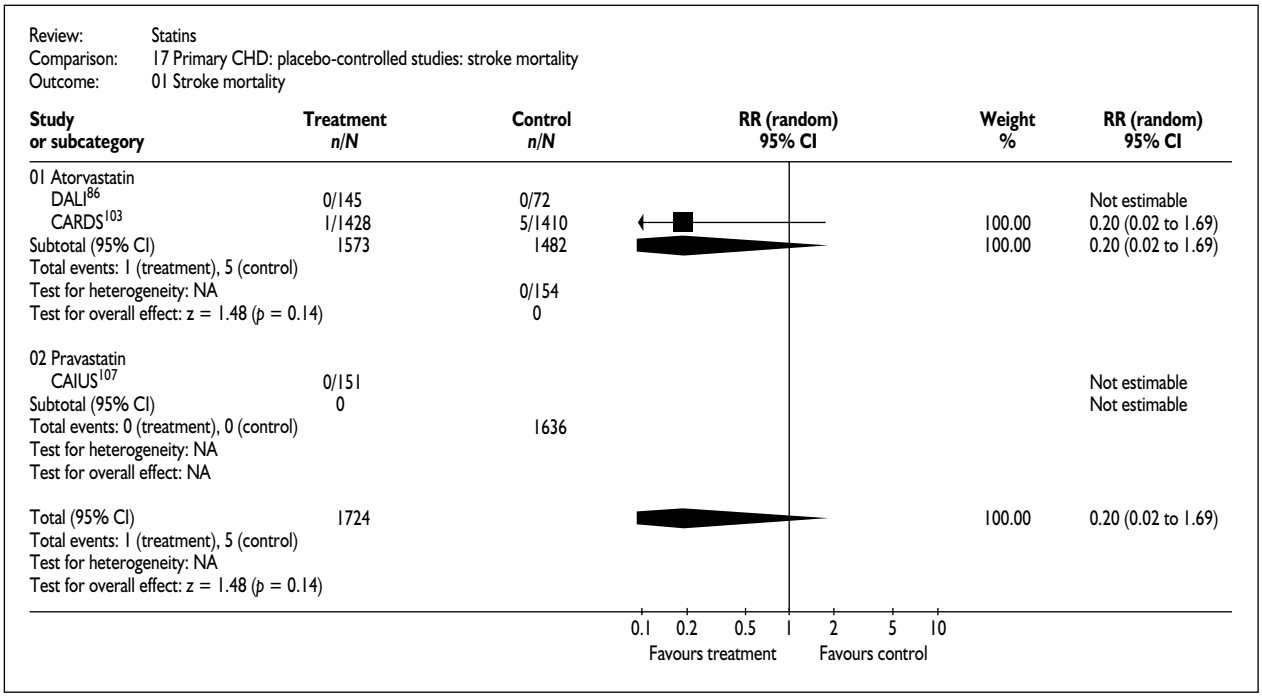

FIGURE 55 *Placebo-controlled studies: statins in primary CHD prevention: stroke mortality*

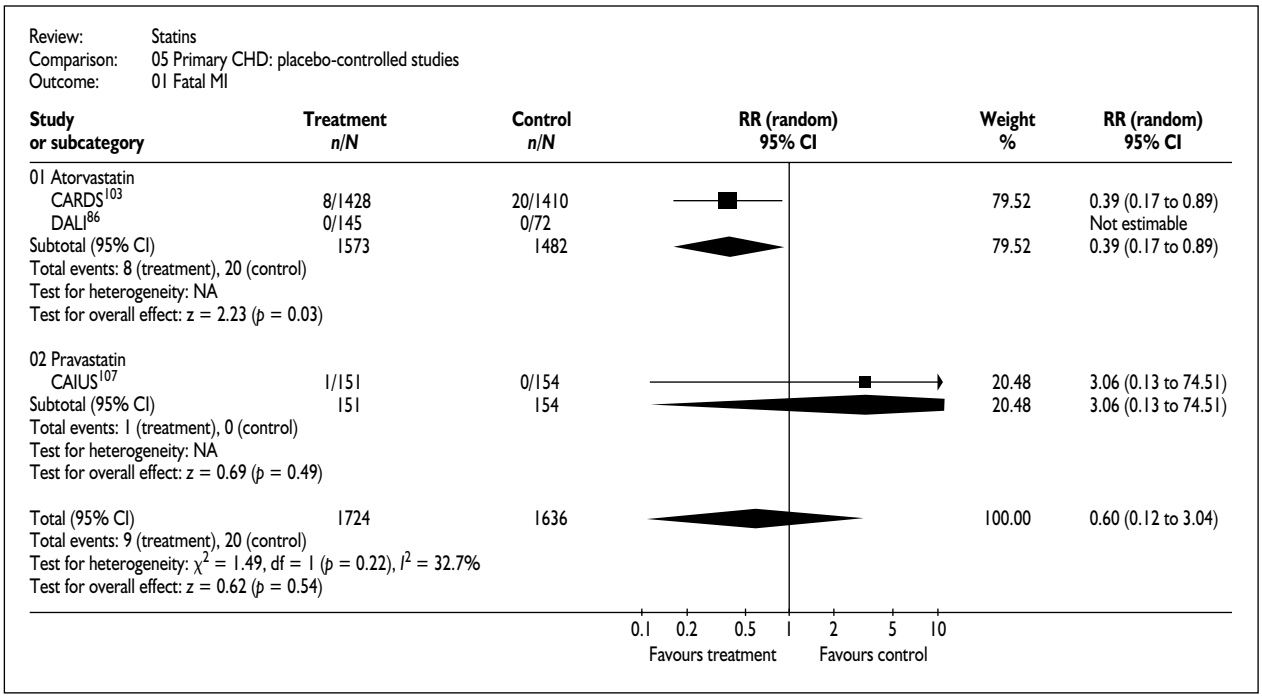

FIGURE 56 *Placebo-controlled studies: statins in primary CHD prevention: fatal MI*

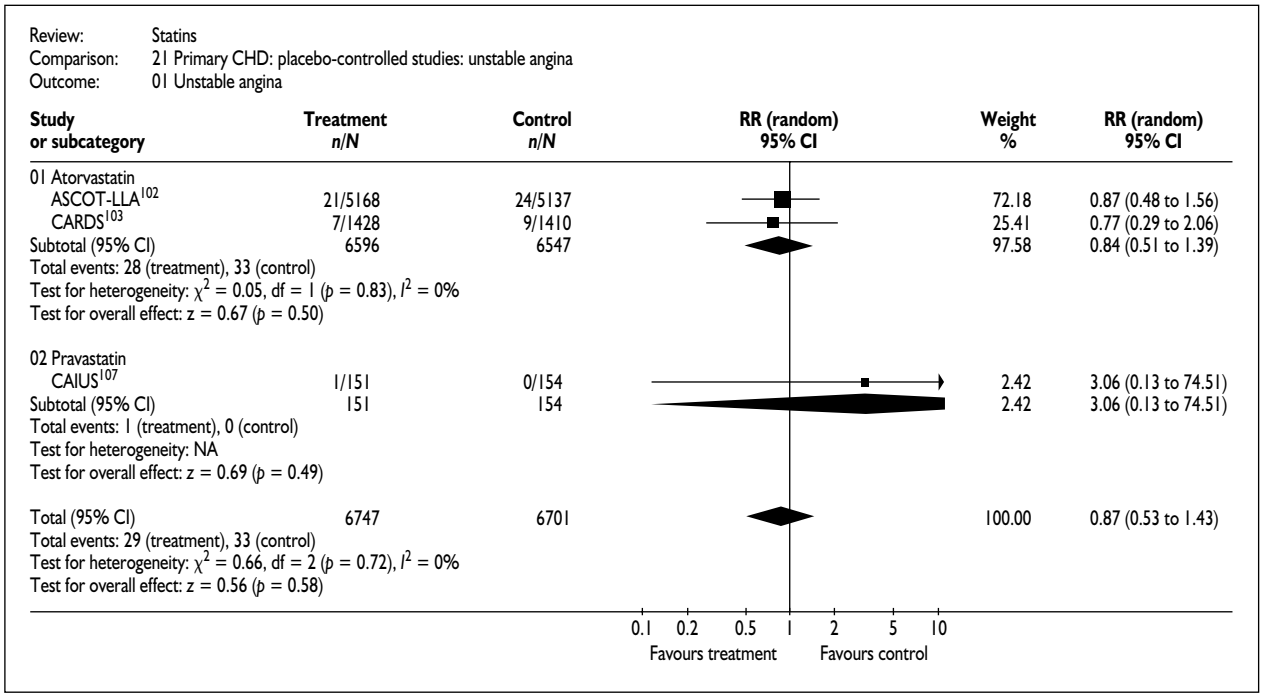

FIGURE 57 *Placebo-controlled studies: statins in primary CHD prevention: unstable angina*

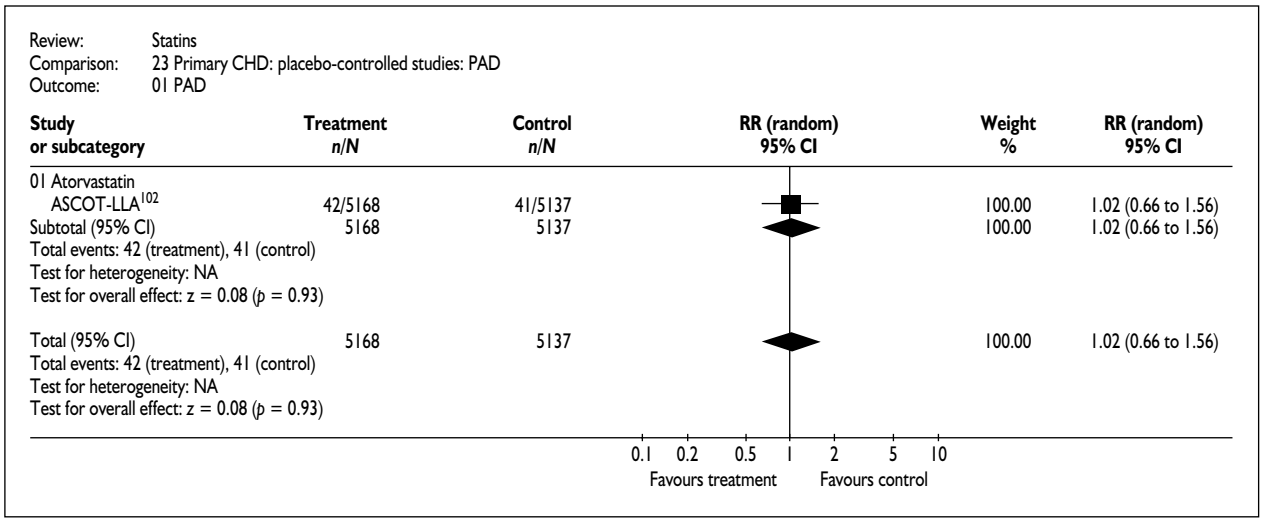

FIGURE 58 *Placebo-controlled studies: statins in primary CHD prevention: PAD*

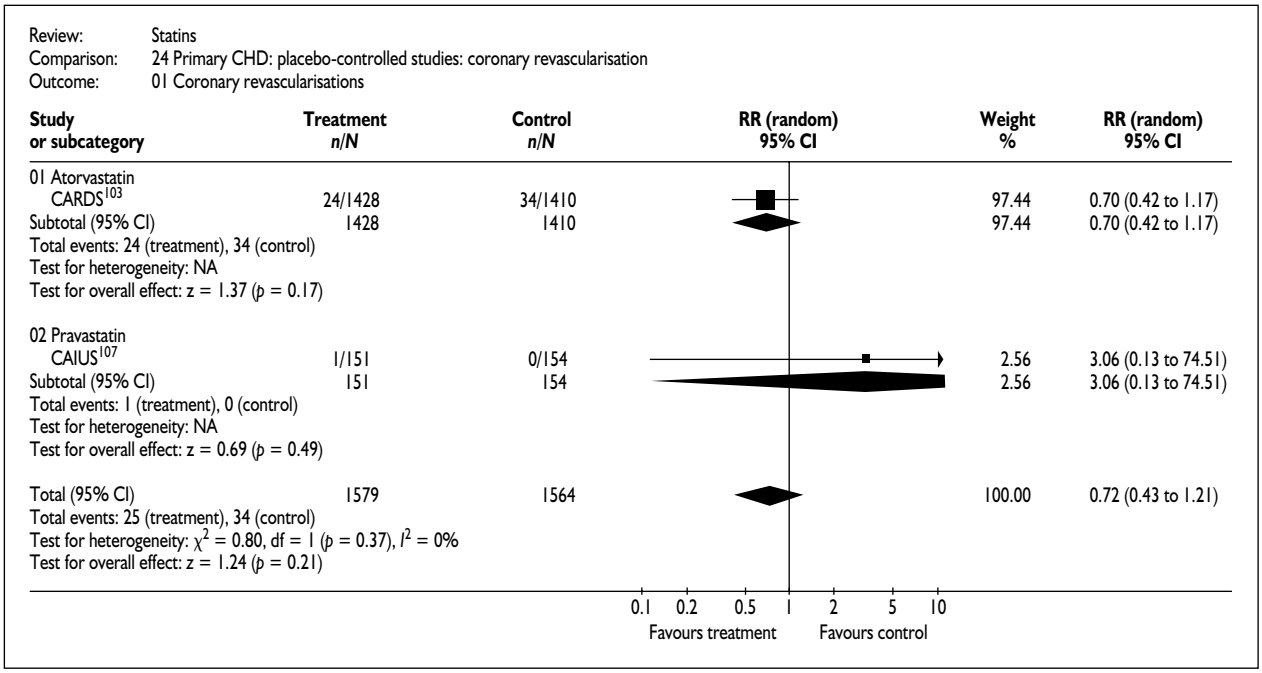

FIGURE 59 *Placebo-controlled studies: statins in primary CHD prevention: coronary revascularisations*

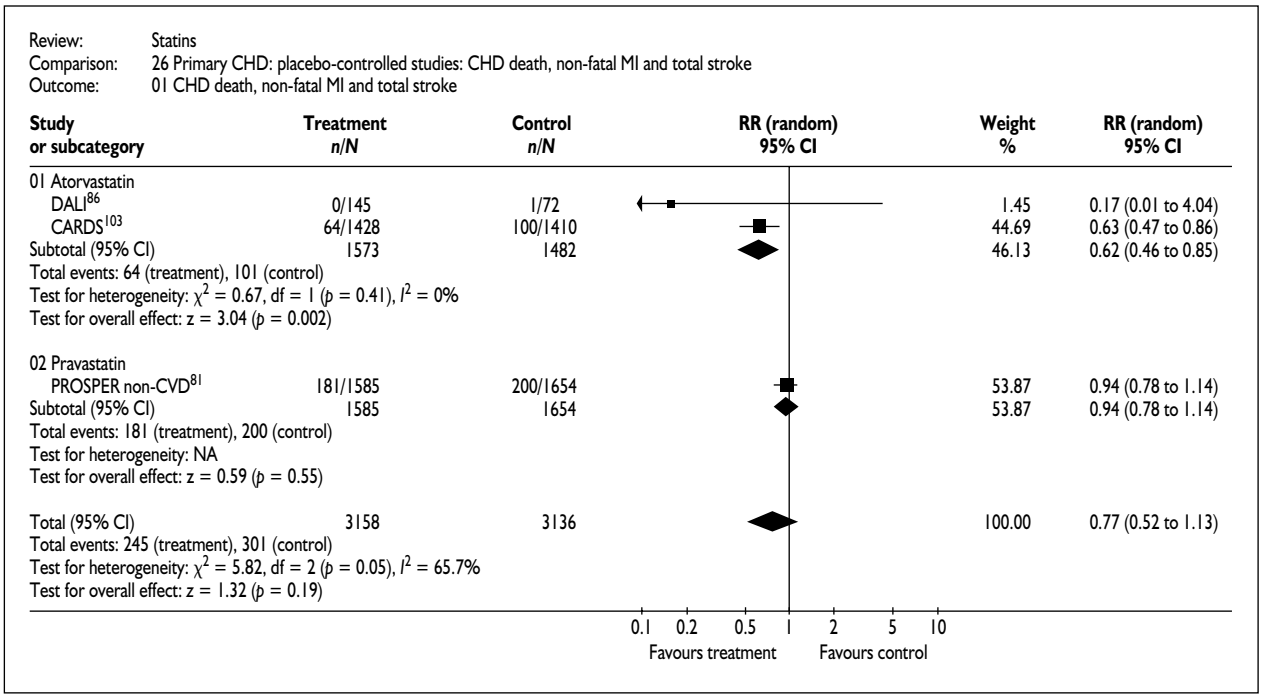

FIGURE 60 *Placebo-controlled studies: statins in primary CHD prevention: CH death, non-fatal MI and fatal or non-fatal stroke*

Appendix 10

Placebo-controlled studies: statins in secondary CHD prevention

TABLE 109 *Placebo-controlled studies: statins in secondary CHD prevention*

Outcome	Studies contributing data	No. with event/total no.: statin	No. with event/total no.: placebo	RR	95% CI
All-cause mortality	FLORIDA, LIPS, PLAC I, PLAC II, REGRESS, CARE, PREDICT, LIPID, 4S, CIS, SCAT	933/11,360	1175/11,326	0.80	0.70 to 0.89
Cardiovascular mortality	FLORIDA, PLAC I, CARE, LIPID, 4S, CIS	589/9414	786/9405	0.75	0.68 to 0.83
CHD mortality	FLARE, LiSA, FLORIDA, LIPS, PLAC I, CARE, LIPID, 4S, MAAS, REGRESS, CIS, SCAT	532/11,727	743/11,693	0.72	0.64 to 0.80
Stroke mortality	FLORIDA, LIPS, PLAC I, CARE, PREDICT, LIPID, CIS	37/8384	34/8363	1.07	0.67 to 1.71
Non-fatal stroke	PLAC I, CARE, LIPID	189/6799	250/6782	0.72	0.53 to 0.95
TIA	4S	19/2221	29/2223	0.66	0.37 to 1.17
PAD (new or worsening intermittent claudication)	4S	52/2221	81/2223	0.64	0.46 to 0.91
Fatal MI	LiSA, FLORIDA, PLAC I, REGRESS, CARE, LIPID, PREDICT, 4S, MAAS, SCAT	114/10,692	201/10,658	0.57	0.45 to 0.72
Non-fatal MI	FLARE, LiSA, LIPS, PLAC I, REGRESS, CARE, PREDICT, 4S, CIS, SCAT	408/7104	596/7076	0.69	0.59 to 0.79
Stable angina	No data				
Unstable angina	LiSA, CARE, 4S	886/4489	1089/4479	0.82	0.72 to 0.94
Patients hospitalised for unstable angina	LIPID, CIS, SCAT	1043/4871	1153/4857	0.90	0.84 to 0.97
CABG	FLARE, LiSA, FLORIDA, PLAC I, REGRESS, CARE, PREDICT, LIPID, 4S, MAAS, SCAT	887/11,101	1183/11,083	0.76	0.66 to 0.87
PTCA	FLARE, LiSA, FLORIDA, REGRESS, CARE, PREDICT, LIPID, 4S, MAAS, SCAT	621/10,895	770/10,881	0.79	0.67 to 0.94
CABG + PTCA	LiSA, LIPS, CARE, PREDICT, LIPID, 4S, CIS, SCAT	1382/10,551	1782/10,517	0.77	0.69 to 0.85

continued

TABLE 109 *Placebo-controlled studies: statins in secondary CHD prevention (cont'd)*

Outcome	Studies contributing data	No. with event/total no.: statin	No. with event/total no.: placebo	RR	95% CI
CHD death plus non-fatal MI	FLARE, LiSA, LIPS, CARE, LIPID, 4S, CIS	1252/10,383	1700/10,364	0.73	0.68 to 0.80
CHD death, non-fatal MI and fatal or non-fatal stroke	No data				
CHD death, non-fatal MI or coronary revascularisation	FLARE, LiSA, CIS	101/725	115/728	0.91	0.71 to 1.17
CHD death, non-fatal MI, fatal or non-fatal stroke or any revascularisation	HPS CHD subgroup	1459/6694	1841/6692	0.79	0.75 to 0.84

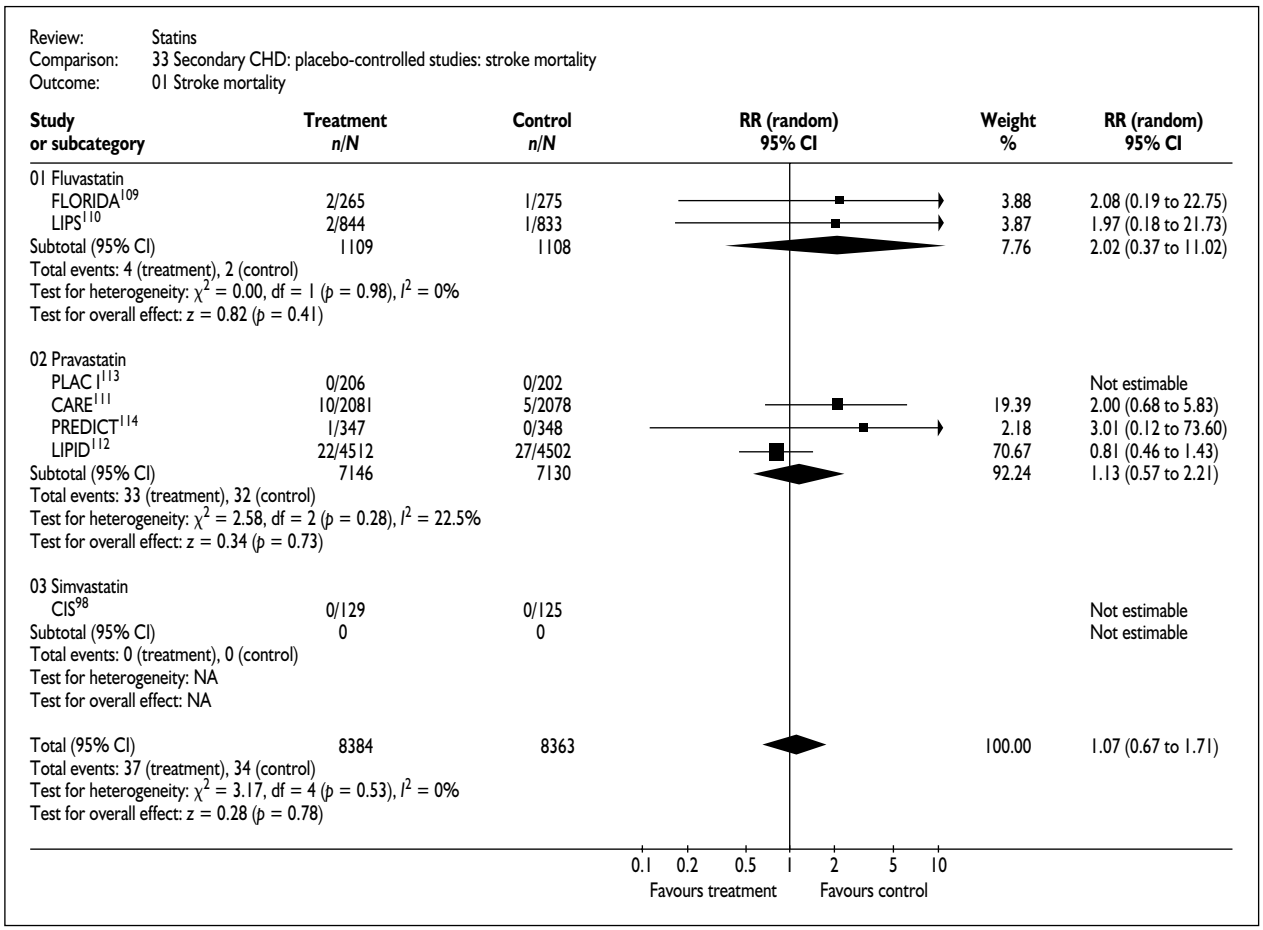

FIGURE 61 *Placebo-controlled studies: statins in secondary CHD prevention: fatal stroke*

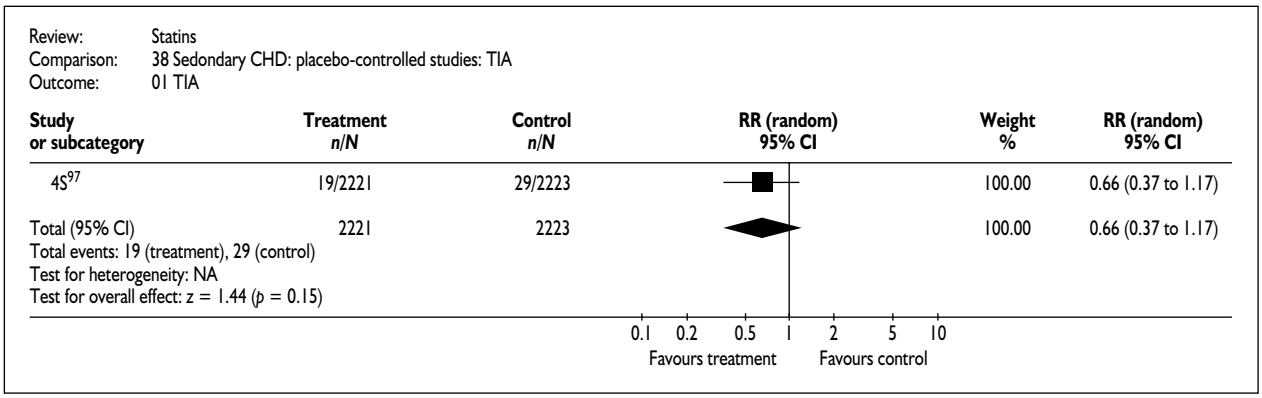

FIGURE 62 *Placebo-controlled studies: statins in secondary CHD prevention: TIA*

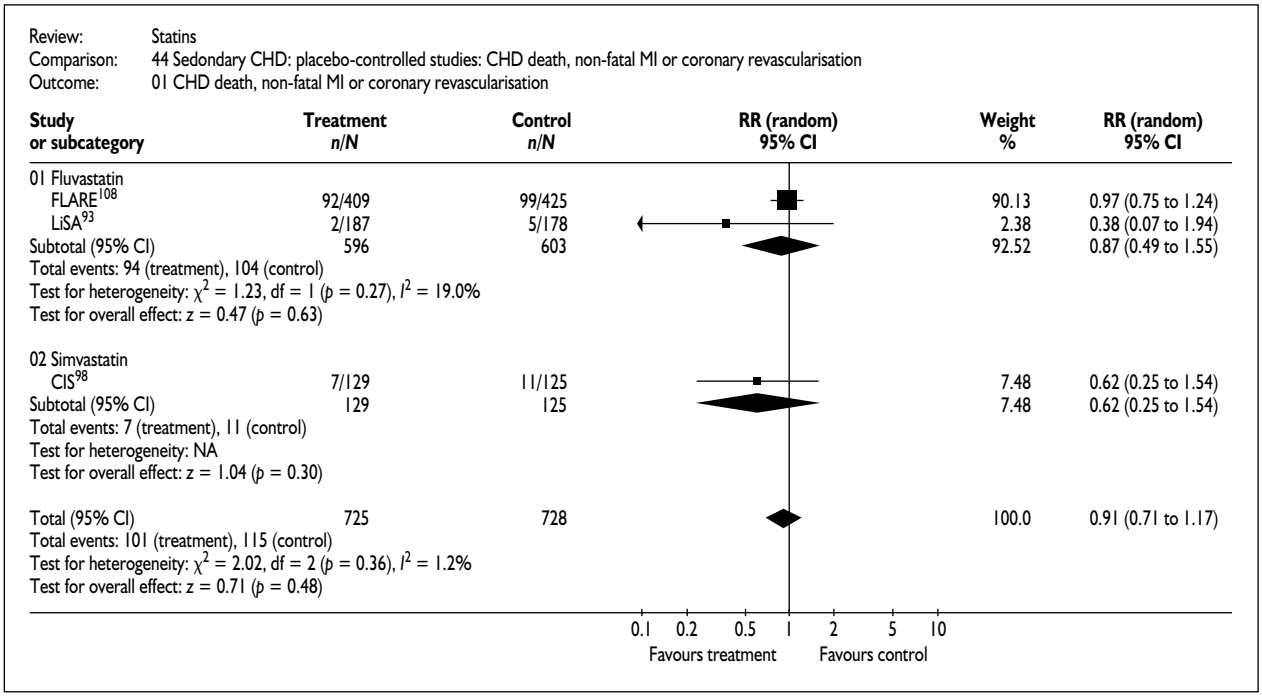

FIGURE 63 *Placebo-controlled studies: statins in secondary CHD prevention: CHD death, non-fatal MI or coronary revascularisation*

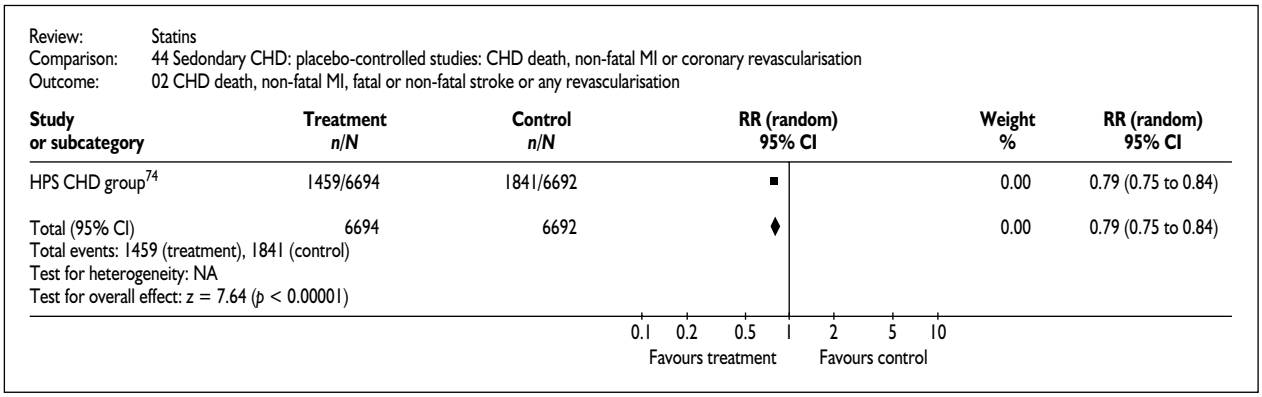

FIGURE 64 *Placebo-controlled studies: statins in secondary CHD prevention: CHD death, non-fatal MI, fatal or non-fatal stroke or revascularisation*

Appendix 11

Placebo-controlled studies: statins in secondary CVD prevention

TABLE 110 *Placebo-controlled studies: statins in secondary CVD prevention (only results that differ from those in secondary CHD prevention)*

Outcome	Studies contributing data	No. with event/total no.: statin	No. with event/total no.: placebo	RR	95% CI
All-cause mortality	Mohler, FLORIDA, LIPS, PLAC I, PLAC II, REGRESS, CARE, PREDICT, LIPID, 4S, CIS, SCAT	938/11,600	1176/11,440	0.80	0.71 to 0.90
CHD mortality	Mohler, Aronow, FLARE, LiSA, FLORIDA, LIPS, PLAC I, CARE, LIPID, 4S, MAAS, REGRESS, CIS, SCAT	537/12,001	750/11,842	0.72	0.64 to 0.80
Stroke mortality	Mohler, FLORIDA, LIPS, PLAC I, CARE, PREDICT, LIPID, CIS	38/8624	34/8477	1.08	0.67 to 1.72
PAD (new or worsening intermittent claudication)	Mohler, 4S	55/2461	90/2337	0.58	0.42 to 0.80
CHD death plus non-fatal MI	Mohler, FLARE, LiSA, LIPS, CARE, LIPID, 4S, CIS	1259/10,774	1703/10,632	0.74	0.69 to 0.79

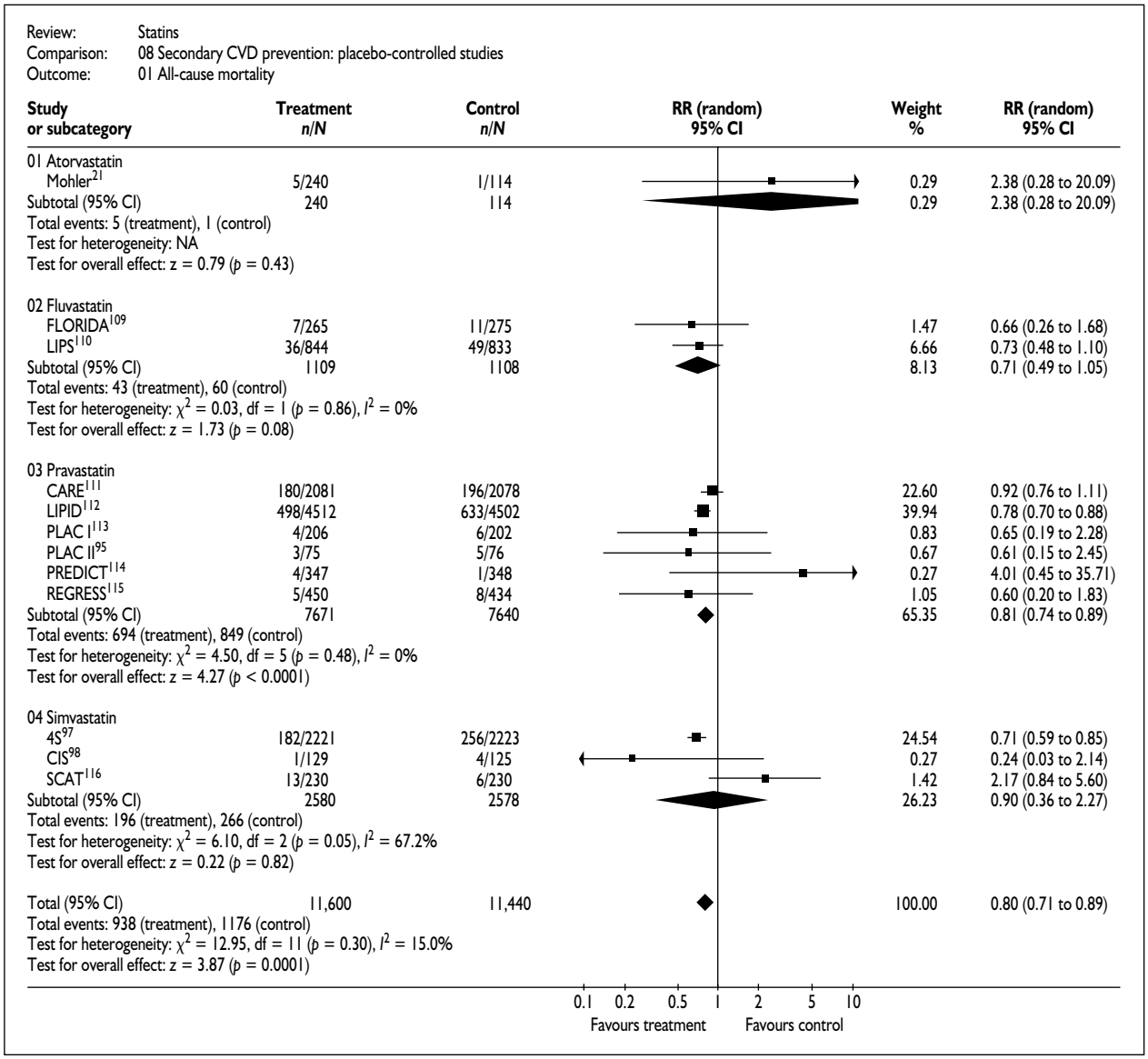

FIGURE 65 *Placebo-controlled studies: statins in secondary CVD prevention: all-cause mortality*

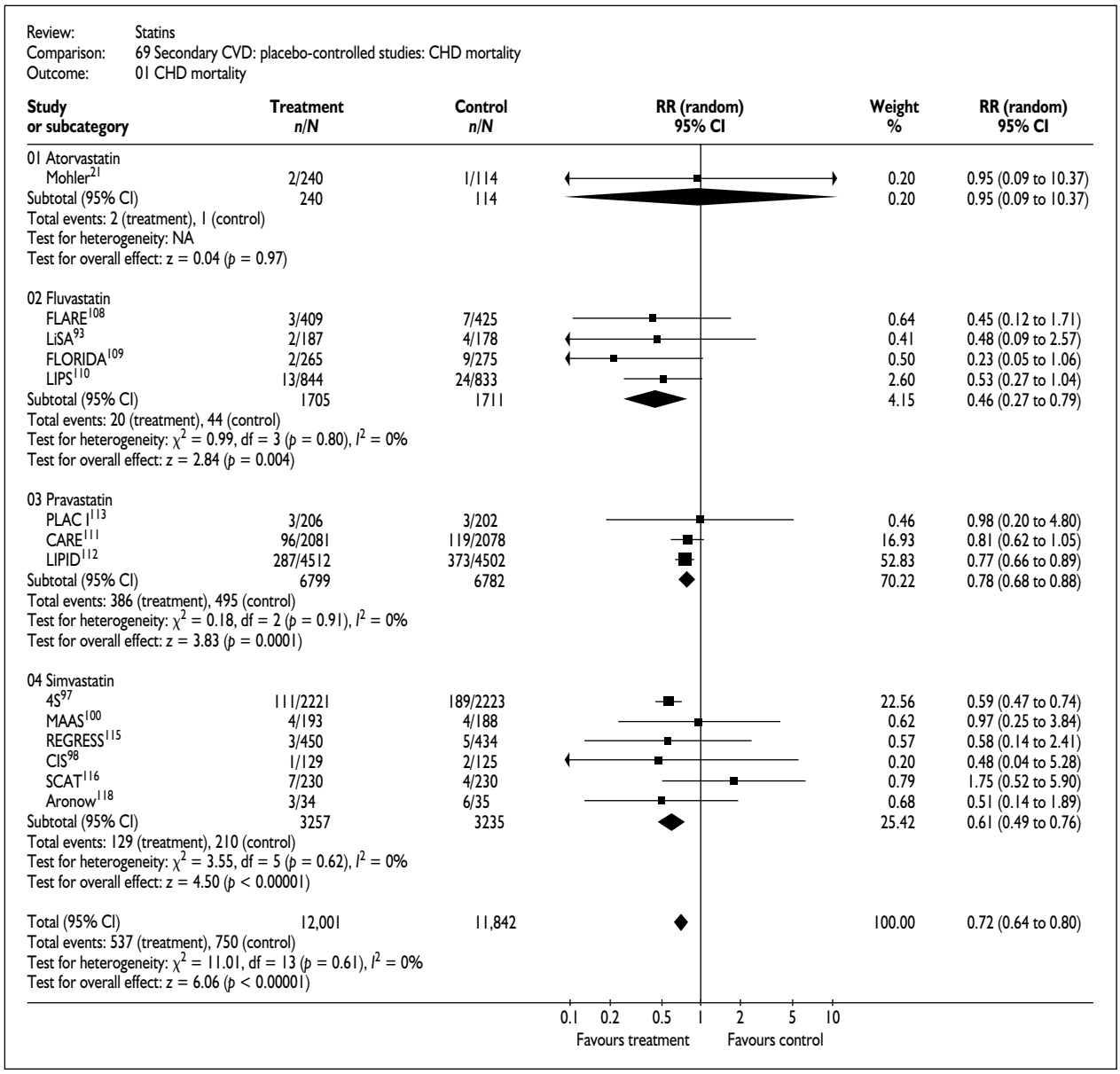

FIGURE 66 *Placebo-controlled studies: statins in secondary CVD prevention: CHD mortality*

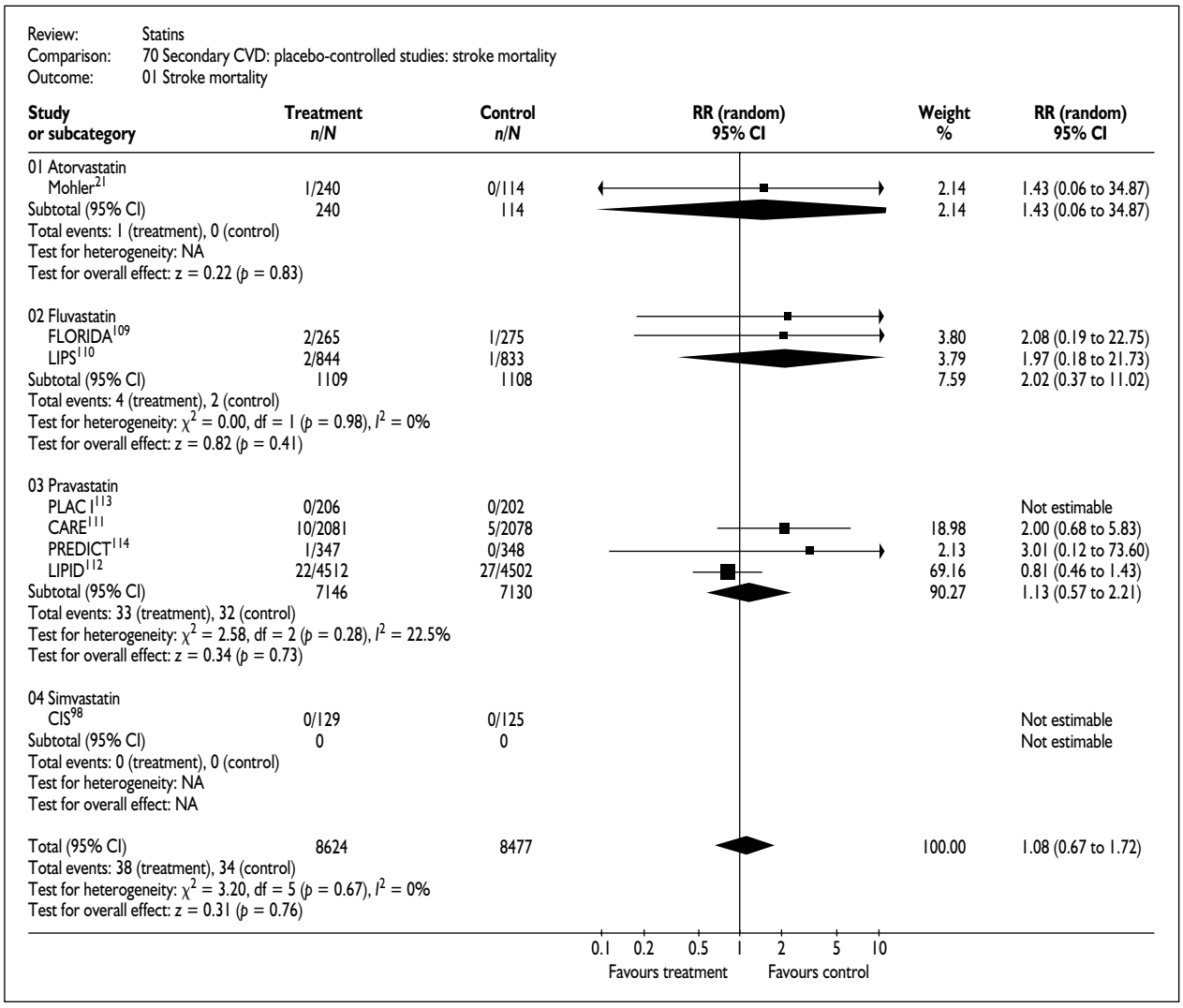

FIGURE 67 *Placebo-controlled studies: statins in secondary CVD prevention: stroke mortality*

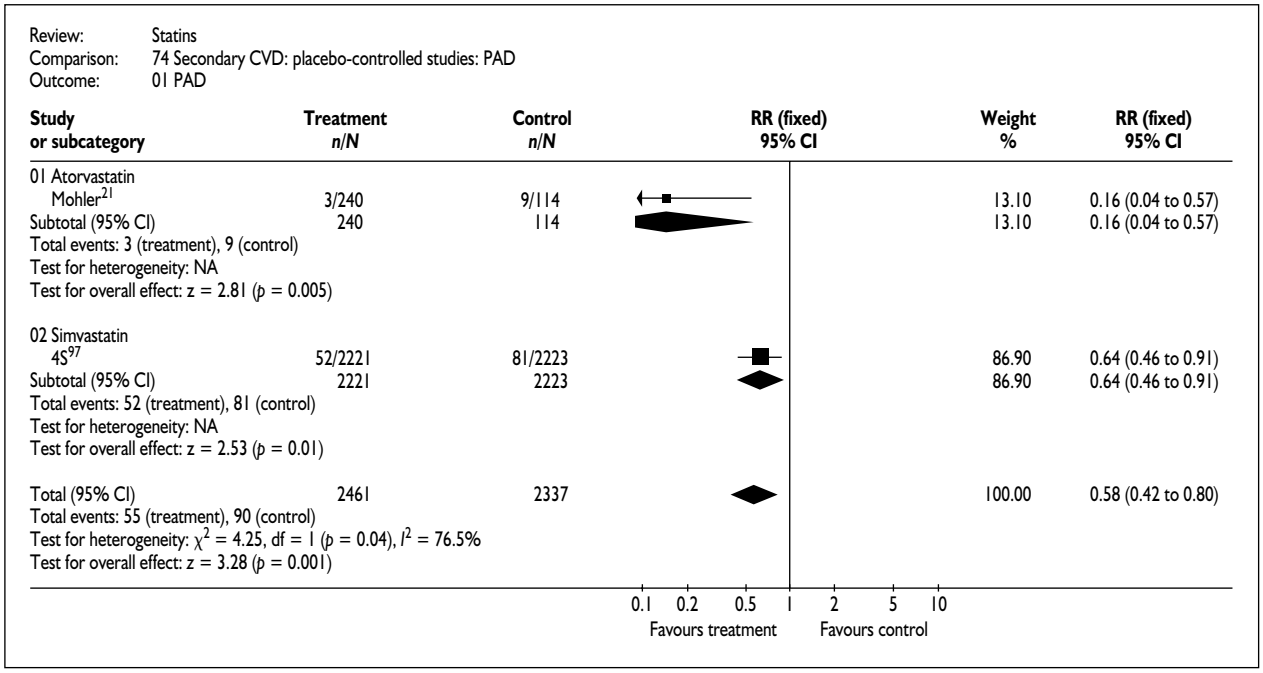

FIGURE 68 *Placebo-controlled studies: statins in secondary CVD prevention: PAD*

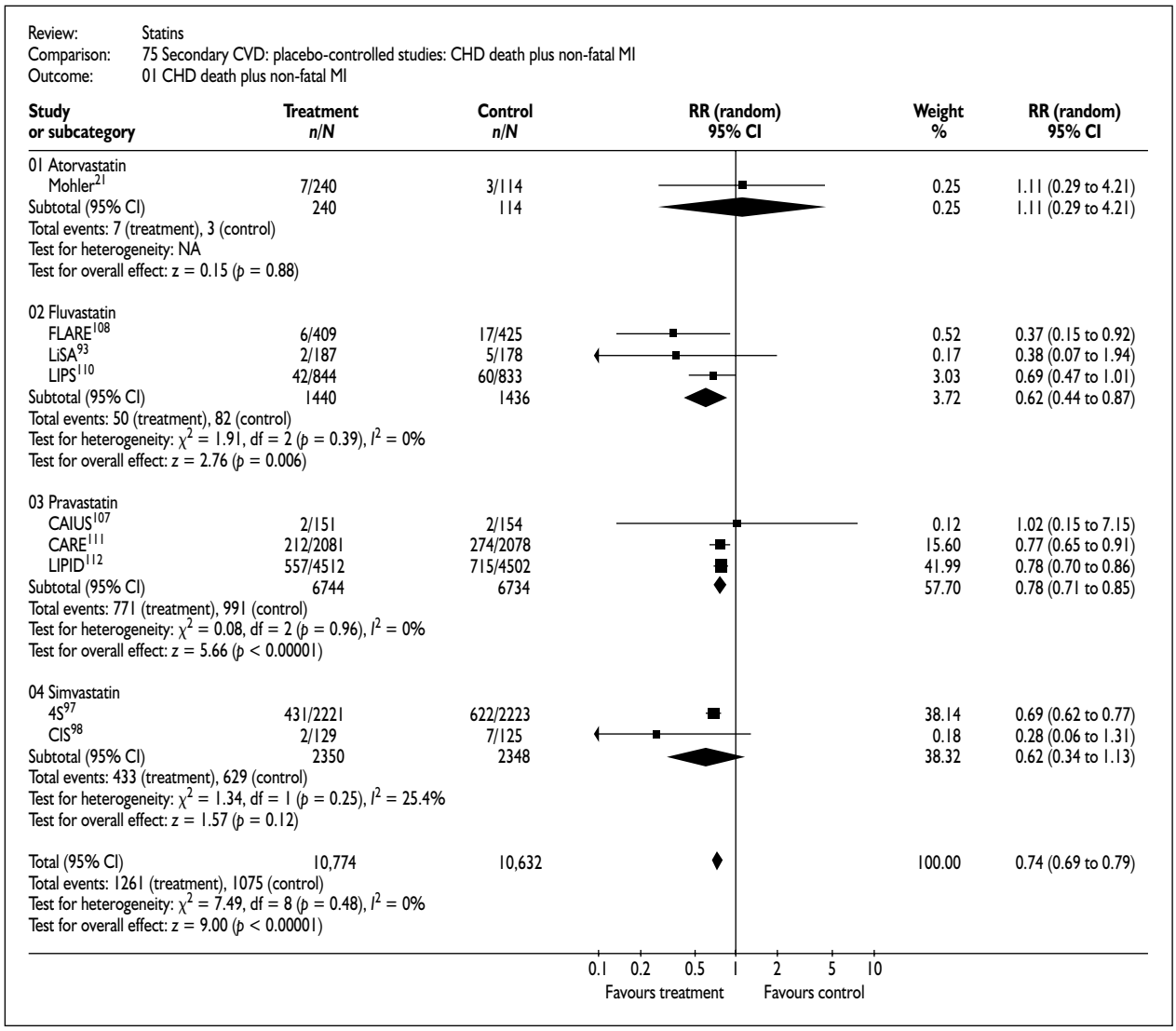

FIGURE 69 *Placebo-controlled studies: statins in secondary CVD prevention: CHD death plus non-fatal MI*

Appendix 12

Direct comparisons with other statins: data sheets

TABLE 111 *Direct comparisons with other statins: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
4522II/ 0026[125]	Primary hypercholes-terolaemia	4.9	NA	Northern Europe	Rosuvastatin 5–80 or 10–80 mg per day vs atorvastatin 10–80 mg per day	AHA Step I diet	No	1	MF	57	138/134/140
4522II/ 0028[126]	Hypercholes-terolaemia	4.9	NA	USA	Rosuvastatin 5–80 or 10–80 mg per day vs pravastatin 20–40 mg per day or simvastatin 20–80 mg per day	NCEP Step I diet	No	1	MF	59	123/116/ 118/120
3T[83]	CVD and dyslipidaemia	5.2	NA	Denmark, Finland, Iceland, Norway, Sweden	Atorvastatin 20 mg per day vs simvastatin 20 mg per day	Dietary counselling	No	1	MF	63	556/537
PROVE IT-TIMI[124]	CHD (recent ACS)	Median 2.8	NA	Australia, Canada, France, Germany, Italy, Spain, UK, USA	Atorvastatin 80 mg per day vs pravastatin 40 mg per day	NCEP diet	2 × 2 factorial design also evaluating a 10-day course of gatifloxacin (antibiotic) or placebo every month during the trial	2	MF	58	2099/2063

continued

TABLE 111 *Direct comparisons with other statins: study characteristics (cont'd)*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
REVERSAL[90]	CHD	3.9	NA	USA	Atorvastatin 80 mg per day vs pravastatin 40 mg per day	None reported	No	1.5	MF	56	328/329

[a] In most studies, many patients were, at randomisation, already receiving medications other than statins to treat conditions such as hypertension and diabetes. This column only lists medications that specifically formed a part of the study protocol.
ACS, acute coronary syndrome.

TABLE 112 *Direct comparisons with other statins: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
4522II/0026[125]	NR	NR	NR	NR	NR	NR	NR	NR
4522II/0028[126]	NR	NR	NR	NR	NR	NR	NR	NR
3T[83]	NR	NR	NR	NR	1/556	0/537	NR	NR
PROVE IT-TIMI[124]	2.2%	3.2%	NR	NR	1.0%	1.0%	8.3%	10.0%
REVERSAL[90]	1/327	1/327	NR	NR	1/327	1/327	NR	NR

Appendix 13

Comparisons with 'usual care': data sheets

TABLE 113 *Comparisons with 'usual care': study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: control arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
Atorvastatin											
ALLIANCE[88]	CHD	3.8	1.2%	USA	Atorvastatin 10–80 mg per day	No	No	4	MF	61	1217/1225
GREACE[128]	CHD	4.7	0.7%	Greece	Atorvastatin 10–80 mg per day	No	No	3	MF	59	800/800
ESTABLISH[89]	CHD (patients who had undergone emergency coronary angiography and PCI for ACS)	3.2	0%	Japan	Atorvastatin 20 mg per day	No	After PCI, all patients received aspirin 100 mg per day and ticlopidine 100 mg b.d. for >3 weeks, and cilostazol 100 mg b.d. for 4 days	0.5	MF	62	35/35
Pravastatin											
ALLHAT-LLT[127]	Moderate hypercholesterolaemia, well-controlled hypertension, with and without CHD	3.3	1.2%	USA, Puerto Rico, US Virgin Islands, Canada	Pravastatin 40 mg per day	NCEP Step I diet	Therapy designed to achieve BP <140/ <90 mmHg	4.8	MF	66	5170/5185

[a] In most studies, many patients were, at randomisation, already receiving medications other than statins to treat conditions such as hypertension and diabetes. This column only lists medications which specifically formed a part of the study protocol.

BP, blood pressure.

TABLE 114 *Comparisons with 'usual care': selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Atorvastatin								
ALLIANCE[88]	121/1217	127/1225	43/1217	61/1225	35/1217	39/1225	95/1217	155/1225
GREACE[128]	23/800	40/800	20/800	38/800	9/800	17/800	41/800	89/800
ESTABLISH[89]	0/35	1/35	0/35	0/35	NR	NR	0/35	0/35
Pravastatin								
ALLHAT-LLT[127]	631/5170	641/5185	160/5170	162/5185	209/5170	231/5185	380/5170	421/5185

Appendix 14

Assessment of clinical effectiveness: comparisons with 'usual care'

All four studies that compared a statin with 'usual care'[88,89,127,128] reported all-cause mortality; the pooled results did not demonstrate a significant effect in favour of statin treatment (*Figure 70*).

The only study to report cardiovascular mortality and stroke mortality (ALLHAT-LLT) did not demonstrate any treatment effect in either case (RR 0.99, 95% CI 0.84 to 1.15, and 0.95, 95% CI 0.65 to 1.38, respectively). All four studies reported CHD mortality, but again the combined results did not demonstrate a significant risk reduction (*Figure 71*).

None of the studies reported fatal MI. However, both studies that reported instances of non-fatal MI found that atorvastatin treatment was associated with a statistically significant risk reduction (*Figure 72*).

Two studies reported outcomes related to unstable angina; neither was statistically significant. The GREACE study found a relative risk of (undefined) unstable angina of 0.48 (95% CI 0.23 to 1.00), while the ALLIANCE study found a relative risk of hospitalisation for unstable angina of 0.72 (95% CI 0.42 to 1.23).

None of the studies reported on stable angina, TIA or peripheral vascular disease. Three studies reported total stroke; again, the combined results were not statistically significant (*Figure 73*). One study (ALLIANCE) reported the number of patients undergoing peripheral revascularisation; the relative risk was not statistically significant (RR 0.87; 95% CI 0.60 to 1.26).

None of the studies reported separately on CABG or PTCA. Although three studies presented information on total cardiac revascularisation,

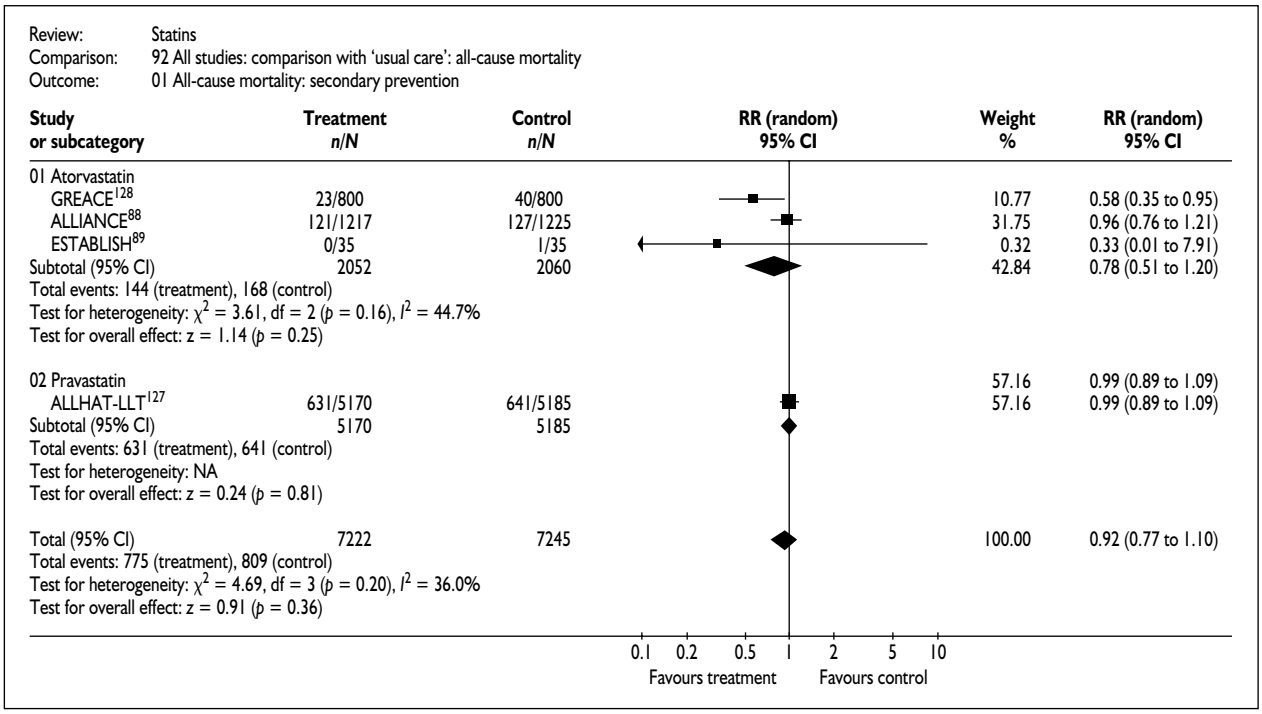

FIGURE 70 *Comparisons with usual care: all-cause mortality*

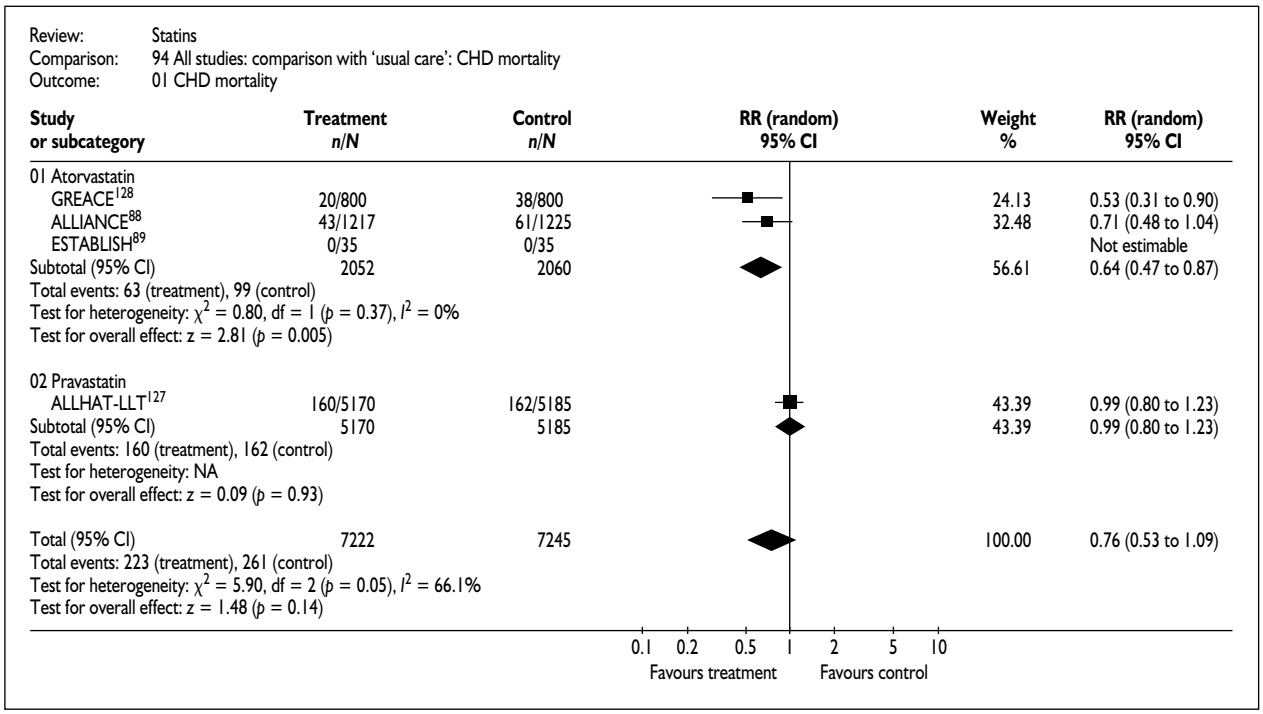

FIGURE 71 *Comparisons with usual care: CHD mortality*

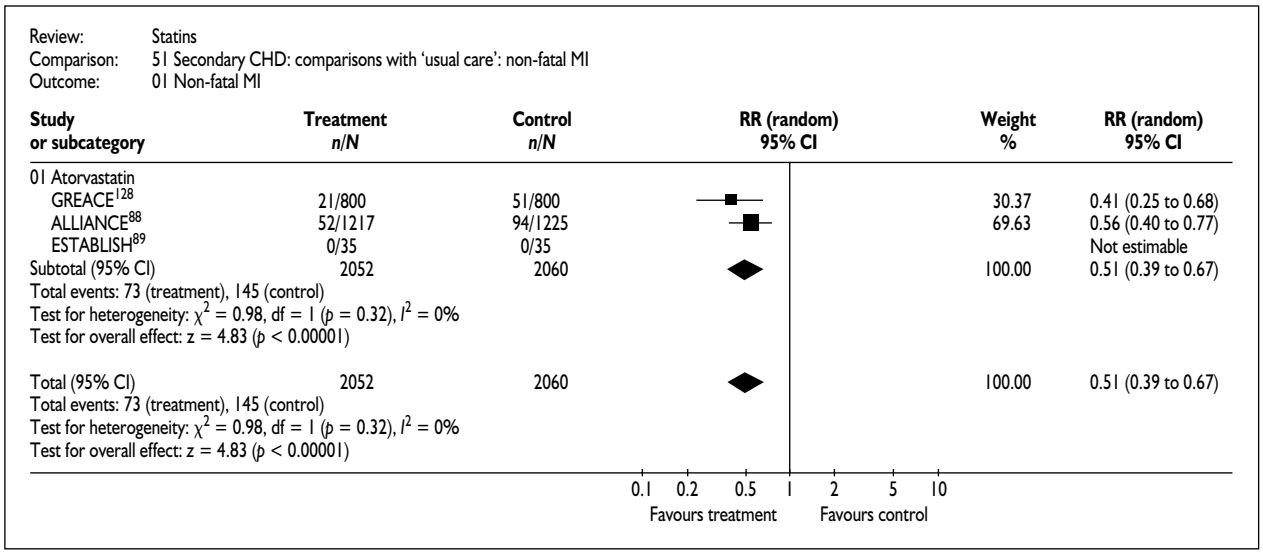

FIGURE 72 *Comparisons with usual care: effect on non-fatal MI*

again the combined result was not statistically significant (*Figure 74*).

Statin treatment was associated with a statistically significant reduction in the composite risk of CHD death or non-fatal MI (*Figure 75*).

Assessment of effectiveness in patients without CHD at baseline: comparison with usual care

The ALLHAT-LLT study presented results relating to all-cause mortality and to a composite of CHD death and non-fatal MI for the subgroup of subjects without CHD at baseline.[127] However, it should be noted that, as randomisation was not

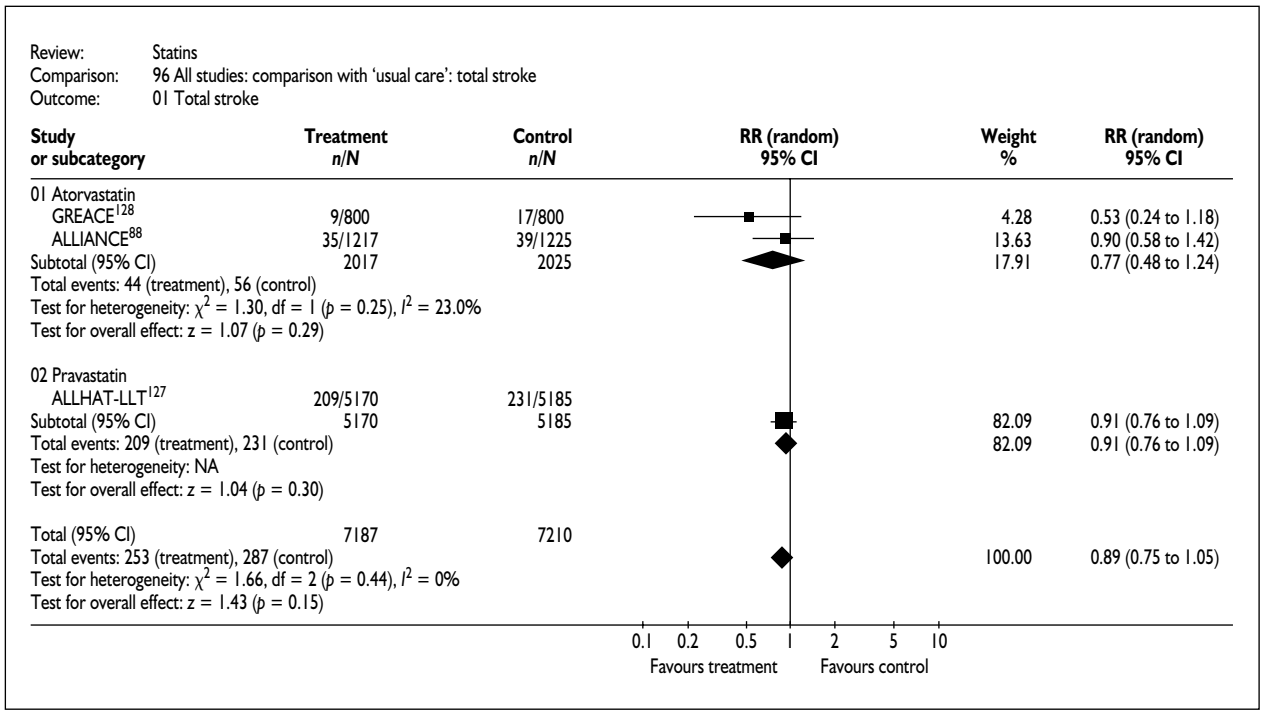

FIGURE 73 *Comparisons with usual care: effect on total stroke*

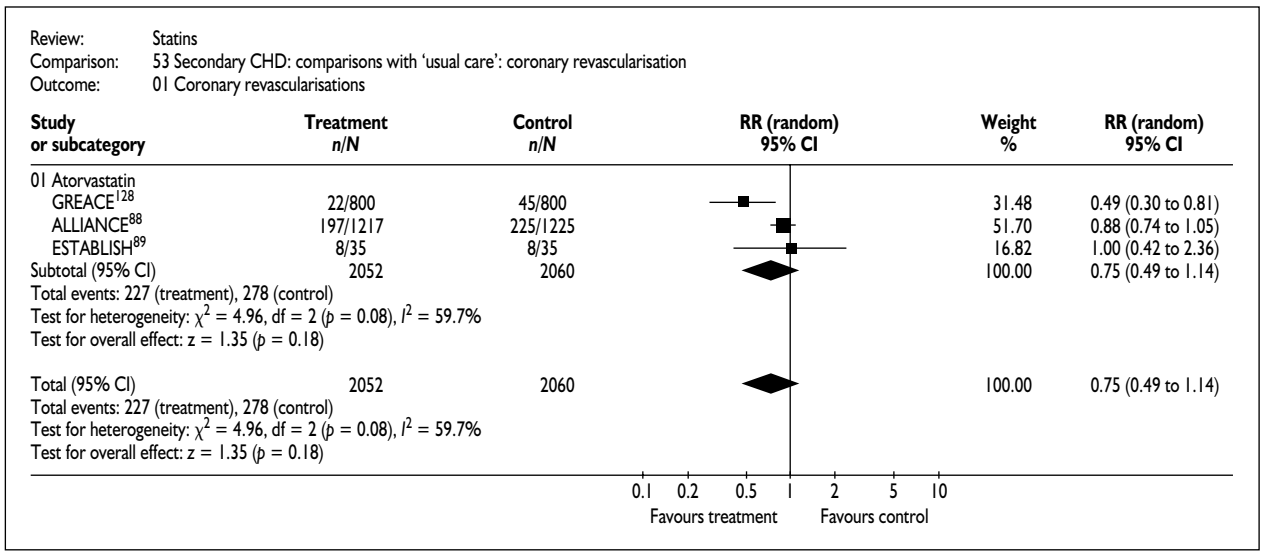

FIGURE 74 *Comparisons with usual care: effect on CABG or PTCA*

stratified by either prior CHD or baseline LDL-C, these are not true randomised comparisons. Moreover, the study does not report the number of patients in each group with each outcome, and thus it is only possible to report the relative risks calculated by the investigators, which have been subdivided by baseline LDL-C; none is statistically significant (*Table 115*).

Assessment of effectiveness in patients with CHD at baseline: comparison with usual care

The ALLIANCE, ESTABLISH AND GREACE studies were carried out in patients with baseline CHD. Their combined results are more favourable to statin therapy than the combined results of all four studies (*Table 116*), and this might be taken to

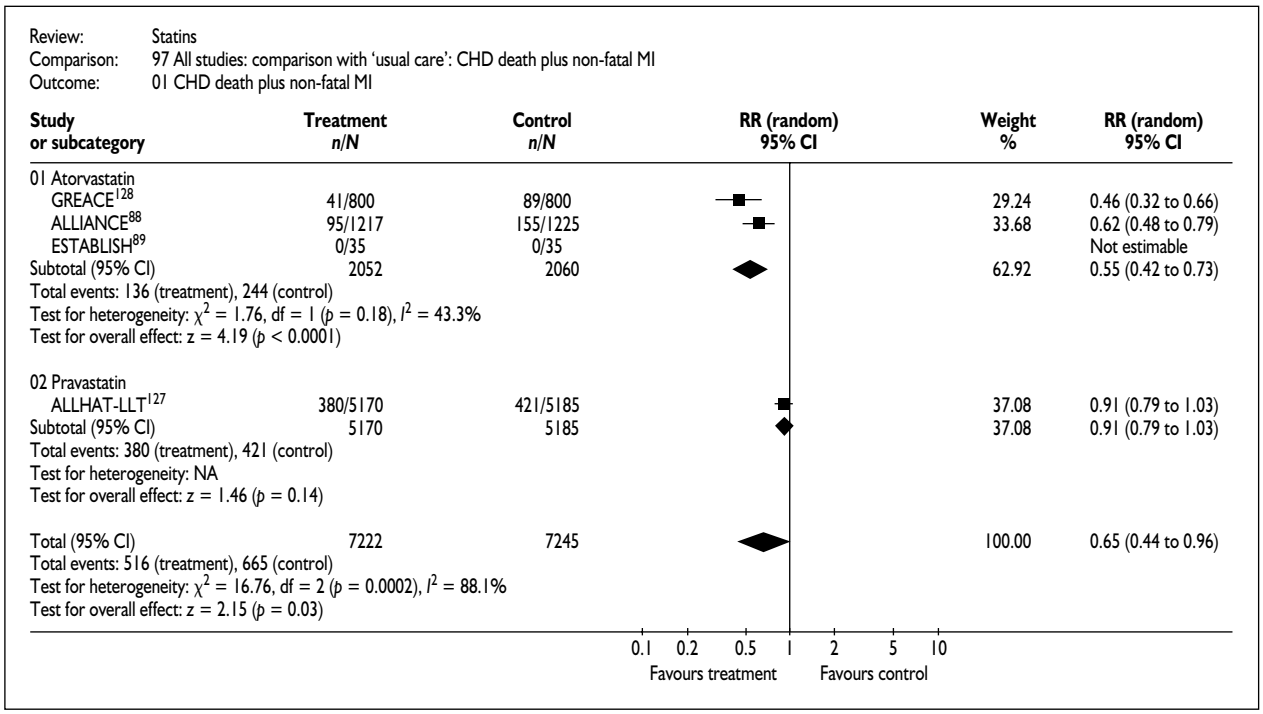

FIGURE 75 *Comparisons with usual care: effect on CHD death plus non-fatal MI*

TABLE 115 *Comparison with usual care: results from the ALLHAT-LLT study non-CHD subgroup*

Outcome	LDL-C	RR (95% CI) (investigators' calculations)
All-cause mortality	≥130 mg dl^{-1}	0.96 (0.84 to 1.11)
	<130 mg dl^{-1}	1.18 (0.90 to 1.56)
CHD death plus non-fatal MI	≥130 mg dl^{-1}	0.92 (0.77 to 1.09)
	<130 mg dl^{-1}	0.73 (0.49 to 1.07)

TABLE 116 *Comparisons with usual care by CHD status: relative risk (95% CI)*

Outcome	Mixed population	Established CHD
All-cause mortality	0.92 (0.77 to 1.10)	0.78 (0.51 to 1.20)
Cardiovascular mortality	0.99 (0.84 to 1.15)	No data
CHD mortality	0.76 (0.53 to 1.09)	0.64 (0.47 to 0.87)
Stroke mortality	0.95 (0.65 to 1.38)	No data
Total stroke	0.89 (0.75 to 1.05)	0.77 (0.48 to 1.24)
PVD (peripheral revascularisation)	0.87 (0.60 to 1.26)	0.87 (0.60 to 1.26)
Non-fatal MI	0.51 (0.39 to 0.67)	0.51 (0.39 to 0.67)
Stable angina	No data	No data
Unstable angina	0.48 (0.23 to 1.00)	0.48 (0.23 to 1.00)
Patients hospitalised for unstable angina	0.72 (0.43 to 1.23)	0.72 (0.43 to 1.23)
CABG + PTCA	0.75 (0.49 to 1.14)	0.75 (0.49 to 1.14)
CHD death plus non-fatal MI	0.65 (0.44 to 0.96)	0.55 (0.42 to 0.73)

indicate that statin therapy is more effective, relative to usual care, in patients with existing CHD than in a mixed population. However, as may be seen from *Figures 70–75*, the results of the GREACE study are consistently more favourable to statin therapy than those of the other studies and, with the removal of the ALLHAT-LLT study from the meta-analysis, the weight given to GREACE rises from 10.77% in analyses that include all four studies to 36.90%.

The ALLHAT-LLT study also reported the relative risks of all-cause mortality and of CHD death plus non-fatal MI in the subgroup with baseline CHD. Although, this time, the results were not subdivided by LDL-C, they were still not statistically significant (RR 0.95, 95% CI 0.74 to 1.23, and 1.03, 95% CI 0.77 to 1.38, respectively).[127]

Appendix 15

Comparisons with 'no statin': data sheets

TABLE 117 *Comparisons with 'no statin': study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
Atorvastatin											
Colivicchi 2002[129]	End-stage CHD	3.4	9.8%	Italy	Conventional medical treatment + atorvastatin 80 mg per day	None reported	No	1	MF	68	40/41
Pravastatin											
GISSI-P[130]	CHD (recent MI)	3.9	1.1%	Italy	Pravastatin 20 mg per day	Diet	Factorial trial also evaluating supplements of n-3 polyunsaturated fatty acids (1 g per day), vitamin E 300 mg per day, a combination of the two, or standard treatment	2	MF	60	2138/2133
Sato 2001[87]	CHD	NR; TC 5.2	2.3%	Japan	Pravastatin 20 mg per day	None reported	No	1.8	MF	60	54/66

TABLE 118 *Comparisons with 'no statin': results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Atorvastatin								
Colivicchi 2002[129]	NR	NR	3/40	4/41	NR	NR	7/40	11/41
Pravastatin								
GISSI-P[130]	72/2138	88/2133	31/2138	49/2133	20/2138	19/2133	67/2138	83/2133
Sato 2001[87]	1/54	4/66	1/54	3/66	0/54	1/66	1/54	3/66

Appendix 16

Assessment of clinical effectiveness: comparisons with 'no statin'

Only one study that compared a statin with 'no statin' (GISSI-P) reported both all-cause and cardiovascular mortality: low-dose pravastatin did not have a statistically significant effect on either outcome (RR 0.82, 95% CI 0.60 to 1.11, and 0.80, 95% CI 0.56 to 1.14, respectively).[130] However, the combined data from the two studies that provided data on CHD mortality[129,130] indicated that statin therapy was associated with a reduced risk of an event (*Figure 76*).

Two studies reported the number of patients suffering any stroke; their combined results did not indicate any benefit from statin therapy (*Figure 77*). One of these studies (GISSI-P) also reported fatal and non-fatal strokes separately; again, no benefit was demonstrated from statin therapy (RR 1.00, 95% CI 0.25 to 3.98, and 1.06, 95% CI 0.53 to 2.15, respectively).

GISSI-P was also the only study to report fatal MI; again, the result was not statistically significant (RR 0.60, 95% CI 0.22 to 1.64).[130] The MIs reported in another study[87] appeared implicitly to have been fatal but, as this was not specified, they have not been included in the analysis. Although two studies reported non-fatal MI, the results were not significant, even when combined (*Figure 78*).

None of the studies reported on angina (either stable or unstable angina), TIA or PVD.

Only one study[130] provided separate data on CABG and PTCA, with relative risks of 0.88 (95% CI 0.68 to 1.14) and 0.90 (0.63 to 1.29), respectively. Although two studies[87,130] provided data relating to total cardiac revascularisations, again the pooled data were not statistically significant (*Figure 79*).

All three studies provided data relating to a composite end-point of CHD death plus non-fatal MI, but again the results were not statistically significant (*Figure 80*).

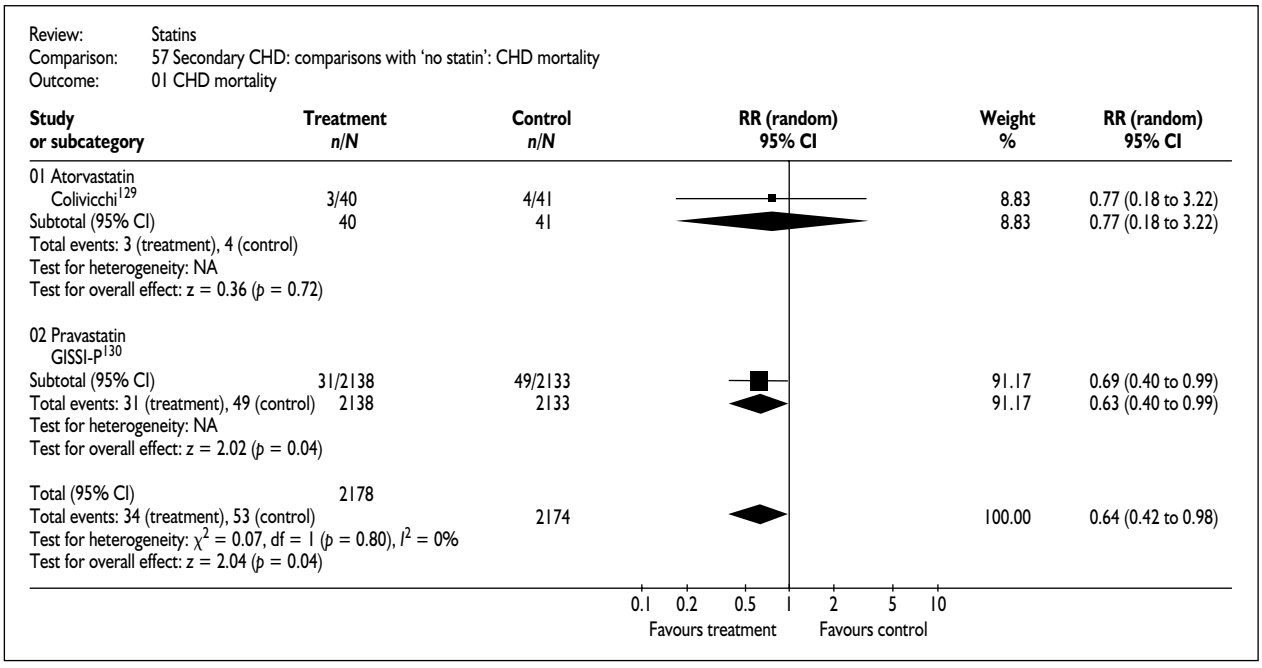

FIGURE 76 *Comparisons with 'no statin': effect on CHD mortality*

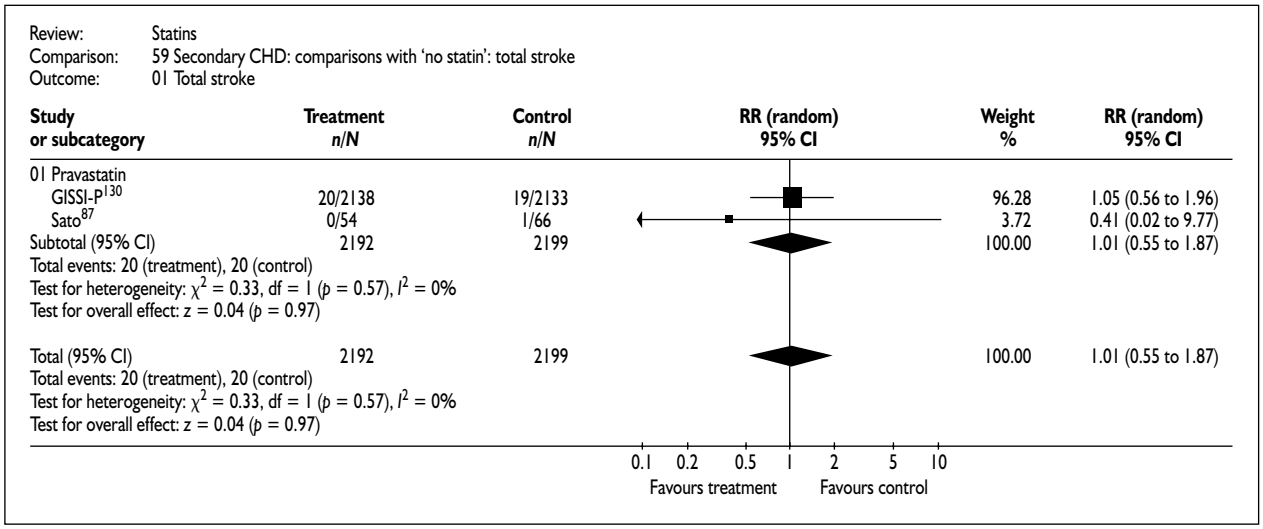

FIGURE 77 *Comparisons with 'no statin': effect on total stroke*

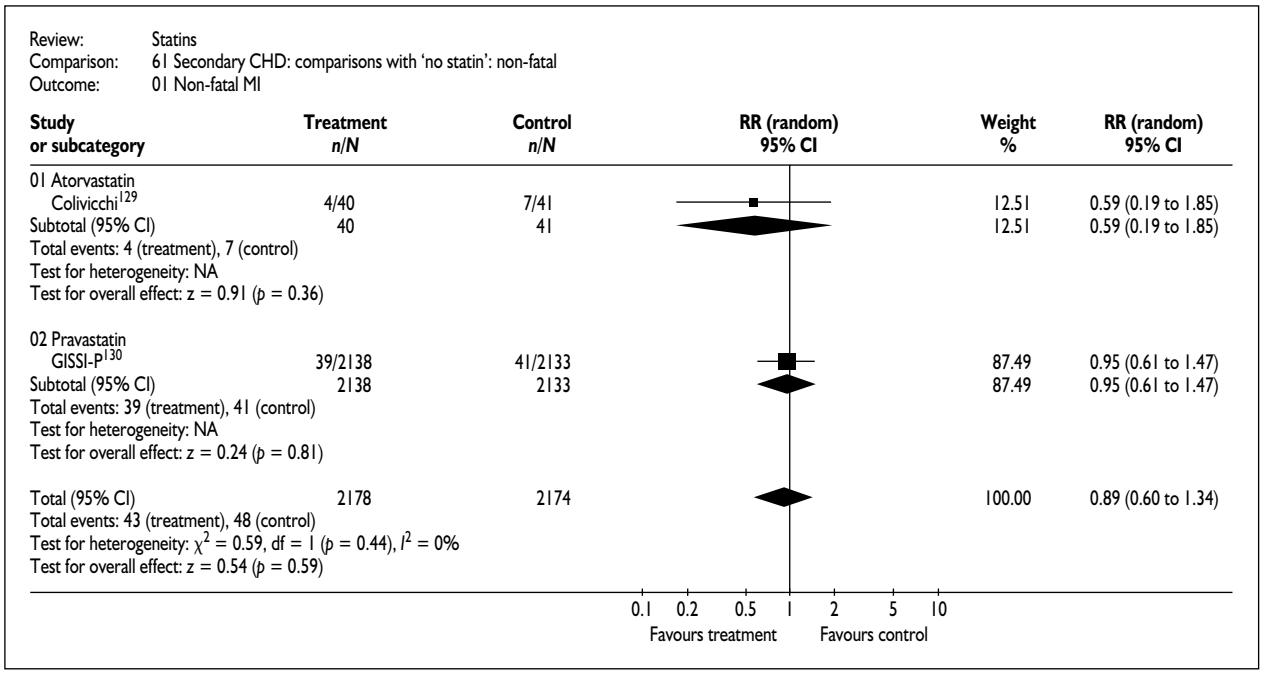

FIGURE 78 *Comparisons with 'no statin': effect on non-fatal MI*

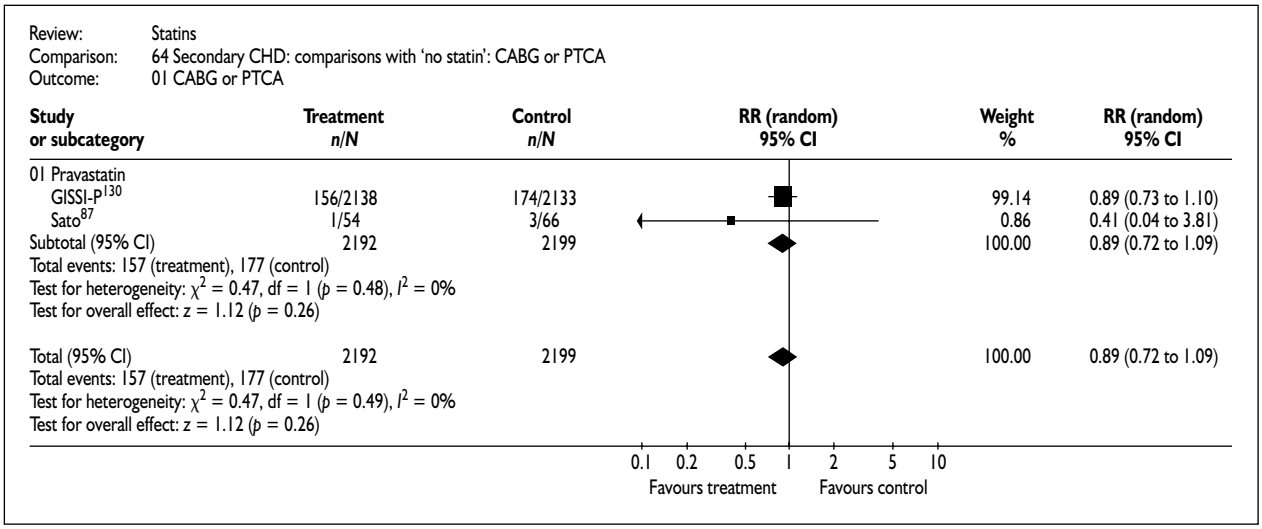

FIGURE 79 *Comparisons with 'no statin': effect on CABG or PTCA*

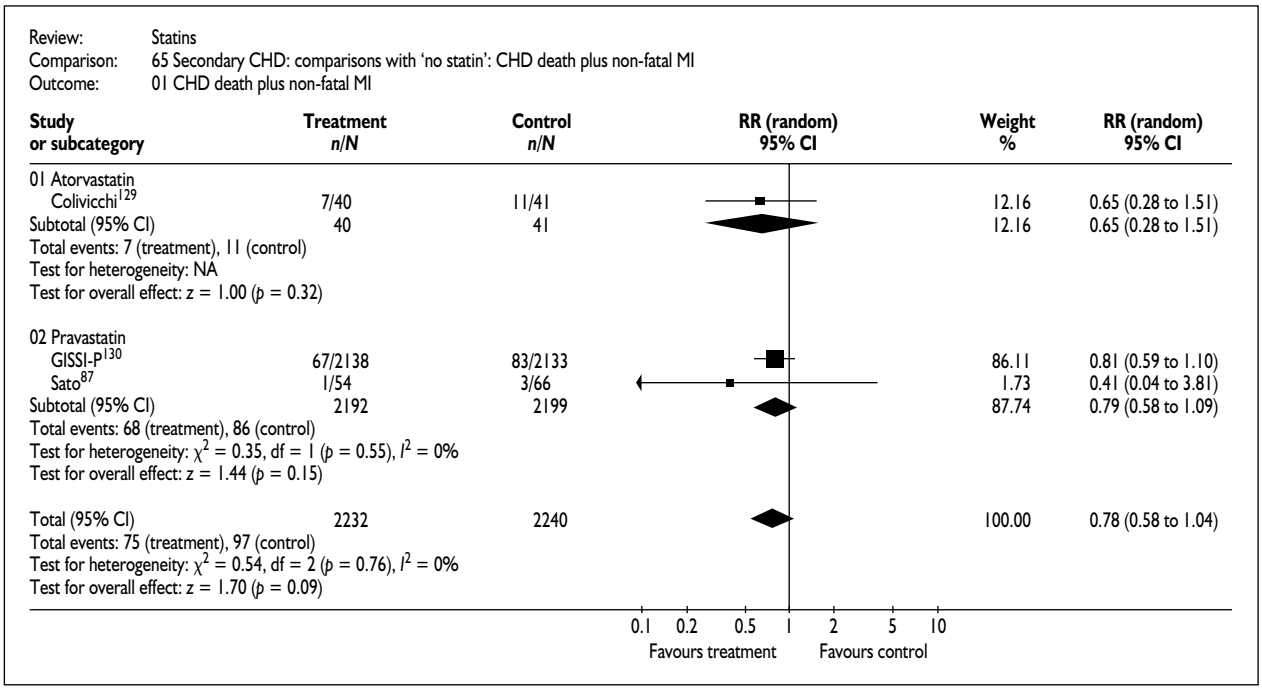

FIGURE 80 *Comparisons with 'no statin': effect on CHD death plus non-fatal MI*

Appendix 17

Dose comparisons: data sheets

TABLE 119 *Dose comparisons: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Comparator	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups[a]	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
A-to-Z[131]	ACS	2.9	NA	41 countries in Europe, Australia, New Zealand, North and South America, South Africa and Asia[399]	Simvastatin 40 mg per day for 30 days, then 80 mg per day	Placebo for 4 months followed by simvastatin 20 mg per day	AHA Step I diet	No	2	MF	61 (median)	2265/2232
PATE[132]	With and without previous CVD	4.3	NA	Japan	Pravastatin 5 mg per day	Pravastatin 10–20 mg per day	None reported	No	3.9	MF	NR	331/334

[a] In most studies, many patients were, at randomisation, already receiving medications other than statins to treat conditions such as hypertension and diabetes. This column only lists medications that specifically formed a part of the study protocol.

TABLE 120 *Dose comparisons: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
A-to-Z[131]	104/2265	130/2232	NR	NR	28/2265	35/2232	NR	NR
PATE[132]	14/331	20/334	NR	NR	NR	NR	NR	NR

Appendix 18

Assessment of clinical effectiveness: dose comparisons

In the A-to-Z study, the use of an aggressive dose of simvastatin was associated with a reduced risk of cardiovascular mortality; other reported outcomes were not statistically significant[131] (for details see *Table 121*).

The PATE study showed no statistically significant results in relation to any clinical end-point, even when all fatal and non-fatal cardiovascular events were pooled (RR of event in low-dose group compared with standard dose 1.44, 95% CI 0.92 to 2.25). The results for the subgroups with and without baseline CVD were therefore not statistically significant.[132]

TABLE 121 *Dose comparisons: aggressive versus lower dose simvastatin in patients with CHD*[131]

Outcome	RR	95% CI
All-cause mortality	0.79	0.61 to 1.01
Cardiovascular mortality	0.75	0.57 to 0.99
Total stroke	0.79	0.48 to 1.29
Total MI	0.96	0.77 to 1.19
Coronary revascularisations	0.95	0.74 to 1.21

Appendix 19

Subgroup data

Women

TABLE 122 *Placebo-controlled studies: results by gender – meta-analysis*

Outcome	Men		Women	
	Studies providing data	**RR (95% CI)**	**Studies providing data**	**RR (95% CI)**
All-cause mortality	KAPS, REGRESS, WOSCOPS, 4S	0.70 (0.61 to 0.82)	4S	1.16 (0.69 to 1.95)
Cardiovascular mortality	WOSCOPS	0.68 (0.48 to 0.98)	No data	
CHD mortality	CARE, REGRESS, WOSCOPS, 4S, CIS	0.66 (0.56 to 0.79)	4S, CARE	0.83 (0.49 to 1.38)
Stroke mortality	WOSCOPS	1.50 (0.42 to 5.30)	No data	
Non-fatal stroke	WOSCOPS	0.85 (0.56 to 1.29)	No data	
Total stroke	CARE, KAPS, PROSPER	0.84 (0.66 to 1.08)	CARE, PLAC I, PROSPER	0.76 (0.50 to 1.13)
TIA	PROSPER	0.72 (0.48 to 1.09)	PROSPER	0.80 (0.53 to 1.21)
PVD	No data		No data	
Fatal MI	CARE, KAPS, REGRESS	0.70 (0.42 to 1.16)	CARE	0.17 (0.02 to 1.39)
Non-fatal MI	CARE, KAPS, WOSCOPS, 4S, CIS	0.73 (0.66 to 0.80)	4S, CARE	0.62 (0.47 to 0.83)
Stable angina	No data		No data	
Unstable angina (unspecified)	CARE	0.88 (0.76 to 1.03)	CARE	0.87 (0.64 to 1.20)
Hospitalisation for unstable angina	CIS	0.97 (0.38 to 2.50)	No data	
CABG	CARE, KAPS	0.77 (0.63 to 0.95)	CARE, PLAC I	0.67 (0.37 to 1.22)
PTCA	CARE, KAPS, REGRESS	0.60 (0.32 to 1.11)	CARE, PLAC I	0.55 (0.33 to 0.93)
CABG + PTCA	CARE, WOSCOPS, 4S, CIS	0.72 (0.65 to 0.81)	4S, CARE	0.51 (0.37 to 0.70)
CHD death plus non-fatal MI	ASCOT-LLA, CARE, LIPID, PROSPER, WOSCOPS	0.70 (0.63 to 0.78)	4S, ASCOT-LLA, CARE, LIPID, PROSPER	0.82 (0.69 to 0.96)
CHD death, non-fatal MI or coronary revascularisation	CARE	0.81 (0.72 to 0.92)	CARE	0.58 (0.42 to 0.81)

TABLE 123 *Placebo-controlled studies: the LIPID and LIPS studies – results by gender*

Outcome	LIPID % RR reduction[a]		LIPS RR[a]	
	Men	Women	Men	Women
All-cause mortality	25 (15 to 34)	11 (–18 to 33)	NR	
CHD mortality	25 (12 to 37)	18 (–24 to 46)	NR	
Total MI	31 (20 to 41)	16 (–19 to 41)	NR	
Hospital admission for unstable angina	16 (7 to 23)	–9 (–33 to 10)	NR	
Total stroke	25 (6 to 40)	–28 (–114 to 23)	NR	
Coronary revascularisation	18 (8 to 28)	25 (–1 to 44)	NR	
CHD death + non-fatal MI	Full data available and incorporated into meta-analysis		NR	
CHD death, non-fatal MI or coronary revascularisation	22 (15 to 29)	17 (–2 to 33)	0.79 (0.64 to 0.98)	0.66 (0.38 to 1.14)

[a] Investigators' calculations.

People with diabetes

TABLE 124 *Placebo-controlled studies: results in people with and without diabetes*

Outcome	People with diabetes		People without diabetes	
	Studies providing data	**RR (95% CI)**	**Studies providing data**	**RR (95% CI)**
All-cause mortality	CARDS, LIPID, 4S	0.72 (0.56 to 0.93)	LIPID, 4S	0.73 (0.60 to 0.87)
Cardiovascular mortality	CARDS	0.67 (0.40 to 1.10)	No data	
CHD mortality	CARDS, CARE, 4S	0.84 (0.61 to 1.17)	CARE, 4S	0.66 (0.50 to 0.87)
Stroke mortality	CARDS	0.20 (0.02 to 1.69)	No data	
Non-fatal stroke	CARDS	0.66 (0.38 to 1.15)	No data	
Total stroke	CARDS, CARE, 4S[a]	0.63 (0.44 to 0.91)	CARE, 4S[a]	0.66 (0.51 to 0.85)
TIA	No data		No data	
PVD	No data		No data	
Fatal MI	CARDS, CARE	0.46 (0.25 to 0.83)	CARE	0.71 (0.38 to 1.31)
Non-fatal MI	CARDS, DALI, CARE, 4S	0.54 (0.32 to 0.91)	CARE, 4S	0.70 (0.57 to 0.85)
Stable angina	No data		No data	
Unstable angina (unspecified)	CARDS, CARE	0.88 (0.64 to 1.20)	CARE	0.89 (0.77 to 1.04)
Hospitalisation for angina	No data		No data	
CABG	CARE	0.71 (0.46 to 1.10)	CARE	0.78 (0.62 to 0.97)
PTCA	CARE	0.70 (0.51 to 0.98)	CARE	0.79 (0.65 to 0.97)
CABG + PTCA	CARDS, 4S	0.70 (0.47 to 1.03)	4S	0.66 (0.56 to 76)
CHD death plus non-fatal MI	ASCOT-LLA, CARE, 4S	0.73 (0.53 to 1.01)	ASCOT-LLA, CARE	0.67 (0.51 to 0.90)
CHD death, non-fatal MI or coronary revascularisation	LIPS, CARE	0.71 (0.54 to 0.94)	LIPS, CARE	0.81 (0.73 to 0.90)

[a] "Cerebrovascular disease event".

TABLE 125 *HPS: results in people with diabetes*

Outcome	HPS Event rate ratio[a]	
	With diabetes	**Without diabetes**
All-cause mortality	NR	NR
CHD mortality	0.80 (0.66 to 0.96)	NR
Total MI	NR	NR
First non-fatal MI	0.67 (0.50 to 0.80)	NR
Hospital admission for unstable angina	NR	NR
Total stroke	0.76 (0.61 to 0.94)	0.74 (0.64 to 0.86)
Coronary revascularisation	NR	NR
Any revascularisation (includes non-coronary)	0.83 (0.70 to 0.97)	0.74 (0.67 to 0.82)
Peripheral macrovascular complications	Event rate ratio NR but $p = 0.03$	NR
CHD death + non-fatal MI	0.73 (0.62 to 0.85)	0.73 (0.66 to 0.81)
CHD death, non-fatal MI or coronary revascularisation	NR	NR

[a] Investigators' calculations.

Elderly patients

TABLE 126 *Placebo-controlled studies: results by age group*

	People aged <65 years		People aged >65 years	
Outcome	**Studies providing data**	**RR (95% CI)**	**Studies providing data**	**RR (95% CI)**
All-cause mortality	4S	0.73 (0.58 to 0.91)	PROSPER, 4S	0.83 (0.58 to 1.19)
Cardiovascular mortality	No data		PROSPER	0.87 (0.69 to 1.08)
CHD mortality	CARE, 4S	0.80 (0.42 to 1.49)	CARE, PROSPER, 4S	0.66 (0.53 to 0.82)
Stroke mortality	No data		PROSPER	1.58 (0.81 to 3.09)
Non-fatal stroke	No data		PROSPER	0.98 (0.76 to 1.26)
Total stroke	CARE	0.80 (0.48 to 1.35)	CARE, PLAC I	0.61 (0.39 to 0.95)
TIA	No data		PROSPER	0.76 (0.57 to 1.02)
PVD	No data		No data	
Fatal MI	No data		No data	
Non-fatal MI	CARE, 4S	0.72 (0.64 to 0.82)	CARE, PROSPER, 4S	0.80 (0.69 to 0.93)
Stable angina	No data		No data	
Unstable angina (unspecified)	CARE	0.81 (0.69 to 0.96)	CARE	1.08 (0.83 to 1.39)
Hospitalisation for angina	No data		No data	
CABG	CARE	0.83 (0.66 to 1.06)	CARE, PLAC I	0.60 (0.42 to 0.85)
PTCA	CARE	0.75 (0.61 to 0.93)	CARE, PLAC I	0.94 (0.62 to 1.42)
CABG + PTCA	CARE, 4S	0.72 (0.63 to 0.82)	CARE, PROSPER, 4S	0.70 (0.58 to 0.84)
CHD death plus non-fatal MI	CARE	0.87 (0.71 to 1.08)	CARE, PROSPER	0.74 (0.56 to 0.97)
CHD death, non-fatal MI or coronary revascularisation	CARE	0.82 (0.72 to 0.94)	CARE	0.70 (0.57 to 0.85)

Appendix 20

Cardiac transplant patients: data sheets

TABLE 127 *Cardiac transplant patients: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: control arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
Fluvastatin											
O'Rourke 2004[139]	Cardiac transplant recipients with hyperlipidaemia	4.4	0%	England	Fluvastatin 40 mg per day vs placebo	AHA Step I diet	Immunosuppressive treatment (Neoral ciclosporin and azathioprine)	1	MF	52	52/27
Pravastatin											
Mehra 2002[94]	Cardiac transplant recipients	4.2	NA	USA	Pravastatin 20 mg per day vs simvastatin 10 mg per day	Dietary counselling (low-fat diet)	Immunosuppressive treatment (ciclosporin, azathioprine and corticosteroids)	≥1	MF	53	24/26
Kobashigawa 1995[140]	Cardiac transplant recipients	NR; TC 4.6	0%	USA	Pravastatin 20–40 mg per day vs 'usual care'	Dietary counselling (low-fat, low-cholesterol diet)	Immunosuppressive treatment (ciclosporin, prednisone and azathioprine)	1	MF	52	47/50
Simvastatin											
Wenke 1997[141]	Cardiac transplant recipients	2.8	NR	Germany	Simvastatin 5–20 mg per day (mean dose 10 mg per day) vs 'usual care'	AHA Step II diet	Immunosuppressive treatment (ciclosporin A, azathioprine and prednisolone)	4	MF	48	35/37

TABLE 128 *Cardiac transplant patients: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Fluvastatin								
O'Rourke 2004[139]	2/52	0/27	NR	NR	NR	NR	NR	NR
Pravastatin								
Mehra 2002[94]	2/24	2/26	NR	NR	NR	NR	NR	NR
Kobashigawa 1995[140]	3/47	10/50	NR	NR	NR	NR	NR	NR
Simvastatin								
Wenke 1997[141]	4/35	11/37	NR	NR	NR	NR	NR	NR

Appendix 21

Cardiac transplant patients: results

The only clinical outcomes reported in the placebo-controlled study of statins in cardiac transplant patients were all-cause mortality and suspected rejection episodes; in neither case was there a statistically significant difference between treatment groups (*Table 129*).

The head-to-head statin comparison again only reported mortality data, and again found no statistically significant difference between treatment groups in terms of clinical outcomes (*Table 130*).

The studies that compared statins with no statin treatment found no statistically significant difference between treatment groups in terms of clinical outcomes (*Table 131*).

TABLE 129 *Statins in cardiac transplant patients: placebo-controlled trial*[139]

Outcome	No. in each group with event	RR (95% CI)
All-cause mortality	Fluvastatin: 2/52 Placebo: 0/27	2.64 (0.13 to 53.14)
Suspected rejection episode	Fluvastatin: 3/52 Placebo: 0/27	3.70 (0.20 to 69.09)

TABLE 130 *Statins in cardiac transplant patients: direct comparison*[94]

Outcome	No. in each group with event	RR (95% CI)
All-cause mortality	Pravastatin: 2/24 Simvastatin: 2/26	1.08 (0.17 to 7.10)
CVD mortality	Pravastatin: 1/24 Simvastatin: 1/26	1.08 (0.07 to 16.38)
CHD mortality	Pravastatin: 1/24 Simvastatin: 0/26	3.24 (0.14 to 75.91)
Stroke mortality	Pravastatin: 0/24 Simvastatin: 1/26	0.36 (0.02 to 8.43)

TABLE 131 *Statins in transplant patients: effect on all-cause mortality – comparisons with no statin*

Study	No. in each group with event	RR (95% CI)
Kobashigawa 1995[140]	Pravastatin 20–40 mg per day: 3/47 Control: 10/50	0.32 (0.09 to 1.09)
Wenke 1997[141]	Simvastatin 5–20 mg per day: 4/35 Control: 11/37	0.38 (0.13 to 1.10)

Appendix 22

Renal transplant patients: data sheets

TABLE 132 *Renal transplant patients: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: placebo arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
ALERT[142]	Renal transplant recipients with mild to moderate hypercholes-terolaemia	4.1	1.0%	Belgium, Canada, Denmark, Finland, Germany, Norway, Sweden, Switzerland, UK	Fluvastatin 40–80 mg per day	None reported	No	5.1	MF	50	1050/1052

TABLE 133 *Renal transplant patients: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
ALERT[142]	143/1050	138/1052	36/1050	54/1052	74[a]/1050	63[a]/1052	70/1050	104/1052

[a] Fatal or non-fatal stroke, TIA, reversible ischaemic neurological deficit, subarachnoid haemorrhage.

Appendix 23

Renal transplant patients: results

The results of the ALERT study are summarised in *Table 134*.

TABLE 134 *Statins in renal transplant recipients: results of the ALERT study*[142]

Outcome	RR	95% CI
All-cause mortality	1.04	0.84 to 1.29
Cardiovascular mortality	0.91	0.66 to 1.25
CHD mortality	0.67	0.44 to 1.01
Cerebrovascular mortality	1.22	0.60 to 2.46
Total cerebrovascular events	1.18	0.85 to 1.63
Non-fatal MI	0.70	0.48 to 1.01
CABG	1.04	0.60 to 1.82
PTCA	0.79	0.49 to 1.27
CHD death plus non-fatal MI	0.67	0.50 to 0.90
CHD death, non-fatal MI or coronary revascularisation	0.84	0.66 to 1.06

Appendix 24

People with familial hypercholesterolaemia: data sheets

TABLE 135 *People with familial hypercholesterolaemia: study characteristics*

Study	Patient group	Mean baseline LDL-C (mmol l^{-1})	Crude annual CHD mortality: control arm	Country of study	Intervention	Lifestyle interventions recommended in both treatment groups	Additional medication given to both treatment groups	Follow-up (years)	Gender	Mean age (years)	No. treated/ no. controls
ASAP[85]	Heterozygous familial hypercholesterolaemia	8.2	NA	The Netherlands	Atorvastatin 80 mg per day vs simvastatin 40 mg per day	None reported	No	2	MF	48	160/165

TABLE 136 *People with familial hypercholesterolaemia: selected results*

Study	All-cause mortality		CHD mortality		Total stroke		CHD death + non-fatal MI	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
ASAP[85]	1/160	2/160	1/160	1/160	NR	NR	NR	NR

Appendix 25

People with familial hypercholesterolaemia: results

The results of the ASAP study are summarised in *Table 137*.

TABLE 137 *Statins in patients with heterozygous familial hypercholesterolaemia: direct comparison*[85]

Outcome	Number in each group with event	RR (95% CI)
All-cause mortality	Atorvastatin 80 mg per day: 1/160 Simvastatin 40 mg per day: 2/160	0.50 (0.05 to 5.46)
CVD mortality	Atorvastatin 80 mg per day: 1/160 Simvastatin 40 mg per day: 1/160	1.00 (0.06 to 15.85)
CHD mortality	Atorvastatin 80 mg per day: 1/160 Simvastatin 40 mg per day: 1/160	1.00 (0.06 to15.85)

Appendix 26

Ethnic minorities

The results of the subgroup analyses of the ALLHAT-LLT study are summarised in *Table 138*.

TABLE 138 *ALLHAT-LLT study: relative risk of event in black and non-black subgroups (95% CI) (investigators' calculations)*[127]

Outcome	Black	Non-black
All-cause mortality	1.01 (0.85 to 1.19)	0.98 (0.85 to 1.13)
CHD death plus non-fatal MI	0.73 (0.58 to 0.92)	1.02 (0.86 to 1.21)

Appendix 27

Drug toxicity: data from studies with non-statin comparator arms

TABLE 139 *Atorvastatin: toxicity*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)	Withdrawals/discontinuation of study medication due to adverse events
ALLIANCE[88]	10–80	No. of patients with event Atorvastatin (n = 1217) / Control (n = 1225) SAE 487 / 515 Cancer 67 / 77	In the atorvastatin arm, 7 patients discontinued as a result of an SAE, and 68 as a result of a non-serious AE. Comparable data were not available for the control arm
ASCOT-LLA[102]	10	Number of SAEs said not to differ between treatment groups, but no details given, except for the following: No. of patients with event Atorvastatin (n = 5168) / Placebo (n = 5137) Cancer death 81 / 87 Development of diabetes mellitus 153 / 134 Development of renal impairment 31 / 24	NR
CARDS[103]	10	No. of patients with event Atorvastatin (n = 1428) / Placebo (n = 1410) Non-CVD death 41 / 48 Cancer/neoplasm 139 / 148 Breast cancer/neoplasm 16 / 15 Accident/suicide/violent death 4 / 3	Any AE Atorvastatin: 122/1428 Placebo: 145/1410 Muscle-related AEs Atorvastatin: 7/1428 Placebo: 9/1410
DALI[86]	10 and 80	No. of patients with event Atorvastatin: 10 mg / 80 mg; Placebo GI disorder 11 / 9 / 8 Mood disturbances 1 / 3 / 3 Headache 3 / 3 / 3 Respiratory tract disorder 4 / 4 / 6 Urinary tract disorder 13 / 9 / 10 Malaise 11 / 1 / 6 Other 19 / 15 / 6	Any AE Atorvastatin 10 mg: 1/73 Atorvastatin 80 mg: 1/72 Placebo: 5/72
GREACE[128]	10–80	No. of patients with event Atorvastatin (n = 800) / Usual care (n = 800) Any side-effect 9 / 30	Atorvastatin: 6/800 Usual care: 3/800

continued

TABLE 139 *Atorvastatin: toxicity (cont'd)*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)			Withdrawals/discontinuation of study medication due to adverse events
ESTABLISH[89]	20	NR			Atorvastatin: none Usual care: NR
Colivicchi 2002[129]	80	No. of patients with event			Atorvastatin: 1/40 Control: NR
			Atorvastatin (n = 40)	No statin (n = 41)	
		Myopathy	1	0	
Mohler 2003[21]	10 and 80	NR			Discontinuation related to study drug: Atorvastatin 10 mg: 7/120 Atorvastatin 80 mg: 3/120 Placebo: 2/114 Discontinuation not related to study drug: Atorvastatin 10 mg: 5/120 Atorvastatin 80 mg: 1/120 Placebo: 8/114

AE, adverse event; GI, gastrointestinal.

TABLE 140 *Fluvastatin: toxicity*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)			Withdrawals/discontinuation of study medication due to adverse events
O'Rourke 2004[139]	40	No. of patients with event			Fluvastatin: 7/52 Placebo: 2/27
			Fluvastatin (n = 52)	Placebo (n = 27)	
		Suspected rejection episode	3	0	
		Minor side-effects (mainly GI)	7	1	
		Swelling of tongue and mouth after taking study capsule	0	1	
ALERT[142]	40–80	No. of patients with event			Fluvastatin: 155/1050 Placebo: 172/1052
			Fluvastatin (n = 1050)	Placebo (n = 1052)	
		Malignancies	296	316	
		Musculoskeletal	526	531	
		Suicide	1	0	
		Graft loss or doubling of serum creatinine	183	165	
LiSA[93]	40–80	There were two SAEs possibly related to study medication: one elevation of creatine phosphokinase on placebo and one possible hypersensitivity reaction to fluvastatin. On a global assessment of tolerability, 92% of fluvastatin patients rated tolerability as good or very good compared with 89% on placebo. However, patients known to be hypersensitive to, or intolerant of, statins were excluded from the study			Fluvastatin: 6.1% Placebo: 4.5%
FLARE[108]	80	No. (%) of patients with event			NR
			Fluvastatin (n = 409)	Placebo (n = 425)	
		Malignant disease	4 (0.8%)	11 (2.1%)	
		Headache	(3.8%)	(1.7%)	
		Nausea	(3.4%)	(2.3%)	
		Other pain	(4.4%)	(2.5%)	
FLORIDA[109]	80	NR			Fluvastatin: 11.3% Placebo: 13.5%
LIPS[110]	80	No. of patients with event			Fluvastatin: 124/844 (14.7%) Placebo: 104/833 (12.5%)
			Fluvastatin (n = 844)	Placebo (n = 833)	
		Fatal cancer	14	18	
		Non-fatal cancer	46	49	
		Death from respiratory failure	3	2	
		Death from sepsis	1	3	
		Other death	3	1	

TABLE 141 *Pravastatin: toxicity*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)			Withdrawals/discontinuation of study medication due to adverse events
Kobashigawa 1995[140]	20–40	No of patients with event			NR
			Pravastatin (n = 47)	Placebo (n = 50)	
		Death due to cardiac rejection	3	10	
		Cancer death	0	1	
		Death due to infection	0	1	
PMSG[96]	20–40	No. of patients with serious adverse events			Pravastatin: 25/530 Placebo: 33/532
			Pravastatin (n = 530)	Placebo (n = 532)	
		Angioedema causing withdrawal	1	0	
		Pulmonary	0	3	
		GI	2	0	
		Diabetes	1	0	
ALLHAT-LLT[127]	40	No. of patients with event			NR
			Pravastatin (n = 5170)	Placebo (n = 5185)	
		Cancer	378	369	
CAIUS[107]	40	No. of patients with SAE			NR
			Atorvastatin (n = 151)	Placebo (n = 154)	
		Cancer	3	4	
CARE[111]	40	No. of patients with event			Pravastatin: 45/2081 (2.2%) Placebo: 74/2078 (3.6%)
			Pravastatin (n = 2081)	Placebo (n = 2078)	
		Cancer	172	161	
		Colorectal cancer	12	21	
		Breast cancer	21	1	
		Violent death	8	4	
KAPS[133]	40	Most common AEs: % of patients with event			Pravastatin: 8/224 Placebo: 12/223
			Pravastatin (n = 224)	Placebo (n = 223)	
		Abdominal pain	11.2%	9.4%	
		Cough	8.9%	8.5%	
		No. of patients discontinuing because of event			
			Pravastatin (n = 224)	Placebo (n = 223)	
		GI complaints	3	7	
		Stroke	1	2	
		Elevated liver enzymes	1	0	
		Pneumonia	1	0	
		Eczema	1	0	
		Nerve pain	1	0	
		Prostate cancer	0	1	
		Chest pain	0	1	
		Depression	0	1	

continued

TABLE 141 *Pravastatin: toxicity (cont'd)*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)			Withdrawals/discontinuation of study medication due to adverse events
LIPID[112]	40	No. of patients with event			NR
			Pravastatin (n = 4512)	Placebo (n = 4502)	
		Newly diagnosed primary cancer	379	399	
		Cancer death	128	141	
		Deaths or hospitalisations due to accident, violence or attempted suicide	213	221	
		Death due to trauma or suicide	6	11	
		Fracture	175	183	
PLAC I[113]	40	% of patients with event			NR
			Pravastatin (n = 206)	Placebo (n = 202)	
		Dyspepsia/heartburn	17%	9%	
PLAC II[95]	20–40	NR			NR
PREDICT[114]	40	NR			6 patients; not attributed to treatment arm
PROSPER[81]	40	No. of patients with event			NR
			Pravastatin (n = 2891)	Placebo (n = 2913)	
		Cancer death	115	91	
		Trauma death/suicide	2	7	
		SAE	1608	1604	
		Incident cancer[a]	245	199	
		[a] Seems to be number of cancers rather than number of patients			
REGRESS[115]	40	No. of patients discontinuing study medication because of event			Pravastatin: 16/450 Placebo: 10/435
			Pravastatin (n = 450)	Placebo (n = 434)	
		Cancer	3	3	
		Endocrine disorders	0	2	
		Back pain	1	1	
		Joint complaints	1	0	
		Skin rash	2	0	
		Abdominal cramps	2	0	
		Worsening vision	1	0	
		Conjunctivitis	1	0	
		Sleep disturbance	1	0	
WOSCOPS[82]	40	No. of patients with event			
			Pravastatin (n = 3302)	Placebo (n = 3293)	
		Incident cancer	116	106	
		Cancer death	44	49	
		Suicide	2	1	
		Trauma death	3	5	

continued

TABLE 141 *Pravastatin: toxicity (cont'd)*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)	Withdrawals/discontinuation of study medication due to adverse events
		Of the 5974 subjects classified as non-diabetic at baseline, 139 developed overt diabetes mellitus over the course of the study. Pravastatin treatment was associated with a significantly reduced risk of developing diabetes (hazard ratio 0.70, 95% CI 0.50 to 0.98, $p = 0.036$)[400]	
Sato 2001[87]	10	Excluded patients with known allergy to pravastatin NR	NR
GISSI-P[130]	20	% of patients with event	Pravastatin: 57/2138

	Pravastatin ($n = 2138$)	Placebo ($n = 2133$)
Cancer	16	25

TABLE 142 *Rosuvastatin: toxicity*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)	Withdrawals/discontinuation of study medication due to adverse events
No studies available with non-statin comparator arms			

TABLE 143 *Simvastatin: toxicity*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)	Withdrawals/discontinuation of study medication due to adverse events
Wenke 1997[141]	5–20	Excluded patients with hypersensitivity to statins No. of patients with event	NR

	Simvastatin ($n = 35$)	Placebo ($n = 37$)
Death due to severe graft rejection	1	5
Death due to severe pulmonary infection	2	2
Death due to graft vessel disease	1	2
Death due to multiple organ failure	0	1
Death due to prostate cancer	0	1
Infection complications	6	5
Diagnosed cytomegalovirus	4	3
Hypertension requiring treatment	16	14

continued

TABLE 143 *Simvastatin: toxicity (cont'd)*

Study	Statin dose (mg per day)	Clinical adverse events (excluding all-cause mortality and cardiovascular events)	Withdrawals/discontinuation of study medication due to adverse events
MAAS[100]	20	Simvastatin was said to produce no significant side-effects or adverse reactions	Simvastatin: 9/193 Placebo: 16/188
4S[97]	20–40	Excluded patients with hypersensitivity to statins No. of patients with event[401] Simvastatin (n = 32221) / Placebo (n = 32223) Serious non-cardiovascular AE: 629 / 683 Total cancer: 89 / 96 Cancer deaths: 33 / 35 Trauma: 9 / 22 Arthritis: 0 / 6 Eczema: 99 / 67 Visual disturbance: 12 / 27 Dry eye syndrome: 5 / 0 Nocturia: 9 / 2	Simvastatin: 126/2221 Placebo: 129/2223 Discontinuation due to non-cardiovascular AE.[401] Simvastatin: 107/2221 Placebo: 105/2223
CIS[98]	20–40	No. of patients with event Simvastatin (n = 129) / Placebo (n = 125) Cancer death: 0 / 2	NR
SCAT[116]	20–40	No. of patients with event Simvastatin (n = 230) / Placebo (n = 230) Cancer: 23 / 13	NR
Aronow 2003[118]	40	NR	NR
HPS[74]	40	No. of patients with event Simvastatin (n = 10,269) / Placebo (n = 10,267) Cancer (excluding non-melanoma skin): 814 / 803 Hospitalisation for fracture: 241 / 230 New diabetes[402]: 335 / 293	Simvastatin: 4.5% Placebo: 5.1%
Mondillo 2003[105]	40	NR	NR

Appendix 28

Quality checklists for sponsor submissions

TABLE 144 *Pfizer: atorvastatin*

Reference ID		
Title		**Clinical and cost effectiveness of 'statins for the prevention of coronary events'**
Authors		**Pfizer**
Year		**2004**
Modelling assessments should include:		
1. A statement of the problem	**Y**	**The economic model is designed to evaluate the cost-effectiveness of atorvastatin compared with placebo and simvastatin in the primary and secondary prevention of (a) CHD and (b) CHD plus stroke**
2. A discussion of the need for modelling vs alternatives	N	
3. A description of the relevant factors and outcomes	Y	Yes: different baseline cholesterol levels; analysis of different subgroups: diabetics, women. Cost-effectiveness is measured in terms of cost per QALY gained. Information is provided for atorvastatin versus placebo (and simvastatin)
4. A description of the model, including reasons for this type of model and a specification of the scope, time frame, perspective, comparators and settings	**Y**	**A Markov modelling approach is used with each Markov cycle lasting for 1 year. The annual likelihood of a patient experiencing a fatal or non-fatal coronary event is determined by one of two risk engines: the Framingham risk prediction model and UKPDS Risk Engine. The Framingham risk algorithm was chosen for non-diabetics on the basis that it is the most widely accepted predictive tool in UK clinical practice** Comparator: both placebo and simvastatin are used as comparators. Simvastatin was selected on the basis that it is the most widely prescribed statin in England and Wales Time-frame: base case – lifetime. The model is flexible: patients can enter the model at any age between 35 and 99 years. If, for example, a men enters the model at the age of 50, he can potentially receive a maximum of 49 years of statin (or placebo) therapy, unless death occurs before the end of the model time-horizon Perspective: UK NHS
5. A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific hierarchy of evidence	Y N	The majority of data sources were identified, although it was not always clear exactly how data are derived. For instance, the distribution of CHD events: primary and subsequent Very limited discussion of the strengths and weaknesses of sources was given
6. A list of assumptions pertaining to the structure of the model (e.g. factors included, relationships and distributions) and the data	Y	The key assumptions relating to the structure of the model were described, although limited explanation of reasons for selection of assumptions was given in some cases
7. A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits for use in sensitivity analysis	N	Base-case parameters were listed; however, parameters for sensitivity analysis were not presented in a readily accessible fashion in the report. No justification is given for the distributions selected for sensitivity analysis

continued

TABLE 144 *Pfizer: atorvastatin (cont'd)*

8. The results derived from applying the model for the base case	Y	However, it would have been useful if a CHD-only scenario had been presented
9. The results of the sensitivity analysis: unidimensional, best/worst case, multidimensional (Monte Carlo/parametric), threshold	?	Very limited univariate sensitivity was undertaken. The results of the PSA in Appendix E are for atorvastatin vs simvastatin only and are the same as the results presented in Table 17 of the main report. The CEACs presented are for atorvastatin vs simvastatin only. No discussion of PSA results was given
10. A discussion of how the modelling assumptions might affect the results	N	
11. A description of the validation undertaken, including concurrence of experts, internal consistency, external consistency and predictive validity	Y	Limited validation was undertaken. The results of the cost-effectiveness analysis were compared with previously published results of other cost-effectiveness evaluations. A limited explanation was offered for differences between results in some cases
12. A description of the setting to which the results can be applied	N	
13. A description of research in progress that could yield new data that could alter the results of the analysis	N	

TABLE 145 *AstraZeneca: rosuvastatin*

Reference ID		
Title		**Cost effectiveness of primary and secondary prevention of CHD, a model based on the STELLAR trial**
Authors		**Davies A, Hutton J (for AstraZeneca)**
Year		**2004**
Modelling assessments should include:		
1. A statement of the problem	Y	To address the longer term cost-effectiveness of statin therapies by estimating the cost per QALY of strategies that differ in terms of both the chosen statin and the chosen starting dose of each statin, with upward titration to achieve a specified TC goal
2. A discussion of the need for modelling vs alternative methodologies	N	No discussion for need of modelling vs alternative methodology
3. A description of the relevant factors and outcomes	Y	Yes: different baseline cholesterol levels; using different starting doses for the less efficacious statins, etc.
	Y	Description of outcomes = Yes
4. A description of the model, including reasons for this type of model and a specification of the scope including time-frame, perspective, comparators and setting. Note: *n* = number of health states within submodel	Y	Description of the model = Yes
	Y	Reason for this type of model = Yes, because no long-term evidence available for rosuvastatin
	Y	Time-frame = Yes
	Y	Perspective = Yes
	Y	Comparator = Yes, no treatment
	N	Setting = No
	Y	Number of health states included in model = Yes
5. A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Y	Description of data sources = Yes for the majority Description of strengths and weaknesses of sources = Some: STELLAR USA source, hence takes baseline cholesterol levels from Wilson (UK); does not reference triglycerides (TRG). States 6 weeks is sufficient to establish level of efficacy: this may be incorrect, could have used long-term data to validate that this initial reduction is maintained over time
	N	References to classification or hierarchy of evidence = No

continued

TABLE 145 *AstraZeneca: rosuvastatin (cont'd)*

6. A list of assumptions pertaining to the structure of the model (e.g. factors included, relationships and distributions) and the data	N	List of assumptions = No, other than assumes cholesterol reduction from rosuvastatin will produce a reduction in events as is evidence based in the other statins. Discusses the uncertainty in how chemically induced reduction in cholesterol translates to actual reductions in cholesterol-related CHD risks over medium and longer terms; hence, only does one secondary event and does not apply the Framingham equation in perpetuity
	Y	List of distributions used in probabilistic = Yes
	Y	List of factors included = Yes
		Costs associated with adverse events excluded as there are no significant differences in adverse event rates among the statins
		Patients' non-compliance, discontinuation and failure to titrate in accordance with guidelines not accounted for in the simulation
7. A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits for use in sensitivity analysis	Y	List of parameter values that will be used for a base case = Yes
	Y	List of ranges that represent CI used in sensitivity analysis = Yes
8. The results derived from applying the model for the base case	Y	Results derived from base case = Yes
9. The results of the sensitivity analyses: unidimensional, best/worst case, multidimensional (Monte Carlo/parametric), threshold		Results of sensitivity analysis:
	Y	Unidimensional = Yes
	N	Best/Worst case = No
	Y	Multidimensional (Monte Carlo/parametric) = Yes
	Y	Threshold = willingness to pay = Yes
10. A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect		Discussion of how assumptions might affect the results Direction of bias = Magnitude of effect = Some: (1) excluding monitoring biases model results to less efficacious drugs as titration monitoring costs not included. (2) Using higher generic simvastatin penetration reduced the difference in cost per patient to target between rosuvastatin and simvastatin. (3) Using different starting doses for the drugs changed the order of cost-effectiveness. (4) Using the higher baseline population cholesterol level increased the cost per patient to target, but the order remained the same. (5) Reducing the baseline population cholesterol levels decreased the estimated cost per patient to target and changed the order to simvastatin, fluvastatin, rosuvastatin, atorvastatin and pravastatin. (6) Lowering the cholesterol targets: the more efficacious (rosuvastatin, atorvastatin, simvastatin) statins were more effective at getting patients to target, therefore average cost-effectiveness ratios (ACERs) were much lower compared with fluvastatin and pravastatin
11. A description of the validation undertaken, including concurrence of experts, internal consistency, external consistency and predictive validity	N	Validation undertaken = No
	N	Concurrence of experts = No
	N	Internal consistency = not discussed
	N	External consistency = not discussed
	N	Predictive validity = not discussed
12. A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	N	Description of settings to which results can be applied = not discussed
	N	List of factors that could limit the applicability of results = not discussed
13. A description of research in progress that could yield new data that could alter the results of the analysis	N	Not discussed, other than the costing and penetration for generic simvastatin

TABLE 146 *Novartis: fluvastatin*

Reference ID		
Title		**Cost-effectiveness of fluvastatin**
Authors		**Novartis**
Year		**2004**
Modelling assessments should include:		
1. A statement of the problem	Y	The economic model is designed to evaluate the cost-effectiveness of fluvastatin for patients following successful PCI
2. A discussion of the need for modelling vs alternative methodologies	N	None given
3. A description of the relevant factors and outcomes	Y	The two arms are described: the treatment group was given dietary and lifestyle counselling and treated with fluvastatin (40 mg) twice daily commencing immediately after first PCI, and the control group was given dietary and lifestyle counselling only. Outcomes are those seen in the LIPS trial on which the model is based. No other details given
4. A description of the model, including reasons for this type of model and a specification of the scope including time-frame, perspective, comparators and setting	Y	The model is well described. No reason is given for choosing a Markov approach. The time-frame, perspective, comparators and setting are specified
5. A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Y	Effectiveness data are based on the only trial available so far to determine the effect of statin treatment on clinical outcomes following a successful PCI. The transition probabilities in the model are based on the individual components of a composite end-point in the trial. These are not published and were estimated by Novartis from actual trial data. It is therefore not possible to verify the accuracy of the state transition probabilities. Sources of quality of life and cost data are well documented. Assumptions made regarding data are likely to have a conservative effect on the results
6. A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	Y	No explicit assumptions pertaining to the structure of the model are given. Assumptions regarding the data are described
7. A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits for use in a sensitivity analysis	Y	
8. The results derived from applying the model for the base case	Y	Costs and health gains only
9. The results of the sensitivity analyses: unidimensional, best/worst case, multidimensional (Monte Carlo/parametric), threshold	Y	All included
10. A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Y	Modelling assumptions are discussed. The effect is likely to underestimate the effectiveness of fluvastatin; however, this is not quantified
11. A description of the validation undertaken, including concurrence of experts, internal consistency, external consistency and predictive validity	N	No validation was undertaken
12. A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Y	Setting described. Applicability of non-UK health utilities discussed
13. A description of research in progress that could yield new data that could alter the results of the analysis	N	No research in progress described

TABLE 147 *Bristol-Myers Squibb: pravastatin*

Reference ID		
Title		**Cost-effectiveness of pravastatin**
Authors		**Bristol-Myers Squibb**
Year		**2004**
Modelling assessments should include:		
1. A statement of the problem	Y	The economic model is designed to evaluate the cost-effectiveness of pravastatin within a range of patient characteristics in primary and secondary prevention
2. A discussion of the need for modelling vs alternative methodologies	N	None given
3. A description of the relevant factors and outcomes	Y	The setting is described as far as treatment arms, costs and effectiveness and economic perspective. Outcomes relate to those evaluated in the RCTs on which the model is based
4. A description of the model, including reasons for this type of model and a specification of the scope including time-frame, perspective, comparators and setting. Note: n = number of health states within submodel	Y	The model is reasonably well described. No reason is given for choosing a Markov approach. The time-frame, perspective, comparators and setting are specified
5. A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Y/N	Effectiveness data are based WOSCOPS (primary) and LIPID (secondary). Brief reasons for including these RCTs and excluding others are given. A description of strengths and weaknesses is not given
6. A list of assumptions pertaining to the structure of the model (e.g. factors included, relationships and distributions) and the data	N	No assumptions are discussed
7. A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits for use in a sensitivity analysis	N	No parameter values are listed
8. The results derived from applying the model for the base case	Y	A full description of the costs and health gains is given for a range of risk parameters, grouped by gender
9. The results of the sensitivity analyses: unidimensional, best/worst case, multidimensional (Monte Carlo/parametric), threshold	Y	Extensive one-way sensitivity analysis is reported, together with a best/worse case scenario. No PSA is undertaken
10. A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	N	No discussion of how assumptions may affect the results
11. A description of the validation undertaken, including concurrence of experts, internal consistency, external consistency and predictive validity	N	No validation was undertaken
12. A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Y	A limited discussion regarding the applicability is given
13. A description of research in progress that could yield new data that could alter the results of the analysis	N	No research in progress described

Appendix 29

Efficacy data from AstraZeneca submission

TABLE 148 *Efficacy data used in the AstraZeneca submission cost-effectiveness model*

	Total cholesterol					HDL					Triglycerides				
	Base lipid	% Change	SE (log-log scale)	Lower confidence limit	Upper confidence limit	Base lipid	% Change	SE (log-log scale)	Lower confidence limit	Upper confidence limit	Base lipid	% Change	SE (log-log scale)	Lower confidence limit	Upper confidence limit
R 10	275	32.9%	7.75%	27.42%	38.48%	51	7.7%	18.91%	2.44%	17.03%	179	19.8%	9.29%	14.33%	25.93%
R 20	274	37.6%	7.96%	31.88%	43.30%	51	9.5%	18.36%	3.43%	19.35%	180	23.7%	9.29%	17.78%	30.12%
R 40	280	40.2%	8.00%	34.44%	45.88%	50	9.6%	18.52%	3.44%	19.59%	183	26.1%	9.26%	19.98%	32.62%
A 10	274	27.1%	7.59%	21.98%	32.46%	50	5.7%	20.08%	1.43%	14.48%	174	20.0%	9.42%	14.43%	26.23%
A 20	275	31.8%	7.71%	26.38%	37.34%	50	4.8%	20.74%	1.05%	13.24%	176	22.6%	9.38%	16.74%	29.01%
A 40	275	35.8%	7.86%	30.17%	41.46%	50	4.4%	21.10%	0.89%	12.68%	178	26.8%	9.41%	20.53%	33.45%
A 80	279	38.9%	7.95%	33.18%	44.58%	51	2.1%	24.75%	0.19%	9.27%	181	28.2%	9.37%	21.85%	34.87%
S 10	275	20.3%	7.49%	15.77%	25.24%	51	5.3%	20.15%	1.28%	13.82%	174	11.9%	9.69%	7.62%	17.20%
S 20	276	25.7%	7.53%	20.70%	30.97%	50	6.0%	19.90%	1.57%	14.88%	182	17.6%	9.23%	12.47%	
S 40	272	27.9%	7.64%	22.70%	33.32%	51	5.2%	20.22%	1.23%	13.68%	172	14.8%	9.58%	9.98%	20.52%
S 80	277	32.9%	7.72%	27.44%	38.46%	51	6.8%	19.28%	1.98%	15.85%	181	18.2%	9.25%	12.97%	24.14%
P 20	276	14.7%	7.56%	10.82%	19.14%	50	3.2%	22.60%	0.47%	10.97%	187	8.2%	9.78%	4.83%	12.69%
P 40	271	17.2%	7.57%	12.98%	21.93%	49	4.4%	21.32%	0.87%	12.79%	179	7.7%	10.09%	4.39%	12.20%
P 80	276	21.5%	7.48%	16.87%	26.52%	50	5.6%	20.14%	1.39%	14.34%	181	13.2%	9.41%	8.76%	18.57%
F 20	275	16.4%	7.53%	12.30%	21.02%	51	4.6%	20.71%	0.98%	12.85%	179	5.5%	10.68%	2.80%	9.51%
F 40	275	19.9%	7.49%	15.41%	24.81%	51	5.2%	20.22%	1.23%	13.68%	179	8.4%	9.96%	4.92%	13.04%
F 80	275	21.4%	7.50%	16.77%	26.42%	51	7.5%	18.98%	2.33%	16.77%	179	14.9%	9.38%	10.15%	20.52%

TABLE 149 *Efficacy data and distributions assigned in the AstraZeneca cost-effectiveness model*

Drug	Dose (mg)	Mean (SD) % reduction in TC	Distribution for TC reduction	Mean (SD) % reduction in LDL-C	Distribution for LDL-C reduction	*n*
Rosuvastatin	10	33 (10)	Beta (1126, 2297)	46 (13)	Beta (1039, 1226)	156
	20	38 (11)	Beta (1261, 2095)	52 (14)	Beta (1122, 1021)	160
	40	40 (11)	Beta (1359, 2020)	55 (13)	Beta (1181, 968)	157
Atorvastatin	10	27 (8)	Beta (1237, 3324)	37 (11)	Beta (1180, 2033)	158
	20	32 (11)	Beta (930, 1999)	43 (14)	Beta (782, 1054)	154
	40	36 (10)	Beta (1243, 2237)	48 (13)	Beta (1114, 1217)	156
	80	39 (11)	Beta (1189, 1874)	51 (14)	Beta (1082, 1037)	165
Fluvastatin	20	13 (6)	Beta (49, 327)	17 (8)	Beta (509, 1288)	12
	40	19 (9)	Beta (43, 184)	23 (10)	Beta (1126, 2094)	12
	80	35 (13)	Beta (222, 632)	26 (9)	Beta (753, 1188)	40
Pravastatin	10	15 (8)	Beta (431, 2501)	20 (11)	Beta (1319, 1562)	160
	20	17 (9)	Beta (507, 2453)	24 (11)	Beta (405, 1608)	164
	40	22 (9)	Beta (687, 2508)	30 (13)	Beta (578, 1801)	161
Simvastatin	10	20 (10)	Beta (524, 2054)	28 (14)	Beta (635, 1504)	165
	20	26 (9)	Beta (981, 2842)	35 (11)	Beta (392, 1415)	162
	40	28 (11)	Beta (722, 1868)	39 (14)	Beta (876, 2441)	158
	80	33 (9)	Beta (1505, 3067)	46 (12)	Beta (1053, 2504)	163

Appendix 30

Cost tables from AstraZeneca submission

TABLE 150 *Resource use for CHD[a] used in the AstraZeneca cost-effectiveness model*

		Distribution	Alpha	Beta	Probability
	Acute PCI (ACS)	Beta	53	980	0.05
	Acute PCI (stable angina)[b]	Beta	100.6	1022.4	0.01
	Repeat revascularisation	Beta	8	157	0.04
	Repeat revascularisation PCI	Beta		0.00	
	Death (revascularisation PCI)	Beta	0		0.00
	MI (revascularisation PCI)	Beta	1	7	0.12
	Death (revascularisation CABG)	Beta		0.00	
	MI (revascularisation CABG)	Beta		0.00	
	Death (no repeat revascularisation)	Beta	5	152	0.02
	MI (no repeat revascularisation)	Beta	5	147	0.04
	CABG (ACS)	Beta	47	933	0.04
	CABG (stable angina)[b]	Beta	9.4	970.6	0.01
	Death (CABG)	Beta	5	42	0.16
	MI (CABG)	Beta	3	39	0.16
	6-month revascularisation	Beta	48	885	0.05
	6-month revascularisation PCI	Beta	23	25	0.64
	Death (6-month revascularisation PCI)	Beta	2	21	0.04
	MI (6-month revascularisation PCI)	Beta	2	19	0.03
	Death (6-month revascularisation CABG)	Beta	0		0.00
	MI (6-month revascularisation CABG)	Beta	4	21	0.16
	Death (no revascularisation)	Beta	68	817	0.08
	MI (no revascularisation)	Beta	40	777	0.04
Angiography	PCI in acute period	Beta	51	2	0.98
	CABG in acute period	Beta	38	9	0.81
	No initial revascularisation	Beta	193	740	0.23
CCU stay	PCI in acute period	Beta	20	33	0.39
	CABG in acute period	Beta	28	18	0.60
	No initial revascularisation	Beta	375	543	0.41
Length of inpatient stay	PCI in acute period	Beta	10.3	8.04	9.11
	CABG in acute period	Beta	15.28	12.32	39.18
	No initial revascularisation	Beta	5.45	4.78	4.82
Length of CCU stay	PCI in acute period	Beta	3.7	4.12	0.81
	CABG in acute period	Beta	4.71	6.61	0.51
	No initial revascularisation	Beta	2.11	1.95	3.05

[a] Extracts from Palmer *et al*. (2002).[214]
[b] Assumed one-fifth of unstable angina intervention rate.
CCU, coronary care unit.

TABLE 151 *Unit costs used in the AstraZeneca cost-effectiveness model*

Procedure	Unit cost	Source
PCI	1410.04	Palmer[214]
CABG	4902.22	Palmer[214]
Angiogram	748.25	Palmer[214]
Repeat PCI	2976	Palmer[214]
Carotid endarterectomy	2541	NHS reference costs, 2003[403] (Q05: Extracranial or upper limb arterial surgery)
Hospital stay/visit		
Non-cardiac	244.00	Palmer[214]
Cardiac	157.47	Palmer[214]
CCU	459.04	Palmer[214]
Day-case non-cardiac	182.00	Palmer[214]
Day-case cardiac	108.58	Palmer[214]
Outpatient	59.70	Palmer[214]
Heart failure clinic	50.00	Stewart[404]
TIA	1015.00	NHS reference costs, 2003 (without complications)[403]
Consumables		
Guidewire	61.75	Palmer[214]
Guide catheter	37.05	Palmer[214]
Stent	599.01	Palmer[214]
3-month ongoing care cost		
At home	326.00	Youman[202]
In institution	3872.00	Youman[202]
Non-statin drug costs (per annum)		
ACEi: 10 mg enalapril 2 day	120.45	Nanas[405]
β-Blockers	163.73	Nanas[405]

TABLE 152 *Stroke costs used in the AstraZeneca cost-effectiveness model*

Cost of stroke		Distribution	Mean cost	SD	*N*	Source
	Mild	Gamma	5,099	2505	83	Youman[202]
	Moderate	Gamma	4,816	2231	114	Youman[202]
	Severe	Gamma	10,555	7246	210	Youman[202]
Cost of TIA		**Distribution**	**Mean**	**Alpha**	**Beta**	
	% Endarterectomy	Beta	11%	6.28	52	Mant[215]
	TIA as % all stroke	Beta	14%	35	164	Mant[215]

TABLE 153 *Other CVD costs used in the AstraZeneca cost-effectiveness model*

Cost of CHF		Distribution	Mean	SD		Source
	Days of hospitalisation	Gamma	12	12		Stewart[404]
	Proportion of other CVD that is CHF	None	50%			Assumption
Cost of PVD		**Distribution**	**Mean**	**SD**	***N***	
	Emergency aortic surgery	Gamma	5366	2303	171	NHS
	Elective abdominal vascular surgery	Gamma	2541	867	4098	reference
	Lower limb arterial surgery	Gamma	3391	2801	4182	costs, 2003[403]
	Bypass to tibial artery	Gamma	2085	874	472	
	Therapeutic endovascular procedures	Gamma	1513	859	10633	
	Diagnostic radiology with complications	Gamma	1453	707	1862	
	Diagnostic radiology without complications	Gamma	1102	661	9646	
	Amputations	Gamma	6152	2405	2341	
	Foot procedure for diabetes or arterial disease	Gamma	2065	930	941	
	PVD > 69 years or co-morbidity	Gamma	1756	1000	2932	
	PVD < 70 years without co-morbidity	Gamma	1309	692	1752	

TABLE 154 *Quarterly CVD event follow up resource use, used in the AstraZeneca cost-effectiveness model*

	Length of stay			No. of patients using resource			
	Distribution	**Mean**	**SD**	**Distribution**	**Alpha**	**Beta**	***N***
Angina							
Cardiac day case	Gamma	8.87	9.58	Beta	1	251	252
Cardiac non-CCU	Gamma	6.82	6.82	Beta	76	176	252
Cardiac CCU	Gamma	3.44	2.5	Beta	17	235	252
Cardiac outpatient visits				Beta	115	137	252
Non-cardiac day case	Gamma	10.39	17.81	Beta	1	251	252
Non-cardiac non CCU	Gamma	4.86	4.91	Beta	67	185	252
Non-cardiac outpatient visits				Beta	138	114	252
Angiography				Beta	20	232	252
PTCA				Beta	2	250	252
CABG				Beta	7	245	252
(Total no. of patient days = 113,222)				Source: Palmer[214]			
MI							
Cardiac non-CCU	Gamma	10.8	7.82	Beta	5	22	27
Cardiac CCU	Gamma	8.8	6.44	Beta	10	17	27
Cardiac outpatient visits	Gamma	3.43	3.08	Beta	21	6	27
Non-cardiac non-CCU	Gamma	12	13.6	Beta	7	20	27
Non-cardiac outpatient visits	Gamma	3.27	3.45	Beta	15	12	27
Angiography				Beta	5	22	27
PTCA				Beta	3	24	27
CABG				Beta	1	26	27
(Total no. of patient days = 7248)				Source: Palmer[214]			
Post-MI							
Cardiac non-CCU	Gamma	5.95	6.05	Beta	5	10	15
Cardiac CCU	Gamma	2	2	Beta	1	14	15
Cardiac outpatient visits	Gamma	2.88	1.73	Beta	8	7	15
Non-cardiac non-CCU	Gamma	7	7.94	Beta	3	12	15
Non-cardiac outpatient visits	Gamma	2.33	1.32	Beta	9	6	15
(Total no. of patient days = 2993)				Source: Palmer[214]			
Stroke							
Proportion discharged home							
Mild							68
Moderate				Beta	207	9	99
Severe				Beta	313	15	196
				Source: Youmann[202]			
CHF				Clinic visits per 12 months			
Clinic visits (per annum)				Beta	6	6	NA
Hospital days (per annum)	Gamma	12	12				
				Source: Stewart[404]			
PVD							
Annual follow-up cost	Gamma	1000	500				
				Source: Jones[406]			

Appendix 31

Summary of key modelling assumptions used in the ScHARR cost-effectiveness model

All assumptions used in the model have been discussed and validated using expert opinion (Yeo W, Royal Hallamshire Hospital, Sheffield: personal communications, October 2004). The impact of changing the assumptions has been explored before making final decisions. Any changes in the assumptions that have a significant impact on the results have been presented in univariate sensitivity analyses.

The following headings refer to subsections in Chapter 4, in the section 'ScHARR economic analysis' (p. 83).

Detailed methodology

A1. Base case: it is assumed that statin treatment does not affect probabilities of stroke or TIA events. This assumption is required to meet the criteria laid down in the research question. Further analyses are conducted (scenarios 1 and 2) to explore the affect of amending this assumption.

Structure of the Markov model

A2. It is assumed that all patients will die if they reach the age of 100 years. As patients in the model are at risk of a CHD event, which increases with age, the majority of patients will die before this age. No sensitivity analysis is conducted to examine the effect of changing this assumption.

Treatment/comparator

A3. It is assumed that all patients are given standard advice regarding dietary control and lifestyle advice and that an equal proportion of patients in each cohort will receive medications such as aspirin, hypertensive treatments or alternative lipid-lowering treatments. Exploring the impact of changing this assumption would require a different methodology and detailed evidence which is beyond the remit of the current evaluation. It is likely that the majority of costs and benefits associated with this assumption will cancel out and no sensitivity analysis is conducted to explore the impact of changing this assumption.

Event rates

A4. In the absence of incidence rates for primary CHD events in older patients, it is assumed that rates increase in proportion to those observed in younger age bands. In addition, the reported rates for first ever stroke are assumed to represent both fatal and non-fatal events, and are apportioned using the reported ratio across all ages.

Holding incidence rates constant from the age of 74 years had little impact on the results, and sensitivity analyses were conducted to explore the impact of changing the ratio across health states.

Annual risk levels modelled

A5. It is assumed that the annual risk of a CHD event increases linearly with age. The ratio between CHD risk and CVD risk changes with age, and uncertainties in the assumption and the ratio are explored in sensitivity analyses.

Secondary event rates

A6. In the absence of more detailed evidence, it was assumed that the regression results for probabilities of subsequent events after a 1-year period free of an event could be used to represent all subsequent events irrespective of the time interval or number of previous events. This is a conservative assumption as it implies that there is no additive effect from previous events. Uncertainty is explored in the probabilistic analyses.

A7. Owing to a lack of detailed evidence to provide probabilities of subsequent events following onset of stable angina or TIA that vary with age, it is assumed that the transitions from both the TIA and stable angina health states could be modified using the respective primary incidence rates.

A8. Owing to a lack of evidence, the probability of a fatal CVD event for patients with a history of stable angina is not modelled.

A9. Owing to a lack of published evidence, it is assumed that the probability of a non-fatal MI following a non-fatal stroke is equivalent to the probability of a non-fatal MI for patients with a history of TIA. Again, uncertainty in this assumption is explored in the probabilistic analyses.

A10. It is assumed that the probabilities of vascular death for patients with a history of stroke could be apportioned equally between CHD and CVD fatal events. This is a conservative assumption as the benefits of reduced fatal CHD events are smaller than the benefits associated with reduced fatal CVD events. Again, uncertainty in this assumption is explored in the probabilistic analyses.

Costs

A11. Assumptions on health state costs are based on published evidence where available and expert opinion (Yeo W: personal communication). Uncertainty in costs is explored in the probabilistic analyses and univariate analyses are performed to explore the impact of changing cost parameters modelled.

A12. It is assumed that statins have a good safety profile and costs associated with possible adverse events are not modelled.

Utility

A linear decrease in utility is assumed as age increases. This assumption is based on a patient-level analysis of the Kind data.[241]

Compliance

The base case assumes that the relative risks derived from the ITT analyses can be generalised to patients taking statin treatment in general clinical practice. This assumption is based on the ITT analysis and the evidence that suggests that after the first few years compliance and continuance stabilise and remain fairly constant in the long term. Uncertainty in this assumption is explored in a series of evaluations that examine the impact of reducing the relative risks applied and the associated statin costs.

Appendix 32

Results of the regression analyses used in the ScHARR cost-effectiveness model

TABLE 155 *Results of linear regression for utility by age modelled in the ScHARR cost-effectiveness model*[241]

(a) Summary output for linear regression								
Regression statistics								
Multiple *R*	0.2005							
R^2	0.0402							
Adjusted R^2	0.0397							
Standard error	0.2576							
Observations	1979							
(b) ANOVA								
	df	**SS**	**MS**	***F***	**Significance *F***			
Regression	1	5.50	5.497	82.822	2.1E-19			
Residual	1977	131.21	0.066					
Total	1978	136.71						
	Coefficients	**SE**	**t statistic**	***p*-Value**	**Lower 95%**	**Upper 95%**	**Lower 95.0%**	**Upper 95.0%**
Intercept	**1.060**	0.029	36.605	2E-224	1.003	1.117	1.003	1.118
x	**–0.004**	0.000	–9.1007	2.13E-19	–0.005	–0.003	–0.005	–0.003

TABLE 156 *Parameters from regression analysis used to calculate the CVD event risk corresponding to the CHD event risk by age and gender*[226] *used in the ScHARR cost-effectiveness model*

	Men		**Women**	
	35–54 years	**55–74 years**	**35–54 years**	**55–74 years**
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**
Slope	1.25 (1.21 to 1.29)	1.27 (1.22 to 1.32)	1.27 (1.22 to 1.32)	1.44 (1.37 to 1.51)
Intercept	0.84 (0.45 to 1.23)	4.92 (3.82 to 6.02)	1.87 (1.58 to 2.16)	3.87 (3.09 to 4.65)

Appendix 33

Diabetes data used in the ScHARR cost-effectiveness model

TABLE 157 *Health state utilities used in the diabetic analysis of the ScHARR cost-effectiveness model*[204]

	Base case	Diabetic
Stable angina	0.808	0.724[a]
Unstable angina	0.770	0.690[a]
1st year MI	0.760	0.681
Post-MI	0.760	0.681
TIA	1.000	1.000
1st stroke year 1	0.629	0.526
Post 1st stroke	0.629	0.526

[a] Adjusted using first year diabetic MI utility and base-case utilities for stable and unstable angina, respectively.

TABLE 158 *Health state costs used in the diabetic analysis of the ScHARR cost-effectiveness model*[200]

	Base case	Diabetic
Stable angina	£171	£464[a]
Post-stable angina	£171	£464[a]
Unstable angina	£440	£464[a]
Post-unstable angina	£171	£464[a]
1st year costs MI	£4,448	£5,104
Ongoing costs MI	£171	£464
Fatal MI	£1,166	£1,567
TIA	£1,064	£1,461
Post-TIA (ongoing costs)	£264	£362[b]
1st year costs stroke	£8,046	£11,047[b]
Ongoing costs stroke	£2,163	£2,970
Fatal stroke	£7,041	£9,667[b]

[a] Assumed equal to ongoing costs for MI.
[b] Costs adjusted using ongoing costs for stroke and base-case costs.

Appendix 34

Results of univariate sensitivity analyses explored in the ScHARR cost-effectiveness model

(a) Discount rates

The new NICE guidelines[406] suggest that future analyses are to be presented using discounting rates of 3.5% for both costs and benefits. To enable comparison with future evaluations of health care interventions, the CHD base case is also presented using the proposed discounting rates (*Table 159*).

When using these values, secondary ICERs range from £16,000 for women aged 65 years to £24,000 per QALY for women aged 45 years. In primary prevention the ICERs estimated range from £19,000 for men aged 45 years at 3% annual risk of a CHD event to £152,000 per QALY for women aged 75 years at 0.5% annual risk.

(b) Relative risks

To explore the sensitivity of the results to changes in the assumptions on relative risk from statin treatment, 1000 samples were generated allowing the relative risk values of statin treatment to vary while holding all other parameters constant at their mean value. As can be seen in *Table 160*, the model is robust to changes in the values used for the relative risk of statin treatment; hence, only a selection of the results by age and risk level is presented.

(c) Health state costs

Health state costs were adjusted by plus or minus 20% (*Tables 161* and *162*). Increasing or decreasing health state cost has minimal impact on the results. In secondary prevention the ICERS are relatively unchanged. In primary prevention analyses the costs per QALY for men aged 85 years at 0.5% risk range between approximately £14,900 and £74,100 relative to the base case of £14,900 and £74,200, respectively. For women the corresponding values are £20,300 and £84,200 compared with the base case of £20,300 and £84,300.

(d) Statin prescribing costs

A reduction of 20% and 40% in the average statin treatment costs was assessed. A full discussion on the rationale for choosing a 20% and 40% price reduction is presented in the section 'Cost of statins' (p. 94).

As can be seen in *Table 163*, decreasing the prices of statins by 20% and 40% reduced the highest cost per QALY in secondary prevention from £16,000 in the base case to £13,000 and £10,000, respectively.

Reducing statin costs by 40% and 20% for primary prevention reduces the highest ICERs estimated,

TABLE 159 *Discounted cost per QALY using 3.5% discounting for both costs and benefits*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£22,606	£19,390	£20,609	£22,585	£25,928	£32,165	£46,485
	55	£18,824	£22,861	£24,675	£27,492	£32,131	£40,647	£60,107
	65	£16,856	£26,697	£29,581	£33,881	£40,791	£53,367	£82,539
	75	£17,801	£36,826	£41,501	£48,354	£59,223	£78,819	£123,983
	85	£19,411	£46,039	£52,139	£60,714	£73,578	£94,902	£136,859
Women	45	£23,707	£29,647	£30,788	£33,071	£37,501	£46,832	£72,409
	55	£19,539	£30,428	£32,106	£35,116	£40,621	£51,816	£81,791
	65	£15,916	£32,130	£35,221	£40,029	£48,099	£63,665	£103,942
	75	£16,390	£46,256	£51,634	£59,629	£72,493	£96,103	£152,222
	85	£17,800	£61,344	£68,134	£77,443	£90,896	£111,891	£148,957

TABLE 160 *Discounted cost per QALY using 1000 Monte Carlo samples for each evaluation on the relative risk from statin treatment (holding all other parameters constant at their mean value)*

		Secondary		Primary prevention 1.5% annual CHD risk	
	Age (years)	SA1	Base case	SA1	Base case
Men	45	£10,203	£10,239	£12,225	£12,209
	55	£9,999	£10,035	£17,345	£17,243
	65	£10,485	£10,525	£25,266	£25,133
	75	£12,692	£12,744	£41,607	£41,489
	85	£15,590	£15,657	£58,100	£57,957
Women	45	£10,029	£10,067	£16,714	£16,571
	55	£9,767	£9,804	£20,730	£20,598
	65	£9,429	£9,466	£28,309	£28,246
	75	£11,232	£11,280	£48,601	£48,526
	85	£13,953	£14,017	£69,244	£69,147

TABLE 161 *Plus 20% on all health state costs*

			Annual CHD risk					
	Age (years)	Secondary	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£10,192	£9,469	£9,951	£10,770	£12,187	£14,846	£20,869
	55	£9,980	£12,644	£13,526	£14,924	£17,247	£21,514	£31,140
	65	£10,477	£16,800	£18,500	£21,043	£25,131	£32,540	£49,490
	75	£12,688	£26,184	£29,380	£34,062	£41,467	£54,729	£84,813
	85	£15,507	£36,668	£41,395	£48,011	£57,872	£74,043	£105,219
Women	45	£10,047	£13,802	£14,113	£14,912	£16,608	£20,312	£30,507
	55	£9,795	£16,041	£16,741	£18,098	£20,667	£25,964	£40,096
	65	£9,463	£19,433	£21,136	£23,816	£28,339	£37,057	£59,351
	75	£11,273	£31,698	£35,177	£40,353	£48,662	£63,800	£99,081
	85	£13,927	£47,545	£52,567	£59,424	£69,264	£84,451	£110,739

TABLE 162 *Minus 20% on all health state costs*

			Annual CHD risk					
	Age (years)	Secondary	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£10,286	£9,467	£9,966	£10,801	£12,231	£14,899	£20,921
	55	£10,090	£12,577	£13,481	£14,899	£17,239	£21,515	£31,132
	65	£10,573	£16,756	£18,475	£21,035	£25,134	£32,545	£49,471
	75	£12,799	£26,196	£29,407	£34,102	£41,511	£54,764	£84,799
	85	£15,807	£36,855	£41,584	£48,196	£58,042	£74,177	£105,267
Women	45	£10,086	£13,612	£13,967	£14,805	£16,534	£20,264	£30,469
	55	£9,813	£15,773	£16,523	£17,924	£20,529	£25,852	£39,985
	65	£9,470	£19,145	£20,887	£23,601	£28,152	£36,887	£59,166
	75	£11,287	£31,333	£34,847	£40,055	£48,389	£63,540	£98,801
	85	£14,107	£47,227	£52,279	£59,164	£69,029	£84,235	£110,531

with cost per QALY estimated to be £72,000 and £92,000 for women aged 85 years at 0.5% annual risk of a CHD event, in comparison to the base-case estimate of £111,000 (*Tables 164–66*).

If the ICERs estimated are compared with those estimated when reducing costs associated with the different health states, it is clear that the cost of statin treatment has a far greater impact on the cost-effectiveness ratio across all ages.

TABLE 163 *CHD analysis: secondary prevention results for a cohort of 1000 patients using a 20% and 40% reduction in the weighted statin cost used in the base case*

		Incremental cost per QALY			
	Age (years)	Base case	Statin cost –40%	Statin cost –20%	Using –20% on health state costs
Men	45	£10,239	£6,470	£8,354	£10,286
	55	£10,035	£6,334	£8,185	£10,090
	65	£10,525	£6,663	£8,594	£10,573
	75	£12,744	£8,082	£10,413	£12,799
	85	£15,657	£9,810	£12,734	£15,807
Women	45	£10,067	£6,412	£8,239	£10,086
	55	£9,804	£6,270	£8,037	£9,813
	65	£9,466	£6,063	£7,764	£9,470
	75	£11,280	£7,231	£9,256	£11,287
	85	£14,017	£8,866	£11,441	£14,107

TABLE 164 *CHD analysis: primary prevention results for a cohort of 1000 patients using a 40% reduction in the weighted statin cost used in the base case*

		Annual CHD risk					
	Age (years)	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£6,107	£6,407	£6,926	£7,831	£9,540	£13,422
	55	£8,202	£8,758	£9,648	£11,138	£13,886	£20,101
	65	£10,898	£11,986	£13,621	£16,258	£21,047	£32,020
	75	£17,010	£19,076	£22,109	£26,914	£35,530	£55,090
	85	£23,906	£26,995	£31,324	£37,782	£48,378	£68,815
Women	45	£9,005	£9,180	£9,672	£10,746	£13,117	£19,678
	55	£10,503	£10,927	£11,776	£13,412	£16,812	£25,923
	65	£12,727	£13,805	£15,516	£18,421	£24,042	£38,450
	75	£20,768	£23,002	£26,338	£31,707	£41,508	£64,382
	85	£31,223	£34,481	£38,937	£45,341	£55,234	£72,373

TABLE 165 *Minus 20% on statin prescribing costs*

			Annual CHD risk					
	Age (years)	Secondary	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£8,354	£7,787	£8,183	£8,856	£10,020	£12,206	£17,159
	55	£8,185	£10,406	£11,131	£12,280	£14,191	£17,700	£25,619
	65	£8,594	£13,838	£15,236	£17,330	£20,695	£26,795	£40,750
	75	£10,413	£21,600	£24,235	£28,096	£34,202	£45,138	£69,948
	85	£12,734	£30,334	£34,243	£39,714	£47,870	£61,244	£87,029
Women	45	£8,239	£11,356	£11,610	£12,265	£13,658	£16,702	£25,083
	55	£8,037	£13,205	£13,779	£14,894	£17,005	£21,360	£32,982
	65	£7,764	£16,008	£17,408	£19,612	£23,333	£30,507	£48,854
	75	£9,256	£26,141	£29,007	£33,271	£40,117	£52,589	£81,662
	85	£11,441	£39,304	£43,452	£49,116	£57,244	£69,788	£91,504

(e) Baseline utility

Using a constant baseline utility of 1 instead of the change in utility by age measured by Kind and colleagues.[241]

In the secondary prevention evaluations, all patients commence the analysis with a history of an event and thus their quality of life throughout the model is reduced to reflect the health of a patient in the health state that they occupy or

TABLE 166 *Minus 40% on statin prescribing costs*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£6,470	£6,107	£6,407	£6,926	£7,831	£9,540	£13,422
	55	£6,334	£8,202	£8,758	£9,648	£11,138	£13,886	£20,101
	65	£6,663	£10,898	£11,986	£13,621	£16,258	£21,047	£32,020
	75	£8,082	£17,010	£19,076	£22,109	£26,914	£35,530	£55,090
	85	£9,810	£23,906	£26,995	£31,324	£37,782	£48,378	£68,815
Women	45	£6,412	£9,005	£9,180	£9,672	£10,746	£13,117	£19,678
	55	£6,270	£10,503	£10,927	£11,776	£13,412	£16,812	£25,923
	65	£6,063	£12,727	£13,805	£15,516	£18,421	£24,042	£38,450
	75	£7,231	£20,768	£23,002	£26,338	£31,707	£41,508	£64,382
	85	£8,866	£31,223	£34,481	£38,937	£45,341	£55,234	£72,373

move to. For the primary prevention evaluations a large proportion of patients commence the analyses in the event-free state. Using 1 as the baseline utility value by age assumes that everyone at all ages who is CHD free is in perfect health.

It is acknowledged that when using the data from Kind[241] there is a small element of double-counting as a proportion of the patients in the sample will have a history of CHD. However, a series of exploratory evaluations was conducted to examine what, if any, impact this had on the results generated. The analyses suggested that using a constant baseline utility of 1 across all ages would bias the results in favour of statin treatment as patients remaining in the event-free health state would potentially accrue a larger health benefit than was appropriate.

Ideally, the most accurate results would be obtained by assigning quality of life values that change with age for the individual health state. Unfortunately this evidence is not available and a series of sensitivity analyses was conducted to explore the impact of varying the values and assumptions that have been used to assign quality of life in the model.

If the baseline utility is assigned a value of 1 across all ages, this reduces the estimated costs per QALY for secondary prevention, producing ICERs ranging from approximately £7,000 for women at aged 65 years to £10,000 for men aged 85 years (as opposed to £9,000 per QALY and £16,000 per QALY, respectively, in the base case).

For the primary prevention analyses, using a baseline utility of 1 gives ICERs ranging from approximately £7000 for men aged 45 years at 3% annual risk to £72,000 per QALY for women aged 85 years at 0.5% annual CHD risk (*Table 167*). For women at 0.5% annual risk the base case estimated cost per QALY is £111,000 and the large reduction is caused by over 50% increase in incremental QALYs gained: 30 QALYs gained by the statin cohort when holding the baseline utility constant as opposed to 20 QALYs gained when varying the baseline utility. Using a constant utility

TABLE 167 *Using constant baseline utility of 1 across all ages*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£7,691	£7,287	£7,638	£8,239	£9,285	£11,249	£15,678
	55	£7,379	£9,385	£10,023	£11,036	£12,720	£15,806	£22,734
	65	£7,554	£12,072	£13,278	£15,080	£17,971	£23,198	£35,095
	75	£8,854	£18,151	£20,345	£23,554	£28,620	£37,666	£58,069
	85	£10,467	£24,476	£27,593	£31,948	£38,421	£48,995	£69,239
Women	45	£7,453	£10,417	£10,624	£11,191	£12,419	£15,118	£22,542
	55	£7,120	£11,712	£12,210	£13,181	£15,023	£18,818	£28,910
	65	£6,733	£13,769	£14,969	£16,852	£20,025	£26,126	£41,643
	75	£7,784	£21,672	£24,040	£27,557	£33,187	£43,405	£67,048
	85	£9,335	£31,334	£34,622	£39,099	£45,504	£55,346	£72,266

of 1 increases the number of incremental QALYs gained by an average of 41% across all secondary and primary evaluations.

(f) Health state utilities

Using plus or minus 10% on all health state utilities, but allowing the baseline utility to vary with age

There is a large degree of uncertainty surrounding the correct valuation of health states particularly when events vary in severity and may have long-term health implications. It is particularly difficult to assign accurate measurements to quality of life when patients move between health states and when they have had a major event such as a non-fatal MI or stroke and then remain event free for a number of years. There is an added complication when assigning the values to patients experiencing an event at different stages in their lives, as younger patients may feel that the disutility due to an unexpected event has a greater impact on their quality of life than an older patient may.

If the utility values assigned to the different health states are increased by 10%, the statin cohorts gain more benefits from the events avoided. Consequently, the estimated costs per QALY decrease slightly for the secondary prevention analyses, ranging from approximately £9000 to £15,100 for women aged 65 years and men aged 85 years, respectively. Conversely, primary prevention results increase, ranging from £10,400 for men aged 45 years to £112,900 for women aged 85 years at 3% and 0.5% annual CHD risk, respectively (*Table 168*).

If the utility values assigned to the different health states are reduced by 10%, the estimated costs per QALY for secondary prevention of CHD increase from approximately £9500 to £10,000 for women aged 65 years and increase from £15,600 to £16,300 for men aged 85 years. For the primary prevention analyses, the estimated cost per QALYs decrease, ranging from approximately £8700 for men aged 45 years at 3% annual CHD risk to £108,400 for women aged 85 years at 0.5% annual risk, in comparison to £9500 for men aged 45 at 3% annual risk and £110,600 for women aged 85 at 0.5% annual risk in the base case (*Table 169*).

Varying the values assigned to the health states has opposite impacts on primary and secondary results depending on whether the values are increased or decreased. All patients in secondary evaluations have a quality of life assigned to them based on their current health state; therefore, increasing or decreasing the quality of life value assigned to the health states has the expected result of either decreasing or increasing the estimated cost per QALY, respectively. However, when exploring the cost-effectiveness of statins in primary prevention, because a large proportion of patients commence in the event-free state, and in the statin arm a greater proportion remain in this health state for a longer period, their utility is unaffected by the changes made to the quality of life experienced by patients having an event. Hence, when the values assigned to health state utilities are decreased, although benefits from patients in event states are decreased, the total incremental benefits of the cohorts are increased as the benefits accrued by patients in the event-free health state outweigh the reduced amounts from patients in the event states. Conversely, increasing utility values for event states produces an overall reduction in the total incremental benefits as fewer patients in the statin arm are affected by the increase in utility.

TABLE 168 *Using plus 10% on all health state utilities, but allowing the baseline utility to vary with age*

			Annual CHD risk					
	Age (years)	Secondary	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£9,793	£10,426	£10,916	£11,768	£13,259	£16,071	£22,447
	55	£9,460	£13,802	£14,710	£16,167	£18,604	£23,086	£33,171
	65	£10,013	£17,812	£19,589	£22,248	£26,519	£34,249	£51,873
	75	£12,193	£27,727	£31,068	£35,960	£43,683	£57,479	£88,601
	85	£15,063	£38,718	£43,609	£50,434	£60,564	£77,062	£108,483
Women	45	£9,568	£15,981	£16,150	£16,875	£18,590	£22,482	£33,306
	55	£9,160	£17,911	£18,549	£19,904	£22,560	£28,114	£42,945
	65	£8,963	£20,580	£22,349	£25,137	£29,846	£38,911	£61,983
	75	£10,691	£33,348	£36,962	£42,334	£50,941	£66,562	£102,670
	85	£13,366	£49,634	£54,762	£61,736	£71,688	£86,921	£112,934

TABLE 169 *Using minus 10% on all health state utilities, but allowing the baseline utility to vary with age*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,727	£8,671	£9,156	£9,954	£11,313	£13,840	£19,544
	55	£10,685	£11,608	£12,480	£13,837	£16,068	£20,143	£29,336
	65	£11,093	£15,858	£17,503	£19,954	£23,884	£30,998	£47,299
	75	£13,346	£24,814	£27,890	£32,390	£39,505	£52,262	£81,323
	85	£16,300	£34,994	£39,567	£45,978	£55,565	£71,375	£102,191
Women	45	£10,620	£12,000	£12,417	£13,273	£14,948	£18,485	£28,110
	55	£10,546	£14,306	£15,075	£16,447	£18,950	£24,023	£37,504
	65	£10,030	£18,150	£19,826	£22,434	£26,808	£35,218	£56,763
	75	£11,939	£29,874	£33,258	£38,278	£46,329	£61,019	£95,474
	85	£14,734	£45,332	£50,276	£57,038	£66,779	£81,913	£108,428

TABLE 170 *Using constant baseline utility across all ages and plus 10% on health state utilities*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£7,359	£8,003	£8,349	£8,965	£10,057	£12,124	£16,800
	55	£6,960	£10,245	£10,891	£11,936	£13,691	£16,923	£24,170
	65	£7,189	£12,801	£14,052	£15,928	£18,941	£24,387	£36,752
	75	£8,475	£19,198	£21,483	£24,828	£30,104	£39,507	£60,610
	85	£10,073	£25,757	£28,979	£33,468	£40,117	£50,906	£71,319
Women	45	£7,085	£12,075	£12,152	£12,642	£13,861	£16,673	£24,518
	55	£6,656	£13,131	£13,562	£14,510	£16,393	£20,351	£30,912
	65	£6,378	£14,668	£15,896	£17,840	£21,128	£27,455	£43,496
	75	£7,381	£22,905	£25,349	£28,983	£34,799	£45,326	£69,498
	85	£8,905	£32,793	£36,136	£40,675	£47,139	£56,996	£73,725

(g) Baseline and health state utilities

Combining the effect of using a constant value of 1 for baseline quality of life and increasing the values assigned to health states by 10% produces secondary prevention costs per QALY ranging from approximately £6400 for women aged 65 years to £10,100 for men aged 85 years (*Table 170*). For primary prevention, using a constant value of 1 for baseline quality of life in conjunction with decreasing the values assigned to health states by 10% produces costs per QALY ranging from approximately £6700 for men aged 45 years at 3% annual risk of a CHD event to £70,800 for women aged 85 years at 0.5% annual risk of a CHD event (*Table 171*). However, as stated previously, it is believed that using a baseline utility that varies with age is the more conservative alternative.

(h) Incidence and prevalence

Incidence and prevalence increased by 150% for each health state individually

To examine uncertainty in the proportion of patients allocated to the different health states, a series of analyses was performed where the proportion of patients assigned to the starting health states was increased by 150% (*Tables 172–175*). Varying the ratio of patients across health states had little impact on the results. Increasing the proportion of patients who commenced the secondary prevention analyses in the non-fatal MI health state by 150% while holding the other values constant reduced the lowest estimated ICER to around £9200 (*Table 174*), while increasing the proportion of patients starting in the non-fatal stroke state increased the lowest estimated ICER to £10,100 and the highest estimated ICER to £16,600 (*Table 175*).

TABLE 171 *Using constant baseline utility across all ages and minus 10% on all health state utilities*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£8,055	£6,689	£7,038	£7,622	£8,624	£10,492	£14,696
	55	£7,851	£8,658	£9,283	£10,262	£11,877	£14,828	£21,460
	65	£7,957	£11,422	£12,584	£14,318	£17,096	£22,120	£33,581
	75	£9,268	£17,213	£19,321	£22,405	£27,275	£35,988	£55,732
	85	£10,893	£23,316	£26,334	£30,559	£36,863	£47,222	£67,277
Women	45	£7,861	£9,160	£9,437	£10,039	£11,248	£13,829	£20,861
	55	£7,652	£10,570	£11,104	£12,075	£13,863	£17,500	£27,152
	65	£7,129	£12,975	£14,143	£15,968	£19,032	£24,919	£39,941
	75	£8,234	£20,564	£22,859	£26,264	£31,718	£41,641	£64,765
	85	£9,809	£30,000	£33,230	£37,641	£43,979	£53,789	£70,864

TABLE 172 *Increasing the incidence and prevalence rates for patients commencing in the stable angina health state*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,527	£9,640	£10,104	£10,903	£12,297	£14,923	£20,880
	55	£10,223	£12,682	£13,533	£14,894	£17,168	£21,359	£30,836
	65	£10,614	£16,787	£18,447	£20,940	£24,955	£32,245	£48,955
	75	£12,888	£26,097	£29,230	£33,828	£41,110	£54,177	£83,902
	85	£15,985	£37,010	£41,697	£48,263	£58,059	£74,139	£105,187
Women	45	£10,364	£13,588	£13,815	£14,521	£16,095	£19,601	£29,352
	55	£9,876	£15,699	£16,309	£17,556	£19,972	£25,012	£38,574
	65	£9,442	£19,082	£20,680	£23,223	£27,547	£35,929	£57,497
	75	£11,315	£30,841	£34,137	£39,071	£47,034	£61,626	£95,955
	85	£14,262	£46,441	£51,298	£57,968	£67,604	£82,605	£108,921

TABLE 173 *Increasing the incidence and prevalence rates for patients commencing in the unstable angina health state*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£9,935	£9,252	£9,744	£10,566	£11,974	£14,601	£20,527
	55	£9,818	£12,290	£13,174	£14,562	£16,855	£21,051	£30,493
	65	£10,175	£16,248	£17,918	£20,410	£24,405	£31,637	£48,178
	75	£12,125	£25,111	£28,217	£32,762	£39,946	£52,821	£82,113
	85	£14,562	£35,250	£39,858	£46,314	£55,961	£71,849	£102,749
Women	45	£9,641	£13,018	£13,384	£14,218	£15,914	£19,558	£29,525
	55	£9,515	£15,352	£16,086	£17,456	£20,006	£25,221	£39,098
	65	£9,114	£18,768	£20,460	£23,106	£27,555	£36,115	£58,020
	75	£10,646	£30,620	£34,044	£39,130	£47,288	£62,163	£96,957
	85	£12,919	£46,197	£51,177	£57,982	£67,769	£82,929	£109,355

A similar series of analyses was performed adjusting the proportion and thus the probability of the distribution across primary events. The largest impact was a result of increasing the proportion of patients assigned to an initial primary non-fatal stroke health state. This adjustment (an increase of 150%) increased the ICERs produced from £9000 to £10,000 for men aged 45 years and from £111,000 to £115,000 for women aged 85 years.

Increasing the proportion of patients assigned to the primary non-fatal MI health state decreased the ICERs to £8900 for men aged 45 years and £106,000 for women aged 85 years.

TABLE 174 *Increasing the incidence and prevalence rates for patients commencing in the non-fatal MI health state*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£9,773	£8,881	£9,368	£10,176	£11,553	£14,117	£19,897
	55	£9,668	£11,853	£12,719	£14,076	£16,315	£20,409	£29,628
	65	£10,255	£15,675	£17,299	£19,722	£23,608	£30,647	£46,775
	75	£12,425	£24,132	£27,146	£31,557	£38,536	£51,064	£79,665
	85	£15,451	£33,918	£38,424	£44,748	£54,220	£69,883	£100,577
Women	45	£9,590	£12,966	£13,310	£14,118	£15,783	£19,373	£29,209
	55	£9,458	£14,974	£15,690	£17,027	£19,520	£24,621	£38,209
	65	£9,227	£18,023	£19,652	£22,203	£26,499	£34,780	£56,043
	75	£11,075	£29,008	£32,280	£37,149	£44,979	£59,313	£93,136
	85	£13,880	£43,654	£48,491	£55,132	£64,745	£79,788	£106,457

TABLE 175 *Increasing the incidence and prevalence rates for patients commencing in the non-fatal stroke health state*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,725	£10,291	£10,804	£11,679	£13,195	£16,043	£22,500
	55	£10,451	£13,869	£14,831	£16,349	£18,866	£23,474	£33,821
	65	£11,048	£18,616	£20,486	£23,274	£27,736	£35,781	£54,016
	75	£13,503	£29,217	£32,740	£37,877	£45,954	£60,296	£92,292
	85	£16,564	£40,687	£45,762	£52,809	£63,199	£79,956	£111,336
Women	45	£10,635	£15,024	£15,392	£16,288	£18,155	£22,192	£33,200
	55	£10,298	£17,466	£18,293	£19,829	£22,677	£28,469	£43,699
	65	£10,078	£21,424	£23,358	£26,359	£31,367	£40,908	£64,857
	75	£12,004	£34,679	£38,540	£44,225	£53,250	£69,455	£106,248
	85	£14,893	£51,310	£56,616	£63,770	£73,877	£89,140	£114,691

TABLE 176 *Increasing the incidence and prevalence rates for patients commencing in the TIA health state*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,306	£9,509	£10,035	£10,901	£12,374	£15,108	£21,259
	55	£10,057	£12,785	£13,723	£15,184	£17,586	£21,961	£31,758
	65	£10,573	£17,172	£18,941	£21,573	£25,780	£33,371	£50,636
	75	£12,820	£26,771	£30,053	£34,848	£42,412	£55,920	£86,430
	85	£15,775	£36,954	£41,706	£48,350	£58,242	£74,445	£105,630
Women	45	£10,149	£13,853	£14,271	£15,178	£16,997	£20,868	£31,367
	55	£9,896	£16,001	£16,795	£18,248	£20,927	£26,371	£40,751
	65	£9,502	£19,539	£21,323	£24,098	£28,747	£37,655	£60,302
	75	£11,394	£32,207	£35,815	£41,156	£49,690	£65,167	£101,005
	85	£14,182	£48,344	£53,470	£60,441	£70,400	£85,680	£111,907

(i) Rate of increase in risk of CHD over time

Using upper and lower 95% CIs for natural increase in CHD and corresponding increase in annual CVD risk in the primary prevention analyses

Increasing both the natural increase in CHD risk with age for the primary prevention population and the corresponding calculated annual CVD risk increases the lowest estimated cost per QALY by 4% for men aged 45 years at a starting annual CHD risk of 3%, and decreases the highest estimated cost per QALY by just 2% for women aged 85 years at 0.5% annual risk of a CHD event (*Table 177*). Using the lower 95% CI for the natural increase in CHD risk with age and the corresponding annual CVD risk has a similar but

TABLE 177 *Upper CI for natural age-increased risk in CHD risk and the corresponding increase in annual CVD risk*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,239	£9,871	£10,329	£11,116	£12,480	£15,027	£20,682
	55	£10,035	£13,014	£13,862	£15,210	£17,443	£21,508	£30,468
	65	£10,525	£17,068	£18,724	£21,195	£25,143	£32,222	£48,040
	75	£12,744	£26,386	£29,504	£34,058	£41,218	£53,917	£82,125
	85	£15,657	£36,842	£41,479	£47,957	£57,582	£73,288	£103,288
Women	45	£10,067	£14,306	£14,566	£15,307	£16,926	£20,490	£30,210
	55	£9,804	£16,439	£17,084	£18,371	£20,835	£25,918	£39,299
	65	£9,466	£19,575	£21,229	£23,831	£28,213	£36,610	£57,752
	75	£11,280	£31,539	£34,921	£39,944	£47,981	£62,538	£96,032
	85	£14,017	£47,148	£52,069	£58,785	£68,415	£83,259	£108,906

TABLE 178 *Lower CI for natural age-increased risk in CHD risk and the corresponding increase in annual CVD risk*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£10,239	£9,074	£9,597	£10,464	£11,947	£14,735	£21,167
	55	£10,035	£12,210	£13,149	£14,617	£17,050	£21,541	£31,901
	65	£10,525	£16,488	£18,250	£20,885	£25,130	£32,894	£51,081
	75	£12,744	£25,992	£29,282	£34,110	£41,774	£55,628	£87,734
	85	£15,657	£36,680	£41,500	£48,253	£58,342	£74,960	£107,291
Women	45	£10,067	£13,112	£13,516	£14,411	£16,216	£20,088	£30,794
	55	£9,804	£15,371	£16,176	£17,646	£20,358	£25,901	£40,837
	65	£9,466	£18,994	£20,786	£23,581	£28,278	£37,349	£60,873
	75	£11,280	£31,485	£35,100	£40,469	£49,089	£64,856	£102,058
	85	£14,017	£47,623	£52,781	£59,813	£69,897	£85,458	£112,423

converse impact on the results, decreasing the lower estimated cost per QALY by 4% and increasing the highest estimated cost per QALY by 2% (*Table 178*).

(j) Time-frame of the model

As the evidence used to model benefits from statin treatment is derived from trials of a relatively short time-horizon in comparison with the lifetime model in the current evaluation, the cost and benefits associated with just 10 years of statin treatment are explored.

Shortening the time-frame of the model to 10 years of statin treatment increases the estimated costs per QALY across all age groups (*Table 179*). The discounted ICERs using the 10-year horizon range from approximately £24,000 to £125,000 per QALY for women and from £20,000 to £100,000 per QALY for men. Using a 10-year horizon as opposed to lifetime has a greater impact on the results for the younger ages, and these results suggest that it is less cost-effective to treat younger patients than older patients. Younger patients are less likely to benefit from statins in the first 10 years of treatment as the risk of subsequent and fatal events is lower in younger patients. However, if treatment is started at an earlier age and continued over the patient's lifetime the costs avoided and health benefits gained accrue to reduce the cost per QALY.

The 10-year results for older patients (£20,000 and £19,000 for men and women aged 85 years) are comparable to those estimated for a lifetime of treatment (£16,000 and £14,000 for men and women aged 85 years).

Examining the costs and benefits over 10 years has a large impact on the primary prevention results, with the ICER for 45-year-old men at 3% annual risk of a CHD event increasing from £10,000 to £36,000 per QALY, and the ICER for 85-year-old women at 0.5% annual risk increasing from £111,000 to £367,000 per QALY (*Table 180*). The impact of assessing only 10 years of benefits is

TABLE 179 *CHD secondary prevention: 10-year results for a cohort of 1000 patients*

		Undiscounted			Discounted		
	Age (years)	Incremental costs	Incremental QALYs	Incremental cost per QALY	Incremental costs	Incremental QALYs	Incremental cost per QALY
Men	45	£3,292,690	29	£115,032	£2,584,265	26	£99,501
	55	£3,175,936	49	£64,353	£2,502,553	45	£55,853
	65	£2,923,748	79	£37,019	£2,319,143	72	£32,309
	75	£2,528,751	92	£27,405	£2,038,551	84	£24,257
	85	£1,836,161	86	£21,399	£1,542,956	79	£19,577
Women	45	£3,351,264	23	£143,962	£2,629,071	21	£124,530
	55	£3,267,634	40	£82,506	£2,570,147	36	£71,537
	65	£3,043,878	78	£39,259	£2,403,566	70	£34,145
	75	£2,735,210	99	£27,761	£2,180,838	90	£24,346
	85	£2,092,025	101	£20,693	£1,724,416	93	£18,634

TABLE 180 *CHD analysis: primary prevention for a cohort of 1000 patients at varying annual CHD risk – 10-year time-frame (discounted cost per QALY)*

		Annual CHD risk					
	Age (years)	3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
Men	45	£35,766	£41,708	£50,574	£65,133	£93,281	£170,072
	55	£42,744	£49,607	£59,836	£76,591	£108,809	£195,489
	65	£44,987	£52,324	£63,225	£81,016	£115,042	£205,498
	75	£52,973	£61,590	£74,357	£95,112	£134,538	£237,735
	85	£52,719	£61,451	£74,349	£95,241	£134,721	£236,928
Women	45	£57,557	£66,842	£80,845	£104,202	£150,605	£286,019
	55	£60,976	£70,144	£84,041	£107,275	£153,367	£286,503
	65	£57,541	£66,586	£80,208	£102,838	£147,376	£273,953
	75	£74,867	£86,730	£104,474	£133,699	£190,430	£346,534
	85	£80,799	£93,862	£113,263	£144,931	£205,551	£367,198

greater at lower levels of baseline risk, as fewer secondary CHD events will occur within the first 10 years.

(k) Compliance

Using the 'worst case', scenario, where full compliance is reduced to 55% and 50% by year 5 for secondary and primary patients, respectively, and the full treatment costs are incurred: in secondary prevention the lowest ICER (for women aged 65 years) increases to £14,000 from £9000, while the highest ICER (for men aged 85 years) increases to £22,000 from £16,000 per QALY (*Table 181*). Using the same scenario, with the full treatment costs, primary analyses produce ICERs ranging from £16,000 for men aged 45 years at 3% annual risk of a CHD event to £133,000 for women aged 75 years at 0.5% annual risk of a CHD event, in comparison with the base-case range of £9000–111,000.

TABLE 181 *Compliance using the worst case scenario with the full treatment costs*

			Annual CHD risk					
	Age (years)	**Secondary**	**3.0%**	**2.5%**	**2.0%**	**1.5%**	**1.0%**	**0.5%**
Men	45	£15,582	£16,079	£17,039	£18,578	£21,155	£25,900	£36,547
	55	£15,071	£21,025	£22,665	£25,180	£29,270	£36,674	£53,209
	65	£15,478	£27,524	£30,486	£34,854	£41,793	£54,239	£82,387
	75	£18,266	£41,748	£46,985	£54,567	£66,397	£87,221	£133,042
	85	£21,518	£54,103	£60,639	£69,534	£82,298	£102,080	£136,721
Women	45	£15,315	£22,108	£22,957	£24,602	£27,741	£34,251	£51,622
	55	£14,694	£25,414	£26,882	£29,418	£33,945	£42,954	£66,305
	65	£13,905	£30,631	£33,621	£38,187	£45,712	£59,886	£94,955
	75	£16,177	£48,588	£54,135	£62,205	£74,824	£97,000	£145,357
	85	£19,312	£66,314	£72,613	£80,859	£92,062	£108,080	£132,743

Appendix 35

Results of additional sensitivity analyses requested by the Appraisal Committee

The additional analyses requested are detailed below.

- the cost-effectiveness of lowering risk thresholds for treatment (scenario 1: CHD plus stroke outcomes)
- sensitivity of economic results to the analytical time-horizon of the model and assumptions impacting on long-term extrapolation (scenario 1: CHD plus stroke outcomes)
- the cost-effectiveness of lowering risk thresholds for treatment using 3.5% discount rates for both costs and benefits (scenario 1: CHD plus stroke outcomes).

The outcomes of these analyses are summarised below.

The cost-effectiveness of lowering risk thresholds for treatment considers the naturally framed question: 'Having accepted a threshold of *x*% CHD risk, what is the cost-effectiveness of lowering that threshold to *y*%, taking into account the increased numbers of people, incurring costs and receiving benefits, who would be eligible for treatment?'

In considering the cost-effectiveness of lowering the risk threshold for treatment from, say, 3% to 2.5%, it is clear that people with a risk of greater than 3% would be treated under both options. The cost and QALY impact in these people can therefore be disregarded. The cost-effectiveness of reducing the threshold is therefore the cost-effectiveness of treating people with a risk level between 2.5 and 3% versus not treating them.

Since incremental costs and QALYs differ with age and risk level, the overall cost-effectiveness for that population group is estimated from the number of people expected to fall into each age and risk category.

The weighted ICERs for men are comparable across all CHD risk levels, ranging between approximately £15,500 and £18,300. The ICERs for women are slightly higher than for men, with a range of £19,500–29,500.

The sensitivity of economic results to the analytical time-horizon of the model and assumptions impacting on long-term extrapolation were examined. The scenarios evaluated in the main report demonstrate the cost-effectiveness of statin treatment over a patient's lifetime, with a sensitivity analysis presented for the base-case CHD scenario using a time-horizon of 10 years. However, the majority of the effectiveness data is derived from RCTs with an average duration of approximately 5 years. Hence, a large proportion of the costs and benefits associated with statin treatment is based on extrapolations within the model. An additional series of analyses was performed exploring the sensitivity of the model to assumptions that impact on long-term estimates of costs and benefits. The economic results at 5, 10, 15 and 20 years, together with the lifetime results for scenario 1 (CHD plus stroke outcomes) are presented.

The analysis demonstrates that for the CHD risks considered (up to 4.5% per annum) the cost-effectiveness of treating people over the age of 75 years who have not experienced a previous CHD event is over £20,000 per QALY for all risk levels and over £30,000 for all but the highest risk groups modelled for over 20 years. It should be noted that the number of people in these categories is small.

With respect to cohorts aged 45, 55 and 65 years, the cost-effectiveness of statin therapy is highly sensitive to the time-horizon of the analysis. For example, for men and women aged 55 years, analysed over the full lifetime, all estimates of cost-effectiveness are £20,000 per QALY or better. However, when using a 10-year horizon all estimates of cost-effectiveness are worse than £30,000 per QALY. Using a time-horizon of 20 years the cost-effectiveness at greater than 3% CHD risk is better than £20,000. The results for the ages of 45 and 65 years show a similar pattern of sensitivity to analytical time-horizon.

Cost-effectiveness of statin treatment weighted by the proportion risk (scenario 1: CHD plus stroke outcomes)

An additional analysis was performed to estimate the cost-effectiveness of treating people between

TABLE 183 *Numbers of people in each age/risk group (derived from HSE 1998[203] and England and Wales population 2003)*[a]

	Men				Women			
Age (years)	**45–54**	**55–64**	**65–74**	**75–84**	**45–54**	**55–64**	**65–74**	**75–84**
Annual CHD risk								
1.0%	147,522	156,160	67,054	7,791	22,579	62,202	116,955	100,450
1.1%	132,769	156,160	75,995	15,582	22,579	74,642	49,481	86,100
1.2%	95,889	131,760	67,054	31,165	12,902	70,495	49,481	57,400
1.3%	73,761	92,720	67,054	23,373	9,677	53,908	67,474	50,225
1.4%	70,073	122,000	75,995	62,329	16,128	41,468	62,976	21,525
1.5%	55,321	107,360	80,465	38,956	9,677	29,028	62,976	43,050
1.6%	51,633	48,800	80,465	0	3,226	24,881	40,484	14,350
1.7%	36,880	78,080	71,525	31,165	6,451	29,028	26,990	0
1.8%	25,816	63,440	75,995	38,956	12,902	16,587	26,990	7,175
1.9%	11,064	53,680	80,465	85,703	0	12,440	40,484	28,700
2.0%	18,440	68,320	58,114	46,747	0	12,440	17,993	35,875
2.1%	33,192	73,200	67,054	15,582	0	16,587	0	7,175
2.2%	14,752	53,680	67,054	62,329	0	12,440	17,993	14,350
2.3%	25,816	48,800	62,584	31,165	3,226	12,440	8,997	0
2.4%	11,064	53,680	35,762	23,373	3,226	8,294	22,491	0
2.5%	7,376	68,320	75,995	31,165	3,226	4,147	22,491	7,175
2.6%	11,064	39,040	31,292	15,582	0	0	4,498	7,175
2.7%	7,376	43,920	44,703	23,373	6,451	8,294	13,495	7,175
2.8%	3,688	19,520	40,233	15,582	0	4,147	8,997	7,175
2.9%	0	19,520	53,644	31,165	0	8,294	8,997	0
3.0%	3,688	9,760	62,584	23,373	3,226	8,294	8,997	7,175

[a] The HSE does not include anyone over the age of 85 years.

x and *y*% compared with not treating them. In considering the cost-effectiveness of lowering the risk threshold for treatment from, say, 3% to 2.5%, it is clear that people with a risk of greater than 3% would be treated under both options. The cost and QALY impact in these people can therefore be disregarded. The cost-effectiveness of reducing the threshold is therefore the cost-effectiveness of treating people with a risk level between 2.5% and 3% versus not treating them.

Since incremental costs and QALYs differ with age and risk level, the overall cost effectiveness for that population group is estimated from the number of people expected to fall into each age and risk category (*Table 183*). The incremental costs and the incremental QALYs obtained from scenario 1 (CHD plus stroke outcomes), using increments of CHD risk of 0.01 per annum, were weighted using the number of people in each of these age and risk groups.

The total incremental costs and QALYs are multiplied by the number of people in each category to give a cost per QALY of treating people at risk levels between *x* and *y*% compared with not treating them.

As can be seen in *Table 184*, the weighted ICERs for men are comparable across all CHD risk levels, ranging between approximately £15,500 and £18,300. The ICERs for women are slightly higher than for men, with a range of £19,500–29,500.

Sensitivity of economic results to the analytical time-horizon of the model and assumptions impacting on long-term extrapolation

The scenarios evaluated in the main report demonstrate the cost-effectiveness of statin treatment over a patient's lifetime. However, the majority of the effectiveness data is derived from RCTs with an average duration of approximately 5 years. Hence, a large proportion of the costs and benefits associated with statin treatment is based on extrapolations within the model. The key assumptions underpinning the extrapolations are:

- Effectiveness of statins is maintained over the time-horizon of the model.

TABLE 184 *Discounted weighted cost per QALY, comparing treating people at CHD risk between x% and y% per annum (scenario 1: CHD plus stroke outcomes)*

Treating between x and y%	Total weighted incremental cost	Total weighted incremental QALY	Weighted cost per QALY
Men			
1.5% to 1.0%	£7,228,416,284	394,220	£18,336
2.0% to 1.5%	£4,403,781,134	249,449	£17,654
3.0% to 2.0%	£5,531,945,178	350,048	£15,803
2.5% to 2.0%	£3,355,782,620	209,889	£15,988
3.0% to 2.5%	£2,176,162,559	140,159	£15,526
Women			
1.5% to 1.0%	£4,284,769,082	145,259	£29,498
2.0% to 1.5%	£1,783,546,414	74,797	£23,845
3.0% to 2.0 %	£1,259,349,710	61,083	£20,617
2.5% to 2.0 %	£772,631,864	36,032	£21,443
3.0% to 2.5 %	£486,717,846	25,051	£19,429

- Compliance is maintained over time, and this is true for individuals identified as low and high risk.
- Events are distributed within global CHD risk levels, by age and gender.
- Multiple events occur over long time-horizons: the complexity of this issue and the lack of robust evidence mean that it is difficult to estimate the direction of any bias introduced.

The NICE methods guidance states:

> "2.2.6.1 The time span used in the appraisal usually reflects the period over which the main differences between technologies from the point of view of both their likely health effects and use of healthcare resources are expected to be experienced, **taking into account the limitations of supporting evidence**."

> "5.8.3 Providing an all-embracing definition of what constitutes a high-quality model is not possible, but some guidelines are available. In general, all structural assumptions and data inputs should be clearly documented and justified. This is particularly important in the case of modelling to extrapolate costs and health benefits over an extended time horizon. **In such circumstances alternative time horizon scenarios should be considered in order to compare the implications of different assumptions for the results**."

The original report presented 10-year results for base-case CHD; therefore, an additional series of analyses was performed exploring a broader range of time-horizons for scenario 1 (CHD plus stroke outcomes). *Tables 185* and *186* present the cost-effectiveness ratios across different horizons for the age and risk groups being considered.

As can be seen, as the time-horizon over which the costs and benefits associated with statin treatment are accrued increases from 5 years to lifetime, the ICERs decrease. In addition, as the initial annual CHD risk decreases, the range in the ICERs across the age groups increases.

The results demonstrate that irrespective of risk, it is not cost-effective to treat cohorts over the age of 75 years. However, the majority of these people will be at a high risk or would be secondary patients and hence will already be receiving statin treatment.

Restricting the discussion of the differing horizon results to cohorts aged 45, 55 and 65 years, the male ICERs estimated are comparable across the ages. For example, the approximate ICERs for men aged 45, 55 and 65 years at 1.5% annual risk are £27,700 (£38,700, £61,400, £135,300), £30,800 (£44,100, £72,100, £162,600) and £33,700 (£46,100, £75,800, £182,300) when using a time-horizon of 20 (15, 10, 5) years.

The female ICERs are also comparable across the age groups 45, 55 and 65 years, and are all higher than those estimated for men. For example, using a 20-year horizon and cohorts at 1.5% annual CHD risk, the estimated ICERs are approximately £45,100, £42,400 and £41,300 for women aged 45, 55 and 65 years, respectively. Similarly, using a 10-year horizon the ICERs for women at 1.5% risk are £62,900, £62,100 and £60,000 for the ages of 45, 55 and 65 years, respectively.

TABLE 185 *Comparing the incremental discounted cost per QALY results across the different time-horizons by age/risk level for men*

Horizon		Annual CHD risk 1.50%	2.00%	2.50%	3.00%	3.50%	4.00%
	Start age	45	45	45	45	45	45
Lifetime		£12,080	£10,664	£9,839	£9,347	£9,061	£8,913
20		£27,724	£22,628	£19,527	£17,482	£16,066	£15,056
15		£38,697	£30,864	£26,085	£22,899	£20,650	£19,001
10		£61,416	£47,791	£39,491	£33,928	£29,960	£27,002
5		£135,290	£102,705	£82,989	£69,788	£60,340	£53,252
	Start age	55	55	55	55	55	55
Lifetime		£17,073	£14,757	£13,357	£12,467	£11,891	£11,525
20		£30,849	£25,353	£21,984	£19,754	£18,206	£17,100
15		£44,083	£35,412	£30,095	£26,542	£24,033	£22,194
10		£72,064	£56,429	£46,878	£40,470	£35,897	£32,490
5		£162,619	£123,966	£100,570	£84,904	£73,694	£65,285
	Start age	65	65	65	65	65	65
Lifetime		£24,867	£20,807	£18,276	£16,579	£15,389	£14,530
20		£33,651	£27,438	£23,590	£21,007	£19,181	£17,843
15		£46,142	£36,926	£31,238	£27,409	£24,683	£22,663
10		£75,769	£59,258	£49,133	£42,317	£37,437	£33,788
5		£182,270	£138,828	£112,519	£94,894	£82,277	£72,809
	Start age	75	75	75	75	75	75
Lifetime		£41,025	£33,684	£29,038	£25,862	£23,578	£21,876
20		£45,111	£36,548	£31,208	£27,591	£25,004	£23,082
15		£55,835	£44,649	£37,704	£33,003	£29,635	£27,123
10		£88,640	£69,439	£57,616	£49,633	£43,903	£39,610
5		£221,243	£168,622	£136,738	£115,373	£100,075	£88,595
	Start age	85	85	85	85	85	85
Lifetime		£57,397	£47,601	£41,031	£36,337	£32,829	£30,121
20		£57,397	£47,601	£41,031	£36,337	£32,829	£30,121
15		£57,397	£47,601	£41,031	£36,337	£32,829	£30,121
10		£89,821	£70,228	£58,120	£49,920	£44,016	£39,577
5		£205,862	£156,884	£127,143	£107,186	£92,881	£82,137

Cost-effectiveness of lowering risk thresholds for treatment using 3.5% discount rates for both costs and benefits (scenario 1: CHD plus stroke outcomes)

As in the first of these additional analyses, the total incremental costs and QALYs were multiplied by the number of people in each category to give a cost per QALY of treating people at risk levels between *x* and *y*% compared with not treating them, the key difference being that costs and benefits are discounted at 3.5% in the following evaluations.

As can be seen in *Table 187*, the weighted ICERs for men range between approximately £26,500 (3.0% to 2.5%) and £44,900 (1.0% to 0.5%) and increase as initial CHD risk level decreases. The weighted ICERs for women are higher than the corresponding results for men and range from approximately £33,300 (3.0% to 2.5%) to £78,000 (1.0% to 0.5%).

Cost-effectiveness of lowering risk thresholds for treatment using different age groups (scenario 1: CHD plus stroke outcomes) with 3.5% discount rates for both costs and benefits

The results presented in *Table 188* use the same methodologies as the first and third of these additional sensitivity analyses, and the results are presented by age group as opposed to an overall weighted ICER by risk level.

TABLE 186 *Comparing the incremental discounted cost per QALY results across the different time-horizons by age/risk level for women*

		Annual CHD risk					
Horizon		**1.50%**	**2.00%**	**2.50%**	**3.00%**	**3.50%**	**4.00%**
	Start age	45	45	45	45	45	45
Lifetime		£16,410	£14,702	£13,879	£13,538	£13,492	£13,647
20		£45,129	£36,817	£31,954	£28,860	£26,800	£25,402
15		£62,913	£50,104	£42,491	£37,520	£34,077	£31,601
10		£98,617	£76,656	£63,496	£54,775	£48,608	£44,047
5		£209,159	£159,135	£129,091	£109,074	£94,800	£84,121
	Start age	55	55	55	55	55	55
Lifetime		£20,387	£17,813	£16,436	£15,705	£15,372	£15,308
20		£42,437	£35,037	£30,741	£28,060	£26,334	£25,230
15		£62,075	£50,067	£42,972	£38,397	£35,295	£33,135
10		£101,235	£79,495	£66,500	£57,937	£51,936	£47,550
5		£219,483	£167,719	£136,658	£115,991	£101,283	£90,307
	Start age	65	65	65	65	65	65
Lifetime		£27,942	£23,439	£20,761	£19,047	£17,908	£17,139
20		£41,306	£33,577	£28,960	£25,956	£23,898	£22,444
15		£57,976	£46,294	£39,282	£34,669	£31,454	£29,127
10		£96,145	£75,140	£62,496	£54,105	£48,174	£43,795
5		£232,074	£176,899	£143,755	£121,681	£105,953	£94,201
	Start age	75	75	75	75	75	75
Lifetime		£47,997	£39,741	£34,589	£31,119	£28,661	£26,864
20		£56,299	£45,518	£38,966	£34,618	£31,566	£29,340
15		£73,427	£58,591	£49,566	£43,552	£39,301	£36,173
10		£123,853	£96,959	£80,623	£69,702	£61,930	£56,152
5		£335,165	£255,719	£207,908	£176,024	£153,282	£136,274
	Start age	85	85	85	85	85	85
Lifetime		£68,600	£58,772	£51,924	£46,907	£43,094	£40,116
20		£68,600	£58,772	£51,924	£46,907	£43,094	£40,116
15		£68,600	£58,772	£51,924	£46,907	£43,094	£40,116
10		£135,256	£105,860	£87,843	£75,710	£67,015	£60,503
5		£368,518	£281,364	£228,683	£193,442	£168,244	£149,358

TABLE 187 *Discounted weighted cost per QALY, comparing treating at CHD risk between x% and y% per annum using 3.5% discounting rates*

Annual CHD risk level	**Cost**	**QALY**	**Weighted cost per QALY**
Men			
1.0% to 0.5%	£13,446,792,896	299,206	£44,942
1.5% to 1.0%	£9,231,474,512	260,269	£35,469
2.0% to 1.5%	£5,493,480,530	172,108	£31,919
2.5% to 2.0%	£4,166,716,702	147,524	£28,244
3.0% to 2.5%	£2,675,731,299	101,084	£26,470
3.0% to 2.0%	£6,842,448,001	248,608	£27,523
Women			
1.0% to 0.5%	£15,740,710,901	204,428	£76,999
1.5% to 1.0%	£5,359,083,526	98,232	£54,555
2.0% to 1.5%	£2,231,518,185	51,501	£43,329
2.5% to 2.0%	£962,071,647	25,226	£38,137
3.0% to 2.5%	£607,172,653	17,705	£34,295
3.0% to 2.0%	£1,569,244,300	42,931	£36,553

TABLE 188 *Discounted weighted cost per QALY for individual age groups, comparing treating at CHD risk between x% and y% per annum using 3.5% discounting rates*

Annual CHD risk level	Age groups (years)			
	45–54	55–64	65–74	75–84
Men				
1.0% to 0.5%	£40,339	£50,131	£63,654	£96,567
1.5% to 1.0%	£29,507	£36,659	£46,851	£65,515
2.0% to 1.5%	£24,625	£30,008	£37,275	£52,193
2.5% to 2.0%	£21,575	£26,098	£31,780	£45,025
3.0% to 2.5%	£20,051	£23,878	£28,103	£38,992
Women				
1.0% to 0.5%	£60,594	£67,543	£84,951	£127,615
1.5% to 1.0%	£42,616	£46,468	£56,480	£87,041
2.0% to 1.5%	£35,419	£38,144	£44,444	£66,969
2.5% to 2.0%	£31,045	£33,537	£37,217	£57,791
3.0% to 2.5%	£30,126	£30,842	£33,731	£49,239

As can be seen, the ICERs for men are lower than those for women across all risk and age groups. In addition, the ICERs increase as the initial risk level decreases and increase as age increases. The ICERs range from approximately £20,100 and £30,100 for men and women, respectively, aged 45–54 years at an initial 3.0% CHD risk, to £96,600 and £127,600 for men and women aged 75–84 years at an initial 1.0% CHD risk.

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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