Comparative Effectiveness of Lipid-Modifying Agents

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Appendix A. Search Strategies

Main search, MEDLINE (1966 to July Week 4 2007)

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. Heptanoic Acids/
3. (Statin$ or reductase inhibitor$).tw.
4. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
5. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
6. or/1-5
7. exp fatty acids, omega-3/
8. fatty acids, essential/
9. Dietary Fats, Unsaturated/
10. linolenic acids/
11. exp fish oils/
12. (n 3 fatty acid$ or omega 3).tw.
13. eicosapenta?noic.tw,hw,rw.
14. docosahexa?noic.tw,hw,rw.
15. alpha linolenic.tw,hw,rw.
16. (linolenate or cervonic or timnodonic).tw,hw,rw.
17. (mediterranean adj diet$).tw.
18. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
19. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
20. (fish adj2 oil$).tw.
21. (cod liver oil$ or marine oil$ or marine fat$).tw.
22. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
23. (fish consumption or fish intake or (fish adj2 diet$)).tw.
24. or/7-23
25. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
26. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
27. Cholestyramine/
28. Colestipol/
29. (colestimide or colestilan or colestipol).tw.
30. or/25-29
31. ezetimibe.mp.
32. 163222-33-1.rn.
33. (cholester$ adj3 inhibit$).tw.
34. or/31-33
35. (fibrate$ or fibric acid$).tw.
36. Clofibric acid/
37. Clofibrate/
38. Bezafibrate/
39. Gemfibrozil/
40. Procetofen/
41. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
42. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
43. or/35-42
44. niacin/
45. nicotinic acid/
46. niacin.tw.
47. or/44-46
48. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
49. Drug Therapy, Combination/
50. (combination adj3 therapy).tw.
51. add-on therapy.tw.
52. or/49-51
53. 6 and (or/24,30,34,43,47-48,52)
54. clinical trial.pt.
55. clinical trials/
56. (randomized or randomly or placebo).ab.
57. trial.ti.
58. randomized controlled trial.pt.

59. or/54-58
60. 53 and 59
61. or/24,30,34,43,47-48,52
62. exp Cardiovascular Diseases/
63. 61 and 62
64. or/6,63
65. limit 64 to systematic reviews
66. limit 64 to meta analysis
67. or/60,65-66
68. limit 67 to (english language and yr="1980 - 2007")
69. remove duplicates from 68

Main search, Embase (1980 to 2007 Week 31)

1. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
2. (Statin$ or reductase inhibitor$).tw.
3. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
4. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
5. or/1-4
6. Omega 3 Fatty Acid/
7. exp Essential Fatty Acid/
8. exp Unsaturated Fatty Acid/
9. Fish oils/
10. (n 3 fatty acid$ or omega 3).tw.
11. eicosapenta?noic.tw,hw,rw.
12. docosahexa?noic.tw,hw,rw.
13. alpha linolenic.tw,hw,rw.
14. (linolenate or cervonic or timnodonic).tw,hw,rw.
15. (mediterranean adj diet$).tw.
16. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
17. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
18. (fish adj2 oil$).tw.
19. (cod liver oil$ or marine oil$ or marine fat$).tw.
20. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
21. (fish consumption or fish intake or (fish adj2 diet$)).tw.
22. or/6-21
23. Bile Acid Sequestrant/
24. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
25. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
26. Cholestyramine/
27. Colestipol/
28. Colestyramine/
29. Colestilan/
30. (colestimide or colestilan or colestipol).tw.
31. or/23-30
32. Ezetimibe/
33. ezetimibe.mp.
34. 163222-33-1.rn.
35. or/32-34
36. Fibric Acid Derivative/
37. (fibrate$ or fibric acid$).tw.
38. Clofibric acid/
39. Clofibrate/
40. Bezafibrate/
41. Gemfibrozil/
42. Procetofen/
43. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
44. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
45. or/36-44
46. nicotinic acid/
47. niacin.tw.
48. or/46-47

49. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
50. Drug Therapy, Combination/
51. (combination adj3 therapy).tw.
52. add-on therapy.tw.
53. or/50-52
54. 5 and (or/22,31,35,45,48-49,53)
55. limit 54 to "treatment (2 or more terms high specificity)"
56. clinical trials/
57. (randomized or randomly or placebo).ab.
58. trial.ti.
59. or/55-58
60. 54 and 59
61. or/22,31,35,45,48-49,53
62. exp Cardiovascular Disease/
63. 61 and 62
64. 5 or 63
65. limit 64 to "reviews (2 or more terms high specificity)"
66. or/60,65
67. limit 66 to (english language and yr="1980 - 2007")

Main search, CENTRAL (The Cochrane Library, Issue 3, 2007)

1. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
2. (Statin$ or reductase inhibitor$).tw.
3. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
4. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
5. or/1-4
6. Omega 3 Fatty Acid/
7. exp Essential Fatty Acid/
8. exp Unsaturated Fatty Acid/
9. Fish oils/
10. (n 3 fatty acid$ or omega 3).tw.
11. eicosapenta?noic.tw,hw,rw.
12. docosahexa?noic.tw,hw,rw.
13. alpha linolenic.tw,hw,rw.
14. (linolenate or cervonic or timnodonic).tw,hw,rw.
15. (mediterranean adj diet$).tw.
16. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
17. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
18. (fish adj2 oil$).tw.
19. (cod liver oil$ or marine oil$ or marine fat$).tw.
20. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
21. (fish consumption or fish intake or (fish adj2 diet$)).tw.
22. or/6-21
23. Bile Acid Sequestrant/
24. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
25. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
26. Cholestyramine/
27. Colestipol/
28. Colestyramine/
29. Colestilan/
30. (colestimide or colestilan or colestipol).tw.
31. or/23-30
32. Ezetimibe/
33. ezetimibe.mp.
34. 163222-33-1.rn.
35. or/32-34
36. Fibric Acid Derivative/
37. (fibrate$ or fibric acid$).tw.
38. Clofibric acid/

39. Clofibrate/
40. Bezafibrate/
41. Gemfibrozil/
42. Procetofen/
43. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
44. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
45. or/36-44
46. nicotinic acid/
47. niacin.tw.
48. or/46-47
49. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
50. Drug Therapy, Combination/
51. (combination adj3 therapy).tw.
52. add-on therapy.tw.
53. or/50-52
54. 5 and (or/22,31,35,45,48-49,53)
55. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
56. Heptanoic Acids/
57. (Statin$ or reductase inhibitor$).tw.
58. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
59. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
60. or/55-59
61. exp fatty acids, omega-3/
62. fatty acids, essential/
63. Dietary Fats, Unsaturated/
64. linolenic acids/
65. exp fish oils/
66. (n 3 fatty acid$ or omega 3).tw.
67. eicosapenta?noic.tw,hw,rw.
68. docosahexa?noic.tw,hw,rw.
69. alpha linolenic.tw,hw,rw.
70. (linolenate or cervonic or timnodonic).tw,hw,rw.
71. (mediterranean adj diet$).tw.
72. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
73. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
74. (fish adj2 oil$).tw.
75. (cod liver oil$ or marine oil$ or marine fat$).tw.
76. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
77. (fish consumption or fish intake or (fish adj2 diet$)).tw.
78. or/61-77
79. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
80. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
81. Cholestyramine/
82. Colestipol/
83. (colestimide or colestilan or colestipol).tw.
84. or/79-83
85. ezetimibe.mp.
86. 163222-33-1.rn.
87. (cholester$ adj3 inhibit$).tw.
88. or/85-87
89. (fibrate$ or fibric acid$).tw.
90. Clofibric acid/
91. Clofibrate/
92. Bezafibrate/
93. Gemfibrozil/
94. Procetofen/
95. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
96. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
97. or/89-96
98. niacin/
99. nicotinic acid/
100. niacin.tw.
101. or/98-100

102. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
103. Drug Therapy, Combination/
104. (combination adj3 therapy).tw.
105. add-on therapy.tw.
106. or/103-105
107. 60 and (or/78,84,88,97,101-102,106)
108. or/54,107
109. remove duplicates from 108
110. limit 109 to yr="1980 - 2007"

Harms search, MEDLINE (1966 to August Week 4 2006)

1. exp Neoplasms/
2. Rhabdomyolysis/
3. Myocardial Infarction/
4. exp Liver Failure/
5. Stroke/
6. mo.fs.
7. or/1-6
8. (ae or po or to or mo or ci or de or et or co or sc).fs.
9. exp Survival Analysis/
10. exp Death/
11. Risk factors/
12. exp Drug Interactions/
13. Critical Illness/
14. exp Mortality/
15. Abnormalities, drug-induced/
16. exp Drug Hypersensitivity/
17. exp Drug Toxicity/
18. exp Product Surveillance, Postmarketing/
19. Cohort Studies/
20. harm$.mp.
21. ((adverse or serious or severe) adj2 (event$ or reaction$)).mp.
22. ((side or unwanted or adverse or undersire$) adj effect$).tw.
23. (ADR or ADRS or SAE).tw.
24. safety.mp.
25. (bleed$ or haemorrhag$ or hemorrhag$).tw.
26. (toxic$ or gastrotoxic$).tw.
27. (tolerability or tolerance or tolerate$).tw.
28. (relative risk or risks).mp.
29. risk.ti.
30. (cohort adj2 stud$).ti,ab.
31. (treatment emergent or complications).tw.
32. or/8-31
33. Databases/ or Databases, factual/ or National Practitioner Data Bank/
34. Prescriptions, Drug/sn
35. Hospitalization/sn
36. Managed Care Programs/sn
37. (administrative adj2 data$).tw.
38. (PHSHG or Public Health Strategic Healthcare Group or Palo Alto Medical Foundation or PAMF or MedPar or MCBS or Medicare Current Beneficiary Survey or Health Insurance Skeleton Eligibility Write-Off or HISKEW or UPIN or Unique Physician Identification Numbers or CAHPS or HOS or Health Outcomes Study or DSH or Providence BC or Partners Health Care or MEPS or Medical Expenditure Panel Survey or USP MEDMARX or Intensive Care Unit Safety Reporting System or ICU-SRS or i3Magnifi or Ingenix or American Heart Association or PCN or Primary Care Network or CORRONA or VA National Patient database or VA National Patient DB or VANPDB or VA Medicare Database or VAMD or Walgreen$ or Marketscan or Illinois Medicaid or Commercial Food Workers Union or CMS or VHA or Baltimore Veterans Healthcare or Thomson Medstat or Omnicare or HMO Research Network or HMORN or Healthinsight or Utah Population Database or NAMCS or National Ambulatory Medical Care

Survey or Pharmetrics or NDTI or Mediplus or Tennessee Medicaid or TENNCARE or GPRD or General Practice Research Database or IMS Disease Analyzer).tw.
39. (California Medicaid or IMS HEALTH National Disease or (Consortium adj Rheumatology Researchers) or Illinois Department or British Columbia).tw.
40. ((French System adj2 Pharmacovigilance) or (ADR Centre adj2 Vietnam) or (WHO Collaborating Programme adj International Drug Monitoring) or (Medicines Evaluation adj Monitoring) or Medicines Evaluation or (Medicaid Pharmaceutical Analysis adj Surveillance)).tw.
41. (VSR or ADRAC or ADR Advisory Committee or CADRMP or Canadian ADR Monitoring Programme or Adverse Reactions Monitoring or BfArM or Voluntary Reporting System or National Reporting System or Farmacovigilanza or Farmacovigilancia or National Drug Monitoring System or National Adverse Reaction Monitoring Programme or Netherlands Pharmacovigilance Foundation or LAREB or National Toxicology Group or Centre for Adverse Reaction Monitoring or Norwegian Medicines Control Authority or Pharmacovigilance or Drug Monitoring Department or Swiss Drug Monitoring Centre or SANZ or Yellow Card or Spontaneous Reporting System or MedMARx or PEM or IMMP or J-PEM or Saskatchewan Administrative Healthcare Utilization Databases or MEMO or BCDSP or Boston Collaborative Drug Surveillance or COMPASS or Uppsala Monitoring).tw.
42. (Saskhealth or Quebec medical claims database or Regie de l'assurance-maladie du Quebec or RAMQ or Nova Scotia Pharmacare or (Health Insurance Commission adj Australia) or Intercontinental Marketing Services Health or medwatch or Linked Health Database or BCLHD).tw.
43. (VAERS or Vaccine Adverse Event Reporting System or adverse events reporting system or AERS or Fallon Health Plan or Harvard Pilgrim or Kaiser Permanente or ACOVE or (Assessing Care adj Vulnerable Elders)).tw.
44. (euromedstat group or euro med stat group).au.
45. or/33-44
46. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
47. Heptanoic Acids/
48. (Statin$ or reductase inhibitor$).tw.
49. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
50. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
51. or/46-50
52. exp fatty acids, omega-3/
53. fatty acids, essential/
54. Dietary Fats, Unsaturated/
55. linolenic acids/
56. exp fish oils/
57. (n 3 fatty acid$ or omega 3).tw.
58. eicosapenta?noic.tw,hw,rw.
59. docosahexa?noic.tw,hw,rw.
60. alpha linolenic.tw,hw,rw.
61. (linolenate or cervonic or timnodonic).tw,hw,rw.
62. (mediterranean adj diet$).tw.
63. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
64. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
65. (fish adj2 oil$).tw.
66. (cod liver oil$ or marine oil$ or marine fat$).tw.

67. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
68. (fish consumption or fish intake or (fish adj2 diet$)).tw.
69. or/52-68
70. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
71. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
72. Cholestyramine/
73. Colestipol/
74. (colestimide or colestilan or colestipol).tw.
75. or/70-74
76. ezetimibe.mp.
77. 163222-33-1.rn.
78. (cholester$ adj3 inhibit$).tw.
79. or/76-78
80. (fibrate$ or fibric acid$).tw.
81. Clofibric acid/
82. Clofibrate/
83. Bezafibrate/
84. Gemfibrozil/
85. Procetofen/
86. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
87. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
88. or/80-87
89. niacin/
90. nicotinic acid/
91. niacin.tw.
92. or/89-91
93. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
94. Drug Therapy, Combination/
95. (combination adj3 therapy).tw.
96. add-on therapy.tw.
97. or/94-96
98. 51 and (or/69,75,79,88,92-93,97)
99. or/7,32,45
100. 98 and 99
101. limit 100 to review
102. 100 not 101
103. limit 102 to (english and human and yr=1980-2007)

Harms search, Embase (1980 to 2007 Week 42)

1. exp neoplasms/
2. Rhabdomyolysis/
3. Myocardial Infarction/
4. exp Liver Failure/
5. Stroke/
6. mo.fs.
7. or/1-6
8. (ae or po or to or mo or ci or de or et or co or sc).fs.
9. exp Survival Analysis/
10. exp Death/
11. Risk factors/
12. exp Drug Interactions/
13. Critical Illness/
14. exp Mortality/
15. Abnormalities, drug-induced/
16. exp Drug Hypersensitivity/
17. exp Drug Toxicity/
18. exp Product Surveillance, Postmarketing/
19. Cohort Studies/
20. harm$.mp.
21. ((adverse or serious or severe) adj2 (event$ or reaction$)).mp.
22. ((side or unwanted or adverse or undersire$) adj effect$).tw.
23. (ADR or ADRS or SAE).tw.
24. safety.mp.
25. (bleed$ or haemorrhag$ or hemorrhag$).tw.
26. (toxic$ or gastrotoxic$).tw.

27. (tolerability or tolerance or tolerate$).tw.
28. (relative risk or risks).mp.
29. risk.ti.
30. (cohort adj2 stud$).ti,ab.
31. (treatment emergent or complications).tw.
32. or/8-31
33. Databases/ or Databases, factual/ or National Practitioner Data Bank/
34. Prescriptions, Drug/
35. Hospitalization/
36. Managed Care Programs/
37. (administrative adj2 data$).tw.
38. (PHSHG or Public Health Strategic Healthcare Group or Palo Alto Medical Foundation or PAMF or MedPar or MCBS or Medicare Current Beneficiary Survey or Health Insurance Skeleton Eligibility Write-Off or HISKEW or UPIN or Unique Physician Identification Numbers or CAHPS or HOS or Health Outcomes Study or DSH or Providence BC or Partners Health Care or MEPS or Medical Expenditure Panel Survey or USP MEDMARX or Intensive Care Unit Safety Reporting System or ICU-SRS or i3Magnifi or Ingenix or American Heart Association or PCN or Primary Care Network or CORRONA or VA National Patient database or VA National Patient DB or VANPDB or VA Medicare Database or VAMD or Walgreen$ or Marketscan or Illinois Medicaid or Commercial Food Workers Union or CMS or VHA or Baltimore Veterans Healthcare or Thomson Medstat or Omnicare or HMO Research Network or HMORN or Healthinsight or Utah Population Database or NAMCS or National Ambulatory Medical Care Survey or Pharmetrics or NDTI or Mediplus or Tennessee Medicaid or TENNCARE or GPRD or General Practice Research Database or IMS Disease Analyzer).tw.
39. (California Medicaid or IMS HEALTH National Disease or (Consortium adj Rheumatology Researchers) or Illinois Department or British Columbia).tw.
40. ((French System adj2 Pharmacovigilance) or (ADR Centre adj2 Vietnam) or (WHO Collaborating Programme adj International Drug Monitoring) or (Medicines Evaluation adj Monitoring) or Medicines Evaluation or (Medicaid Pharmaceutical Analysis adj Surveillance)).tw.
41. (VSR or ADRAC or ADR Advisory Committee or CADRMP or Canadian ADR Monitoring Programme or Adverse Reactions Monitoring or BfArM or Voluntary Reporting System or National Reporting System or Farmacovigilanza or Farmacovigilancia or National Drug Monitoring System or National Adverse Reaction Monitoring Programme or Netherlands Pharmacovigilance Foundation or LAREB or National Toxicology Group or Centre for Adverse Reaction Monitoring or Norwegian Medicines Control Authority or Pharmacovigilance or Drug Monitoring Department or Swiss Drug Monitoring Centre or SANZ or Yellow Card or Spontaneous Reporting System or MedMARx or PEM or IMMP or J-PEM or Saskatchewan Administrative Healthcare Utilization Databases or MEMO or BCDSP or Boston Collaborative Drug Surveillance or COMPASS or Uppsala Monitoring).tw.
42. (Saskhealth or Quebec medical claims database or Regie de l'assurance-maladie du Quebec or RAMQ or Nova Scotia Pharmacare or (Health Insurance Commission adj Australia) or Intercontinental Marketing Services Health or medwatch or Linked Health Database or BCLHD).tw.

43. (VAERS or Vaccine Adverse Event Reporting System or adverse events reporting system or AERS or Fallon Health Plan or Harvard Pilgrim or Kaiser Permanente or ACOVE or (Assessing Care adj Vulnerable Elders)).tw.
44. (euromedstat group or euro med stat group).au.
45. or/33-44
46. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
47. Heptanoic Acids/
48. (Statin$ or reductase inhibitor$).tw.
49. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
50. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
51. or/46-50
52. exp fatty acids, omega-3/
53. fatty acids, essential/
54. Dietary Fats, Unsaturated/
55. linolenic acids/
56. exp fish oils/
57. (n 3 fatty acid$ or omega 3).tw.
58. eicosapenta?noic.tw,hw.
59. docosahexa?noic.tw,hw.
60. alpha linolenic.tw,hw.
61. (linolenate or cervonic or timnodonic).tw,hw.
62. (mediterranean adj diet$).tw.
63. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
64. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
65. (fish adj2 oil$).tw.
66. (cod liver oil$ or marine oil$ or marine fat$).tw.
67. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
68. (fish consumption or fish intake or (fish adj2 diet$)).tw.
69. or/52-68
70. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
71. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
72. Cholestyramine/
73. (colestimide or colestilan or colestipol).tw. [(colestimide or colestilan or colestipol).tw. as keyword]
74. Colestipol/ [Colestipol/ as keyword]
75. or/70-74
76. ezetimibe.mp.
77. 163222-33-1.rn.
78. (cholester$ adj3 inhibit$).tw.
79. or/76-78
80. (fibrate$ or fibric acid$).tw.
81. Clofibric acid/
82. Clofibrate/
83. Bezafibrate/
84. Gemfibrozil/
85. Procetofen/
86. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
87. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
88. or/80-87
89. niacin/
90. nicotinic acid/
91. niacin.tw.
92. or/89-91
93. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
94. Drug Therapy, Combination/
95. (combination adj3 therapy).tw.
96. add-on therapy.tw.
97. or/94-96
98. 51 and (or/69,75,79,88,92-93,97)
99. or/7,32,45
100. 98 and 99
101. limit 100 to review

102. 100 not 101

103. limit 102 to (english and human and yr=1980-2007)

Date and RCT filters removed, Medline (1950 to October Week 2 2007)

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. Heptanoic Acids/
3. (Statin$ or reductase inhibitor$).tw.
4. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
5. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
6. or/1-5
7. exp fatty acids, omega-3/
8. fatty acids, essential/
9. Dietary Fats, Unsaturated/
10. linolenic acids/
11. exp fish oils/
12. (n 3 fatty acid$ or omega 3).tw.
13. eicosapenta?noic.tw,hw,rw.
14. docosahexa?noic.tw,hw,rw.
15. alpha linolenic.tw,hw,rw.
16. (linolenate or cervonic or timnodonic).tw,hw,rw.
17. (mediterranean adj diet$).tw.
18. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
19. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
20. (fish adj2 oil$).tw.
21. (cod liver oil$ or marine oil$ or marine fat$).tw.
22. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
23. (fish consumption or fish intake or (fish adj2 diet$)).tw.
24. or/7-23
25. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
26. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
27. Cholestyramine/
28. Colestipol/
29. (colestimide or colestilan or colestipol).tw.
30. or/25-29
31. ezetimibe.mp.
32. 163222-33-1.rn.
33. (cholester$ adj3 inhibit$).tw.
34. or/31-33
35. (fibrate$ or fibric acid$).tw.
36. Clofibric acid/
37. Clofibrate/
38. Bezafibrate/
39. Gemfibrozil/
40. Procetofen/
41. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
42. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
43. or/35-42
44. niacin/
45. nicotinic acid/
46. niacin.tw.
47. or/44-46
48. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
49. Drug Therapy, Combination/
50. (combination adj3 therapy).tw.
51. add-on therapy.tw.
52. or/49-51
53. 6 and (or/24,30,34,43,47-48,52)
54. or/24,30,34,43,47-48,52

55. exp Cardiovascular Diseases/
56. 54 and 55
57. or/6,56
58. limit 57 to systematic reviews
59. limit 57 to meta analysis
60. or/53,58-59
61. limit 60 to english language
62. remove duplicates from 61

Appendix B – Excluded Studies

Excluded Studies –FullText Relevance

Do not directly address the key questions.

Aberg J A, Zackin R A, Brobst S W et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. AIDS Research & Human Retroviruses 2005;21(9):757-767.

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Anonymous. Combination therapy for mixed dyslipidemia in an elderly man with diabetes. Cardiol Rev 2007;24(4):28

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Appendix C - Within-trial, within-treatment pooling of multiple treatment group data

These tables present a summary of pooling undertaken during the present work. Pooling by authors of manuscripts was also incorporated in data syntheses, but is not summarized here.

Arms in **bold type** were used in data syntheses.

Arms in "plain type" were not used in data syntheses.

Arms in *italics* were pooled in the course of this work. Pooled arms were comprised of the arms immediately above. Pooled arms used in data syntheses (in bold print) were within the a priori acceptable limits for heterogeneity (I^2 or Chi^2 statistics ≤ 50%; p-value ≥ 0.05 as appropriate).

When more than one comparator arm is in **bold**, different arms were used depending upon the analysis. Doses were matched for global ("all participants, all doses") analyses, while higher monotherapy doses were used to assess the benefits and harms of increasing the statin dose compared with adding a nonstatin medication.

Clinical outcomes

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	All cause mortality		
Durrington (2004)[1]	**Rosuvastatin 40**	***NONE***	**53**
	Rosuvastatin 10	Fenofibrate 67	*53*
	Rosuvastatin 5	Fenofibrate 67	*60*
	Rosuvastatin 5-10	***Fenofibrate 67***	***113***
Davidson (2001)[2]	**Lovastatin 10**	***NONE***	**26**
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	***C-lam 2300***	***50***
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**219**
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20-40	***Ezetimibe 10***	***442***
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10	Niacin (ER) 2500	34

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Lovastatin 10	***Niacin (ER) 2500***	***100***
Kos Pharm (MA-06)[5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 40	***Niacin (ER) 1000-2000***	***114***
All cause mortality - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 5-10	***Fenofibrate 67***	***113***
All-cause mortality in participants with diabetes mellitus			
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 5-10	***Fenofibrate 67***	***113***
Constance (2007)[3]	**Atorvastatin 20**	***NONE***	**219**
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 20-40	***Ezetimibe 10***	***442***
Fatal myocardial infarction			
Kos Pharm (MA-06)[5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 40	***Niacin (ER) 1000-2000***	***114***
Vascular death			
Hunninghake (2003)[6]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 40	***Niacin (ER) 1000-2000***	***114***

Abbreviations: C-amine = colestyramine, C-lam = colesevelam, C-pol – colesipol, ER = extended release

Surrogate outcomes

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Achieving ATP III target		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**51**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	**Fenofibrate 67**	**53**
	Rosuvastatin 5-40	*Fenofibrate 67*	*113*
McKenney (2007-2)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Atorvastatin 40	Niacin (ER) 2000	60
	Rosuvastatin 20	Niacin (ER) 1000	65
	Mixed 20-40	***Niacin (ER) 1000-2000***	***125***
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**218**
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	219
	Simvastatin 20-40	***Ezetimibe 10***	***439***
	Achieving ATP III targets - participants with CAD		
Bays (2003); Bays (2005)[8]	Atorvastatin 40	NONE	16
	Simvastatin 40	NONE	18
	Mixed	***NONE***	***34***
	Lovastatin 40	Niacin (ER) 2000	17
	Lovastatin 40	Niacin (ER) 1000	15
	Lovastatin 40	***Niacin (ER) 1000-2000***	***32***
	Achieving ATP III targets - participants with diabetes mellitus		
Durrington (2004)[1]	**Rosuvastatin**	NONE	**50**
	Rosuvastatin 10	Fenofibrate 67	50
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 5-10	***Fenofibrate 67***	***110***
Goldberg (2006)[9]	Atorvastatin 20	NONE	240
	Atorvastatin 10	NONE	237
	Atorvastatin	***NONE***	***241***
	Simvastatin 10	Ezetimibe 10	242

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Simvastatin 10	Ezetimibe 10	238
	Simvastatin 10	***Ezetimibe 10***	***480***
Constance (2007)[3]	**Atorvastatin**	**NONE**	**219**
	Simvastatin 10	Ezetimibe 10	222
	Simvastatin 10	Ezetimibe 10	220
	Simvastatin 10	***Ezetimibe 10***	***442***
		LDL-c	
Feldman(2004)[10]	**Simvastatin 20**	**NONE**	**246**
	Simvastatin 20	**Ezetimibe 10**	**108**
	Simvastatin 40	*Ezetimibe 10*	*96*
	Simvastatin 10	*Ezetimibe 10*	*242*
	Simvastatin 10-40	*Ezetimibe 10*	*446*
Insull (2004)[11]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 40	**Niacin (ER) 2500**	**32**
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 10-40	*Niacin (ER) 2500*	*100*
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**51**
	Rosuvastatin 10	**Fenofibrate 67**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 5-10	*Fenofibrate 67*	*113*
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**31**
	Rosuvastatin 10	**Niacin (ER) 2000**	**36**
	Rosuvastatin 40	Niacin (ER) 1000	35
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***71***
Gagne (2002)[13]	**Atorvastatin 80**	**NONE**	**12**
	Simvastatin 80	**NONE**	**5**
	Mixed 80	***NONE***	***17***
	Atorvastatin 40	Ezetimibe 10	12
	Simvastatin 40	Ezetimibe 10	4
	Atorvastatin 80	**Ezetimibe 10**	**12**
	Simvastatin 80	**Ezetimibe 10**	**5**
	Mixed 40-80	*Ezetimibe 10*	*33*

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Hunninghake (2001)[14]	**Atorvastatin 10**	**NONE**	**18**
	Atorvastatin 80	**NONE**	**20**
	Atorvastatin 10-80	***NONE***	***38***
Davidson (2001)[2]	**Atorvastatin 10**	**C-lam 3800**	**18**
	Lovastatin 10	**NONE**	**26**
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	***C-lam 2300***	***50***
Knapp (2001)[15]	**Simvastatin 20**	**C-lam 2300**	**37**
	Simvastatin 10	**C-lam 3800**	**34**
	Simvastatin 10-20	***C-lam 2300-3800***	***71***
	Simvastatin 20	**NONE**	**39**
	Simvastatin 10	**NONE**	**35**
	Simvastatin 10-20	*NONE*	*74*
Sprecher (1994)[16]	**Fluvastatin 20**	**NONE**	**38**
	Fluvastatin 10	**NONE**	**38**
	Fluvastatin 10-20	***NONE***	***76***
Sprecher (1994)[16]	**Fluvastatin 20**	**C-amine 16000**	**35**
	Fluvastatin 10	**C-amine 16000**	**35**
	Fluvastatin 10-20	***C-amine 16000***	***70***
PMSG II (1993)[17]	**Pravastatin 80**	**NONE**	**62**
	Pravastatin 40	**NONE**	**57**
	Pravastatin 40-80	*NONE*	*119*
Simons (1992)[18]	**Pravastatin 40**	**C-amine 24000**	**61**
	Simvastatin 40	**NONE**	**22**
	Simvastatin 40	**C-pol 5000**	**19**
	Simvastatin 40	**C-pol 10000**	**20**
	Simvastatin 40	***C-pol 5000-10000***	***39***
McKenney (2007-2)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Atorvastatin 40	**Niacin (ER) 2000**	**60**
	Atorvastatin 20	**Niacin (ER) 1000**	**65**

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Mixed 20-40	*Niacin (ER) 1000-2000*	*125*
Goldberg (2006)[9]	**Atorvastatin 20**	**NONE**	**240**
	Atorvastatin 10	NONE	237
	Atorvastatin 40	**NONE**	**241**
	Atorvastatin 10-40	*NONE*	*718*
	Simvastatin 40	**Ezetimibe 10**	**242**
	Simvastatin 20	**Ezetimibe 10**	**238**
	Simvastatin 20-40	*Ezetimibe 10*	*480*
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**213**
	Simvastatin 40	Ezetimibe 10	215
	Simvastatin 20	**Ezetimibe 10**	**210**
	Simvastatin 20-40	*Ezetimibe 10*	*425*
Isaacsohn (1997)[19]	**Atorvastatin 80**	**NONE**	**16**
	Atorvastatin 40	C-pol 20000	11
	Simvastatin 40	C-pol 20000	10
	Mixed 40	***C-pol 20000***	***21***
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**29**
	Lovastatin 40	**Niacin (ER) 2500**	**23**
	Lovastatin 20	Niacin (ER) 2500	24
	Lovastatin 10	Niacin (ER) 2500	30
	Lovastatin 10-40	*Niacin (ER) 2500*	*77*
Kos Pharm (MA-06)[5]	**Lovastatin 40**	**NONE**	**53**
	Lovastatin 20	Niacin (ER) 1000	40
	Lovastatin 40	**Niacin (ER) 2000**	**42**
	Lovastatin 20-40	*Niacin (ER) 1000-2000*	*82*
		HDL-c	
Feldman(2004)[10]	**Simvastatin 20**	**NONE**	**248**
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Simvastatin 10-40	***Ezetimibe 10***	***451***
Insull (2004)[11]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**51**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5-10	***Fenofibrate 67***	***113***
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**31**
	Rosuvastatin 10	**Niacin (ER) 2000**	**36**
	Rosuvastatin 40	**Niacin (ER) 1000**	**35**
	Rosuvastatin 10-40	*Niacin (ER) 1000-2000*	*71*
Davidson (2001)[2]	**Lovastatin 10**	**NONE**	**26**
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	***C-lam 2300***	***50***
PMSG II (1993)[17]	Pravastatin 80	NONE	62
	Pravastatin 40	NONE	57
	Pravastatin 40	***NONE***	***119***
Simons (1992)[18]	**Pravastatin 40**	**C-amine 24000**	**61**
	Simvastatin 40	**NONE**	**22**
	Simvastatin 40	C-pol 5000	19
	Simvastatin 40	C-pol 10000	20
	Simvastatin 40	***C-pol 5000-10000***	***39***
McKenney (2007-2)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Atorvastatin 40	Niacin (ER) 2000	60
	Rosuvastatin 20	Niacin (ER) 1000	65
	Mixed 20-40	***Niacin (ER) 1000-2000***	***125***

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**218**
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	219
	Simvastatin 20-40	***Ezetimibe 10***	***439***
Isaacsohn (1997)[19]	**Atorvastatin 80**	**NONE**	**16**
	Simvastatin 40	C-pol 20000	10
	Atorvastatin 40	C-pol 20000	11
	Mixed 40	***C-pol 20000***	***21***
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**29**
	Lovastatin 10	Niacin (ER) 2500	30
	Lovastatin 20	Niacin (ER) 2500	24
	Lovastatin 40	Niacin (ER) 2500	23
	Lovastatin 10-40	***Niacin (ER) 2500***	***77***
Kos Pharm (MA-06)[5]	**Lovastatin 40**	**NONE**	**53**
	Lovastatin 20	Niacin (ER) 1000	40
	Lovastatin 40	**Niacin (ER) 2000**	**42**
	Lovastatin 40	*Niacin (ER) 1000-2000*	*82*
	Total cholesterol: HDL-c ratio		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**51**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	**Fenofibrate 67**	**53**
	Rosuvastatin 5-40	*Fenofibrate 67*	*113*
McKenney (2007-2)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Atorvastatin 40	Niacin (ER) 2000	60
	Rosuvastatin 20	Niacin (ER) 1000	65
	Mixed 20-40	**Niacin (ER) 1000-2000**	***125***
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**218**
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	219
	Simvastatin 20-40	**Ezetimibe 10**	***439***

Abbreviations: C-amine = colestyramine, C-lam = colesevelam, C-pol – colesipol, ER = extended release (niacin)

Adverse Events and Treatment Adherence

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	Myalgia		
Kosoglou (2004-b)[20]	**Lovastatin 20**	**NONE**	**8**
	Lovastatin 20	Ezetimibe 10	8
	Lovastatin 40	Ezetimibe 10	7
	Lovastatin 20-40	***Ezetimibe 10***	***15***
	CPK above 10 times the upper limit of normal		
Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**248**
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***451***
	Elevated serum AST, ALT or hepatitis		
Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**248**
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***451***
	Rhabdomyolysis		
Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**253**
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***457***
	Serious adverse events		
Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**253**
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***457***
	Total adverse events		
Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**253**
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***457***
	Withdrawal due to adverse events		

Feldman(2004)[10]	**Simvastatin 40**	**NONE**	**253**
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 10-40	***Ezetimibe 10***	***457***
	Elevated serum AST, ALT or hepatitis		
Insull (2004)[11]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Total adverse events		
Insull (2004)[11]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	CPK above 10 times the upper limit of normal		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	***Fenofibrate 67***	***115***
	Elevated serum AST, ALT or hepatitis		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	***Fenofibrate 67***	***115***
	Myalgia		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	***Fenofibrate 67***	***115***
	Total adverse events		
Durrington (2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55

	Rosuvastatin 5-10	***Fenofibrate 67***	***115***
	Withdrawal due to adverse events		
Durrington(2004)[1]	**Rosuvastatin 40**	**NONE**	**53**
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	***Fenofibrate 67***	***115***
	CPK above 10 times the upper limit of normal		
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**46**
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***152***
	Elevated serum AST, ALT or hepatitis		
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**46**
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***152***
	Myalgia		
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**46**
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***152***
	Total adverse events		
Capuzzi (2003) [12]	**Rosuvastatin 40**	**NONE**	**46**
	Rosuvastatin 10	Niacin (ER) 2000	78
	Rosuvastatin 40	Niacin (ER) 1000	71
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***149***
	Treatment Adherence		
Capuzzi (2003)[12]	**Rosuvastatin 40**	**NONE**	**46**
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	***Niacin (ER) 1000-2000***	***152***
	Elevated serum AST, ALT or hepatitis		
Hunninghake (2003)[6]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	***Niacin (ER) 1000-2000***	***114***
	Withdrawal due to adverse events		

Gagne (2002)[13]	**Mixed 80**	**NONE**	**17**
	Mixed 40	Ezetimibe 10	16
	Mixed 80	Ezetimibe 10	17
	Mixed 40-80	***Ezetimibe 10***	***33***
	Elevated serum AST, ALT or hepatitis		
Athyros (2001)[21]	**Atorvastatin 20**	**NONE**	**131**
	Pravastatin 20	Gemfibrozil 1200	133
	Simvastatin 20	Gemfibrozil 1200	129
	Mixed 20	***Gemfibrozil 1200***	***262***
	Myalgia		
Athyros (2001)[21]	**Atorvastatin 20**	**NONE**	**131**
	Simvastatin 20	Gemfibrozil 1200	129
	Pravastatin 20	Gemfibrozil 1200	133
	Mixed 20	***Gemfibrozil 1200***	***262***
	Withdrawal due to adverse events		
Athyros (2001)[21]	**Atorvastatin 20**	**NONE**	**134**
	Simvastatin 20	**Gemfibrozil 1200**	**136**
	Pravastatin 20	Gemfibrozil 1200	135
	Mixed 20	**Gemfibrozil 1200**	**271**
	Treatment Adherence		
Hunninghake (2001)[14]	Atorvastatin 10	NONE	19
	Atorvastatin 80	NONE	20
	Atorvastatin 10-80	***NONE***	***39***
	Atorvastatin 10	**C-lam 3800**	**19**
	Withdrawal due to adverse events		
Hunninghake (2001)[14]	Atorvastatin 10	NONE	19
	Atorvastatin 80	NONE	20
	Atorvastatin 10-80	***NONE***	***39***
	Atorvastatin 10	**C-lam 3800**	**19**
	Elevated serum AST, ALT or hepatitis		
Davidson (2001)[2]	**Lovastatin 10**	**NONE**	**26**
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	***C-lam 300***	***50***
	Myalgia		
Davidson (2001)[2]	**Lovastatin 10**	**NONE**	**26**
	Lovastatin 10	C-lam 2300	27

	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	***C-lam 2300***	***50***
	Withdrawal due to adverse events		
Davidson (2001)[2]	**Lovastatin 10**	**NONE**	**26**
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	***C-lam 2300***	***50***
	Treatment Adherence		
Eriksson (1998)[22]	Pravastatin 20	NONE	403
	Pravastatin 40	NONE	409
	Pravastatin 20-40	***NONE***	***812***
	Pravastatin 20	**chlestyramine 000**	**261**
	Withdrawal due to adverse events		
PMSG II (1993)[17]	Pravastatin 40	NONE	63
	Pravastatin 80	NONE	63
	Pravastatin 40-80	***NONE***	***126***
	Pravastatin 40	**chlestyramine 24000**	**64**
	Total adverse events		
Johansson (1995)[23]	**Simvastatin 40**	**NONE**	**26**
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
	Simvastatin 20	***C-pol 5000-10000***	***57***
	Treatment Adherence		
Johansson (1995)[23]	**Simvastatin 40**	**NONE**	**26**
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
	Simvastatin 20	***C-pol 5000-10000***	***57***
	CPK above 10 times the upper limit of normal		
McKenney (2007-1)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Simvastatin 40	**Ezetimibe 10**	**72**
	Rosuvastatin 40	**NONE**	**73**
	Rosuvastatin 20	Niacin (ER) 1000	65
	Atorvastatin 40	Niacin (ER) 2000	60
	Mixed 20-40	***Niacin (ER) 1000-2000***	***125***
	Treatment Adherence		

McKenney (2007-1)[7]	**Rosuvastatin 40**	**NONE**	**73**
	Simvastatin 40	**Ezetimibe 10**	**72**
	Rosuvastatin 40	**NONE**	**73**
	Rosuvastatin 20	Niacin (ER) 1000	65
	Atorvastatin 40	Niacin (ER) 2000	60
	Mixed 20-40	***Niacin (ER) 1000-2000***	***125***
	Elevated serum AST, ALT or hepatitis		
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**219**
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20-40	***Ezetimibe 10***	***442***
	Withdrawal due to adverse events		
Constance (2007)[3]	**Atorvastatin 20**	**NONE**	**219**
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20-40	***Ezetimibe 10***	***442***
	CPK above 10 times the upper limit of normal		
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Elevated serum AST, ALT or hepatitis		
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
Rhabdomyolysis			
Kos Pharm (MA-14)[4] Lovastatin 40		**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Serious adverse events		

Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Total adverse events		
Kos Pharm (MA-14)[4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Withdrawal due to adverse events		
Kos Pharm (MA-14) [4]	**Lovastatin 40**	**NONE**	**33**
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10-40	***Niacin (ER) 2500***	***100***
	Cancer		
Kos Pharm (MA-06) [5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	***Niacin (ER) 1000-2000***	***114***
	CPK above 10 times the upper limit of normal		
Kos Pharm (MA-06) [5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 40	***Niacin (ER) 1000-2000***	***114***
	Total adverse events		
Kos Pharm (MA-06) [5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	***Niacin (ER) 1000-2000***	***114***
	Withdrawal due to adverse events		
Kos Pharm (MA-06) [5]	**Lovastatin 40**	**NONE**	**61**
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	***Niacin (ER) 1000-2000***	***114***

Abbreviations: C-amine = colestyramine, C-lam = colesevelam, C-pol – colesipol, ER = extended release (niacin)

Appendix D - Included Evidence

This appendix contains details of all trial treatment groups included in syntheses.

Abbreviations: 1° HC = primary hypercholesterolemia, AAC = adequate allocation concealment, ALT = alanine transaminase, AST = aspartate transaminase, ATP III = Adult Treatment Panel III (of the National Cholesterol Education Program), C-amine = cholestyramine, C-lam = colesevelam, C-pol = colestipol, CAD = coronary artery disease, CHD = coronary heart disease, combo = combination therapy, CPK = creatine phosphokinase, DM = diabetes mellitus, Ext Rls = extended release (niacin), FHC = familial hypercholesterolemia, HC = hypercholesterolemia, HDL-c = high density lipoprotein cholesterol, Imm Rls = immediate release (niacin), ITTA = intention to treat analysis, LDL-c = low density lipoprotein cholesterol, mono = monotherapy, N = number, Slow Rls = slow release (niacin), T2DM = type 2 diabetes mellitus, wk = week

Included Evidence for Ezetimibe plus Statin Therapy Compared With Statin Monotherapy

Table 1. Longer-term outcomes (clinical outcomes, serious adverse events and cancer) using ezetimibe plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
All-cause Mortality, all trials											
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	0/0	unclear	2	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	yes	4	No
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	98	Simvastatin 20	102	24	119	3/0 7.51 (0.38, 147.37)	yes	2	Yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	0/0	unclear	3	No
Rodney (2006)[28] Pharm. Fund Multicentre	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	yes	5	No
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	184	Pravastatin 10-40	192	12	178	0/0	yes	4	Yes
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	Yes
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.49 (0.03, 7.94)	yes	3	No
Farnier (2005)[31] International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	0/0	unclear	5	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/1 0.35 (0.01, 8.56)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	No
Pearson (2005)[34] EASE North America Pharm. Fund Multicentre	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1965	Mixed	992	6	129	0/0	yes	4	No
Blagden (2007)[35] Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	Yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	1/0 2.91 (0.12, 71.84)	unclear	1	No
Patel (2006)[37] Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	76	Simvastatin 20	75	6	160	0/1 0.32 (0.01, 8.10)	unclear	3	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/1 0.49 (0.02, 12.13)	yes	3	No
Catapano (2006_1)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20	492	Rosuvastatin 10	492	6	173	0/0	yes	3	No
Catapano (2006_2)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 40	493	Rosuvastatin 20	495	6	173	0/0	yes	3	No
Catapano (2006_3)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 80	493	Rosuvastatin 40	494	6	173	0/0	yes	3	No
All-cause mortality , trials ≥ 24 weeks duration											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	0/0	unclear	2	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	yes	4	No
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	98	Simvastatin 20	102	24	119	3/0 7.51 (0.38, 147.37)	yes	2	Yes
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	0/0	unclear	3	No
All-cause mortality – adequate allocation concealment											
Rodney (2006)[28] Pharm. Fund Multicentre	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	yes	5	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	98	Simvastatin 20	102	24	119	3/0 7.51 (0.38, 147.37)	yes	2	Yes
Pearson (2005)[34] EASE North America Pharm. Fund Multicentre	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1965	Mixed	992	6	129	0/0	yes	4	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	yes	4	No
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	184	Pravastatin 10-40	192	12	178	0/0	yes	4	Yes
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/1 0.49 (0.02, 12.13)	yes	3	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Catapano (2006_1)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20	492	Rosuvastatin 10	492	6	173	0/0	yes	3	No
Catapano (2006_2)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 40	493	Rosuvastatin 20	495	6	173	0/0	yes	3	No
Catapano (2006_3)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 80	493	Rosuvastatin 40	494	6	173	0/0	yes	3	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.49 (0.03, 7.94)	yes	3	No
All-cause mortality in participants requiring intensive lipid lowering therapy (DM, trial duration 24 wks) - Lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy											
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	0/0	unclear	3	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
All-cause mortality in participants requiring intensive lipid lowering therapy											
Farnier (2005)[31] International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	0/0	unclear	5	No
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/1 0.35 (1.41, 8.56)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	No
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	0/0	unclear	3	No
Blagden (2007)[35] Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	Yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2007)[36] Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	1/0 2.91 (0.12, 71.84)	unclear	1	No
Patel (2006)[37] Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	76	Simvastatin 20	75	6	160	0/1 0.32 (0.01, 8.10)	unclear	3	No
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/1 0.49 (0.02, 12.13)	yes	3	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.49 (0.03, 7.94)	yes	3	No
All-cause mortality in participants requiring intensive lipid lowering therapy (DM) - Adequate allocation concealment											
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/1 0.49 (0.02, 12.13)	yes	3	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.49 (0.03, 7.94)	yes	3	No
All-cause mortality in participants with diabetes											
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	0/0	unclear	3	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.49 (0.03, 7.94)	yes	3	No
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/1 0.49 (0.02, 12.13)	yes	3	No
All-cause mortality in participants with established vascular disease											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Blagden (2007)[35] Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	Yes
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/1 0.35 (1.41, 8.56)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	No
Farnier (2005)[31] International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	0/0	unclear	5	No
Patel (2006)[37] Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	76	Simvastatin 20	75	6	160	0/1 0.32 (0.01, 8.10)	unclear	3	No
All-cause mortality in of African descent [28]											
Rodney (2006)[28] Pharm. Fund Multicentre	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	yes	5	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Vascular Death, all trials (and adequate allocation concealment)											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2/1 2.04 (0.18, 22.59)	yes	3	No
Davidson (2002_1)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 10	61	12	179	0/0	yes	4	No
Davidson (2002_2)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 20	53	12	179	1/0 2.79 (0.11, 70.01)	yes	4	No
Davidson (2002_3)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	68	Simvastatin 40	60	12	179	0/0	yes	4	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_4)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	52	Simvastatin 80	63	12	179	0/0	yes	4	No
Vascular death - Lower dose simvastatin combination therapy versus higher dose of the same as monotherapy											
Davidson (2002_5)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 40	60	12	179	0/0	yes	4	No
Davidson (2002_6)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 80	63	12	179	1/0	yes	4	No
Vascular death in participants requiring intensive lipid lowering therapy, with - LDL>190											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2/1 2.04 (0.18, 22.59)	yes	3	No
Fatal Myocardial Infarction, all trials											
Ballantyne (2007)[36] Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	1/0 2.91 (0.12, 71.84)	unclear	1	No
Stein (2004)[41] International Pharm. fund	Those with LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	14	186	0/1 0.35 (0.01, 8.54)	unclear	3	Yes
Stroke											
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	98	Simvastatin 20	102	24	119	10 3.15 (0.13, 78.35)	yes	2	Yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Serious Adverse Events, all trials											
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	17/5 0.74 (0.26, 2.12)	unclear	2	No
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	43/13 0.58 (0.29, 1.16)	unclear	3	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	28/6 2.04 (0.83, 4.99)	yes	4	No
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	87	Simvastatin 10-80	22	48	179	8/4 0.46 (0.12, 1.68)	yes	4	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	36/25 1.66 (0.90, 3.04)	yes	2	Yes
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	5/1 5.51 (0.63, 47.94)	unclear	3	No
Feldman (2004)[10] North America Pharm. Fund Multicentre	Participants with CHD or risk equivalent	Simvastatin 10-40	457	Simvastatin 40	253	23	169	27/12 1.26 (0.63, 2.53)	unclear	2	No
Stein (2004)[41] International Pharm. fund	Those with LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	9/12 0.77 (0.32, 1.86)	unclear	3	Yes
Bays (2004)[43] North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	11/13 0.87 (0.39, 1.96)	yes	5	No
Rodney (2006)[28] Pharm. Fund Multicentre	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	2/1 2.00 (0.18, 22.35)	yes	5	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Shankar (2007)[44] Asia Pharm. Fund Multicentre	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	0/0	unclear	2	Yes
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	221	Atorvastatin 20	214	6	124	5/2 1.97 (0.18, 22.23)	unclear	3	No
Farnier (2005)[31] International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	4/1 0.35 (0.01, 8.66)	unclear	5	No
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	3/4 4.29 (0.48, 38.78)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	5/0 11.38 (0.63, 207.10)	unclear	5	No
Blagden (2007)[35] Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/1 2.45 (0.47, 12.79)	unclear	4	Yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2007)[36] Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	5/4 0.78 (0.17, 3.53)	unclear	1	No
Patel (2006)[37] Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	77	Simvastatin 20	75	6	160	2/1 1.21 (0.32, 4.57)	unclear	3	No
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicentre	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	3/10 0.44 (0.12, 1.61)	yes	3	No
Catapano (2006)[38] North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Rosuvastatin 20-80	1437	Rosuvastatin 10-40	1447	6	173	16/17 0.95 (0.48, 1.88)	yes	4	No
Serious Adverse Events - Follow-up ≥ 24 weeks duration											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	17/5 0.74 (0.26, 2.12)	unclear	2	No
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	43/13 0.58 (0.29, 1.16)	unclear	3	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	28/6 2.04 (0.83, 4.99)	yes	4	No
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicentre	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	87	Simvastatin 10-80	22	48	179	8/4 0.46 (0.12, 1.68)	yes	4	No
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	36/25 1.66 (0.90, 3.04)	yes	2	Yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	5/1 5.51 (0.63, 47.94)	unclear	3	No
Serious Adverse Events - Lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy, both ≥ 24 wks follow up											
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	5/1 5.51 (0.63, 47.94)	unclear	3	No
Feldman (2004)[10] North America Pharm. Fund Multicentre	Participants with CHD or risk equivalent	Simvastatin 10-20	360	Simvastatin 40	253	23	169	23/12 1.26 (0.63, 2.53)	unclear	2	No
Serious Adverse Events - Lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in those requiring intensive lipid lowering therapy, fixed dose only											
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	5/1 5.51 (0.63, 47.94)	unclear	3	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Serious Adverse Events - Lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in those requiring intensive lipid lowering therapy, fixed and/or conditional titration											
Gaudiani (2005)[27] North America Pharm. Fund Multicentre	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	5/1 5.51 (0.63, 47.94)	unclear	3	No
Feldman (2004)[10] North America Pharm. Fund Multicentre	Participants with CHD or risk equivalent	Simvastatin 10-20	360	Simvastatin 40	253	23	169	23/12 1.26 (0.63, 2.53)	unclear	2	No
Cancer, all trials											
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	6/1 2.57 (0.31, 21.44)	yes	4	No
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicentre	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	4/0 9.27 (0.49, 174.53)	yes	2	Yes

Table 2. Surrogate outcome – Achieving ATP-III target LDL-c using ezetimibe plus statin therapy compared with statin monotherapy

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Relative probability of attaining ATPIII LDL-c goal – All trials											
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 40	248	23	169	363/147 2.83 (2.01, 4.00)	unclear	2	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	14	186	67/22 3.87 (2.31, 6.47)	unclear	3	yes
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 10-80	252	Atorvastatin 10-80	245	12	183	215/180 2.10 (1.34, 3.29)	unclear	2	no
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	64	Fluvastatin 80	69	12	174	54/41 3.69 (1.61, 8.44)	yes	5	yes
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	127/107 2.06 (1.38, 3.08)	unclear	3	yes

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	203	12	178	144/97 2.62 (1.74, 3.94)	yes	4	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	268	Simvastatin 10-80	261	12	179	207/167 1.91 (1.30, 2.80)	yes	4	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	101/78 3.79 (1.89, 7.59)	unclear	2	yes
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	217	Atorvastatin 20	210	6	124	169/109 3.26 (2.14, 4.96)	unclear	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	all with vascular disease LDL-c>190 and/or DM	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	178/49 15.59 (9.80, 24.81)	unclear	4	no
Ballantyne (2005)[47] VYVA North America Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Simvastatin 10-80	923	Atorvastatin 10-80	927	6	178	828/752 2.03 (1.55, 2.65)	yes	2	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	66/36 12.22 (4.73, 31.58)	unclear	4	yes
Goldberg (2006_1)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20	238	Atorvastatin 20	240	6	145	215/197 2.04 (1.19, 3.51)	yes	3	no
Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	226/214 1.78 (0.93, 3.40)	yes	3	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	6	94	392/154 3.31 (2.19, 5.00)	yes	3	no
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1940	Mixed	968	6	129	1377/199 9.45 (7.86, 11.36)	yes	4	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	221/182 4.16 (2.22, 7.79)	unclear	1	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	1368/1328 1.75 (1.25, 2.43)	yes	3	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	179	Simvastatin 10-20	186	6	123	133/31 14.46 (8.67, 24.10)	unclear	5	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	164/36 19.48 (11.83, 32.06)	unclear	5	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	37	Simvastatin 40	33	6-24	93	28/13 4.79 (1.72, 13.35)	unclear	3	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 20	73	Simvastatin 40	80	23	136	61/14 23.96 (10.28, 55.84)	unclear	3	no
Simvastatin - Lower dose simvastatin in combination versus higher dose monotherapy											

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	109	Simvastatin 40	248	23	169	90/147 3.25 (1.87, 5.67)	unclear	2	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	37	Simvastatin 40	33	6-24	93	28/13 4.79 (1.72, 13.35)	unclear	3	no
Participants requiring intensive lipid lowering therapy											
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	221/182 4.16 (2.22, 7.79)	unclear	1	no
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	217	Atorvastatin 20	210	6	124	169/109 3.26 (2.14, 4.96)	unclear	3	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	66/36 12.22 (4.73, 31.58)	unclear	4	yes
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	164/36 19.48 (11.83, 32.06)	unclear	5	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	768	Mixed	395	6	129	546/83 9.25 (6.93, 12.33)	yes	4	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	6	94	392/154 3.31 (2.19, 5.00)	yes	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	all with vascular disease LDL-c>190 and/or DM	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	178/49 15.59 (9.80, 24.81)	unclear	4	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	179	Simvastatin 10-20	186	6	123	133/31 14.46 (8.67, 24.10)	unclear	5	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 40	248	23	169	363/147 2.83 (2.01, 4.00)	unclear	2	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	37	Simvastatin 40	33	6-24	93	28/13 4.79 (1.72, 13.35)	unclear	3	no
Goldberg (2006_1)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20	238	Atorvastatin 20	240	6	145	215/197 2.04 (1.19, 3.51)	yes	3	no
Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	226/214 1.78 (0.93, 3.40)	yes	3	no
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	30	Fluvastatin 80	33	12	174	24/14 5.43 (1.75, 16.80)	yes	5	yes
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 20	73	Simvastatin 40	80	23	136	61/14 23.96 (10.28, 55.84)	unclear	3	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	85	Simvastatin 10	85	12	127	75/59 3.31 (1.48, 7.39)	unclear	2	yes
Simvastatin - Lower dose simvastatin in combination versus higher dose monotherapy (all participants required intensive treatment)											
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	109	Simvastatin 40	248	23	169	90/147 3.25 (1.87, 5.67)	unclear	2	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	37	Simvastatin 40	33	6-24	93	28/13 4.79 (1.72, 13.35)	unclear	3	no
Participants with diabetes mellitus											
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	6	94	392/154 3.31 (2.19, 5.00)	yes	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	all with vascular disease LDL-c>190 and/or DM	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	178/49 15.59 (9.80, 24.81)	unclear	4	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	37	Simvastatin 40	33	6-24	93	28/13 4.79 (1.72, 13.35)	unclear	3	no
Goldberg (2006_1)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20	238	Atorvastatin 20	240	6	145	215/197 2.04 (1.19, 3.51)	yes	3	no
Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	226/214 1.78 (0.93, 3.40)	yes	3	no
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	768	Mixed	395	6	129	546/83 9.25 (6.93, 12.33)	yes	4	no

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 20	73	Simvastatin 40	80	23	136	61/14 23.96 (10.28, 55.84)	unclear	3	no
Participants with established vascular disease											
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	66/36 12.22 (4.73, 31.58)	unclear	4	yes
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	164/36 19.48 (11.83, 32.06)	unclear	5	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	all with vascular disease LDL-c>190 and/or DM	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	178/49 15.59 (9.80, 24.81)	unclear	4	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	179	Simvastatin 10-20	186	6	123	133/31 14.46 (8.67, 24.10)	unclear	5	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	85	Simvastatin 10	85	12	127	75/59 3.31 (1.48, 7.39)	unclear	2	yes
Participants of Hispanic origin											

ATP III target for LDL-c											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Trial Baseline LDL-c (mg/dL)**	**Combo/mono Number of participants with events Odds ratio (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	71	Mixed	42	6	129	46/8 7.82 (3.14, 19.45)	yes	4	no
Participants of African origin											
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	135	Mixed	73	6	129	85/24 3.47 (1.90, 6.33)	yes	4	no

Table 3. Surrogate outcome – LDL-c using ezetimibe plus statin therapy compared with statin monotherapy

Low density lipoprotein cholesterol											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI) mg/dL**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in LDL-c post-treatment mean or mean change score from baseline (mg/dL)											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-51.40 (-59.67, -43.13)	yes	3	no
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	29	Mixed 80	16	12	309	-72.00 (-140.80, -3.20)	unclear	3	no
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	-5.00 (-9.79, -0.21)	unclear	2	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	-6.30 (-15.61, 3.01)	unclear	2	yes

Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	-18.00 (-25.79, -10.21)	yes	2	yes
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-28.64 (-31.94, -25.34)	unclear	5	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-24.60 (-29.39, -19.81)	unclear	1	no
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	-13.54 (-35.19, 8.11)	unclear	2	no
Kosoglou (2004_a)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	11	Rosuvastatin 10	11	2	158	-34.06 (-48.37, -19.75)	unclear	2	yes
Kosoglou (2004_b)[20] North America Pharm. Fund Single centre	Healthy participants of European descent with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Lovastatin 20-40	15	Lovastatin 20	8	2	177	-34.16 (-46.91, -21.41)	unclear	1	yes

Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	11	Simvastatin 10	12	2	169	-25.50 (-43.55, -7.45)	unclear	2	no
Berthold (2006)[51] Europe Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 40	24	Simvastatin 40	24	2-3	114	-20.00 (-31.63, -8.37)	unclear	2	yes
Chenot (2007)[52] Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	-35.00 (-55.26, -14.74)	unclear	1	yes
Participants in need of intensive lipid lowering therapy - all trials											
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-28.64 (-31.94, -25.34)	unclear	5	no
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	29	Mixed 80	16	12	309	-72.00 (-140.80, -3.20)	unclear	3	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-24.60 (-29.39, -19.81)	unclear	1	no
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	-13.54 (-35.19, 8.11)	unclear	2	no
Chenot (2007)[52] Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	-35.00 (-55.26, -14.74)	unclear	1	yes

Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-51.40 (-59.67, -43.13)	yes	3	no
Lower dose atorvastatin in combination versus higher dose monotherapy of the same In those requiring intensive lipid lowering											
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	-13.54 (-35.19, 8.11)	unclear	2	no
Participants with LDL-c≥190											
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	29	Mixed 80	16	12	309	-72.00 (-140.80, -3.20)	unclear	3	no
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-51.40 (-59.67, -43.13)	yes	3	no
Participants with vascular disease											
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-28.64 (-31.94, -25.34)	unclear	5	no
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	-13.54 (-35.19, 8.11)	unclear	2	no
Chenot (2007)[52] Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	-35.00 (-55.26, -14.74)	unclear	1	yes
Combination – monotherapy: difference in mean percentage change from baseline (%)											

Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, -16.37)	yes	3	no
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	-10.00 (-15.76, -4.24)	unclear	2	no
Ballantyne (2004_b)[53] North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	432	Atorvastatin 80	223	24	180	-6.90 (-9.27, -4.53)	unclear	3	no
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	simvastatin 20	101	24	119	-21.00 (-30.74, -11.26)	yes	2	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-20.50 (-26.60, -14.40)	unclear	3	no

Bays (2004)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 10-80	559	4-26	178	-14.90 (-16.46, -13.34)	yes	5	no
Berthold (2006)[51] Europe Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 40	24	Simvastatin 40	24	2-3	114	-18.90 (-24.97, -12.83)	unclear	2	yes
Stein (2004)[41] International Pharm. fund	LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	14	186	-13.60 (-16.10, -11.10)	unclear	3	yes
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	-17.20 (-21.13, -13.27)	yes	5	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	344	Simvastatin 80	78	12	136	-27.00 (-34.80, -19.20)	unclear	3	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	statin naïve, 1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	-14.70 (-17.13, -12.27)	yes	4	no
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	-13.40 (-15.89, -10.91)	yes	4	yes

Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	181	Lovastatin 10-40	202	12	179	-15.00 (-17.78, -12.22)	unclear	3	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	-15.20 (-17.70, -12.70)	yes	4	no
Gagne (2002_1)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Atorvastatin 80	12	Atorvastatin 80	12	12	309	-21.16 (-30.97, -11.35)	unclear	3	no
Gagne (2002_2)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Simvastatin 80	5	Simvastatin 80	5	12	309	-18.83 (-36.43, -1.23)	unclear	3	no
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	-4.00 (-8.95, 0.95)	unclear	2	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	-7.40 (-16.33, 1.53)	unclear	2	yes

Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, subgroup with DM	Simvastatin 80	88	Simvastatin 80	94	8	136	-26.10 (-30.69, -21.51)	unclear	3	no
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	-12.50 (-15.83, -9.17)	unclear	3	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	102	Simvastatin 10-20	101	6	123	-24.30 (-27.78, -20.82)	unclear	5	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	224	6	122	-26.90 (-29.80, -24.00)	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-23.00 (-25.86, -20.14)	unclear	5	no
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1940	Mixed	968	6	129	-23.10 (-24.45, -21.75)	yes	4	no
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, African descent subgroup	Simvastatin 20	174	Simvastatin 20	93	6	129	-23.00 (-27.55, -18.45)	yes	4	no

Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, Hispanic subgroup	Mixed	94	Mixed	53	6	129	-21.10 (-27.16, -15.04)	yes	4	no
Ballantyne (2005_1)[47] VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c	Simvastatin 20	233	Atorvastatin 20	230	6	178	-6.90 (-9.49, -4.31)	yes	2	no
Ballantyne (2005_2)[47] VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c	Simvastatin 40	236	Atorvastatin 40	232	6	178	-9.10 (-11.69, -6.51)	yes	2	no
Ballantyne (2005_3)[47] VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c	Simvastatin 80	224	Atorvastatin 80	230	6	178	-5.70 (-8.39, -3.01)	yes	2	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	-14.10 (-17.92, -10.28)	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-24.60 (-29.39, -19.81)	unclear	1	no

Patel (2006)[37] Europe Pharm. Fund Multicenter	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	72	Simvastatin 20	71	6	160	-14.60 (-19.06, -10.14)	unclear	3	no
Goldberg (2006_1)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20	238	Atorvastatin 20	240	6	145	-9.00 (-11.55, -6.45)	yes	3	no
Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	-6.70 (-9.25, -4.15)	yes	3	no
Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	-4.20 (-5.03, -3.37)	yes	3	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20	210	Atorvastatin 20	213	6	94	-17.66 (-22.78, -12.54)	yes	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	108	Simvastatin 20	246	5	169	-15.00 (-17.83, -12.17)	unclear	2	no

Kosoglou (2004)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	11	Rosuvastatin 10	11	2	158	-15.90 (-22.32, -9.48)	unclear	2	yes
Participants in need of intensive lipid lowering therapy											
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	-12.50 (-15.83, -9.17)	unclear	3	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	102	Simvastatin 10-20	101	6	123	-24.30 (-27.78, -20.82)	unclear	5	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	224	6	122	-26.90 (-29.80, -24.00)	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-23.00 (-25.86, -20.14)	unclear	5	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, subgroup with DM	Simvastatin 80	88	Simvastatin 80	94	8	136	-26.10 (-30.69, -21.51)	unclear	3	no

Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-20.50 (-26.60, -14.40)	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	108	Simvastatin 20	246	5	169	-15.00 (-17.83, -12.17)	unclear	2	no
Gagne (2002_2)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Simvastatin 80	5	Simvastatin 80	5	12	309	-18.83 (-36.43, -1.23)	unclear	3	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	-14.10 (-17.92, -10.28)	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-24.60 (-29.39, -19.81)	unclear	1	no
Patel (2006)[37] Europe Pharm. Fund Multicenter	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	72	Simvastatin 20	71	6	160	-14.60 (-19.06, -10.14)	unclear	3	no

Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	-6.70 (-9.25, -4.15)	yes	3	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20	210	Atorvastatin 20	213	6	94	-17.66 (-22.78, -12.54)	yes	3	no
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, -16.37)	yes	3	no
Lower dose simvastatin in combination versus higher dose monotherapy of the same - Participants in need of intensive lipid lowering therapy - All with diabetes mellitus											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-20.50 (-26.60, -14.40)	unclear	3	no
Participants with baseline LDL-c>190 mg/dL											
Gagne (2002_2)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Simvastatin 80	5	Simvastatin 80	5	12	309	-18.83 (-36.43, -1.23)	unclear	3	no

Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, -16.37)	yes	3	no
Participants with diabetes mellitus											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-20.50 (-26.60, -14.40)	unclear	3	no
Goldberg (2006_2)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 40	242	Atorvastatin 40	241	6	145	-6.70 (-9.25, -4.15)	yes	3	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20	210	Atorvastatin 20	213	6	94	-17.66 (-22.78, -12.54)	yes	3	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, subgroup with DM	Simvastatin 80	88	Simvastatin 80	94	8	136	-26.10 (-30.69, -21.51)	unclear	3	no
Participants with vascular disease											

Patel (2006)[37] Europe Pharm. Fund Multicenter	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	72	Simvastatin 20	71	6	160	-14.60 (-19.06, -10.14)	unclear	3	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	102	Simvastatin 10-20	101	6	123	-24.30 (-27.78, -20.82)	unclear	5	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	224	6	122	-26.90 (-29.80, -24.00)	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-23.00 (-25.86, -20.14)	unclear	5	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	-14.10 (-17.92, -10.28)	unclear	4	yes
All participants of African descent											
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, African subgroup	Mixed	174	Mixed	93	6	129	-23.00 (-25.55, -18.45)	yes	4	no
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	124	12	176	-17.20 (-21.13, -13.27)	yes	5	no
All participants of Hispanic descent											

Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, Hispanic subgroup	Mixed	94	Mixed	53	6	129	-21.10 (-27.16, -15.04)	yes	4	no

Table 4. Surrogate outcome – HDL-c using ezetimibe plus statin therapy compared with statin monotherapy

High density lipoprotein - cholesterol											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in HDL-c post-treatment mean or mean change score from baseline											
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	0.70 (-1.74, 3.14)	unclear	1	No
Berthold (2006)[51] Europe Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 40	24	Simvastatin 40	24	2-3	114	-5.00 (-13.51, 3.51)	unclear	2	Yes
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	0.20 (-1.81, 2.21)	yes	3	No
Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	11	Simvastatin 10	12	2	169	-3.70 (-10.16, 2.76)	unclear	2	No
Kosoglou (2004_a)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	11	Rosuvastatin 10	11	2	158	-5.41 (-12.40, 1.58)	unclear	2	Yes
Kosoglou (2004_b)[20] North America Pharm. Fund Single centre	Healthy participants of European descent with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Lovastatin 20-40	15	Lovastatin 20	8	2	177	-6.40 (-11.73, -1.07)	unclear	1	Yes

Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	1.00 (-0.95, 2.95)	yes	2	Yes
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	2.32 (-5.78, 10.42)	unclear	2	No
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	1.00 (-1.28, 3.28)	unclear	2	Yes
Participants requiring intensive lipid lowering therapy											
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	0.70 (-1.74, 3.14)	unclear	1	No
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	0.20 (-1.81, 2.21)	yes	3	No
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	2.32 (-5.78, 10.42)	unclear	2	No
Lower (fixed) dose atorvastatin in combination versus higher dose atorvastatin monotherapy – Participants (with CHD) requiring intensive lipid lowering therapy											
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	2.32 (-5.78, 10.42)	unclear	2	No
Participants with LDL-c>190 mg/dL											

Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	0.20 (-1.81, 2.21)	yes	3	No
Participants with vascular disease											
Piorkowski (2007)[48] Europe Single centre	Participants with CAD and on low dose atorvastatin	Atorvastatin 10	26	Atorvastatin 40	25	4	136	2.32 (-5.78, 10.42)	unclear	2	No
Combination – monotherapy: difference in HDL-c mean percentage change from baseline											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2.40 (-0.23, 5.03)	yes	3	No
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	0.90 (-3.04, 4.84)	unclear	2	No
Ballantyne (2004_b)[53] North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	432	Atorvastatin 80	223	24	180	5.80 (3.43, 8.17)	unclear	3	No
Stein (2004)[41] International Pharm. Fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Rosuvastatin 40	278	Atorvastatin 80	290	14	186	2.70 (0.76, 4.64)	unclear	3	Yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	2.40 (0.18, 4.62)	yes	4	No
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	0.60 (-1.33, 2.53)	yes	4	No

Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	181	Lovastatin 10-40	202	12	179	5.00 (2.22, 7.78)	unclear	3	Yes
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	344	Simvastatin 80	78	12	136	2.60 (-2.17, 7.37)	unclear	3	No
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	3.00 (-1.95, 7.95)	unclear	2	No
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	1.40 (-0.82, 3.62)	yes	4	Yes
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	2.70 (-2.56, 7.96)	unclear	2	Yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	2.32 (-0.83, 5.47)	unclear	1	No
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	2.20 (-0.02, 4.42)	unclear	3	No
Blagden (2007)[35] COMPELL study North America Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	197	-0.30 (-4.22, 3.62)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-0.40 (-2.91, 2.11)	unclear	5	No

Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	0.00 (-0.83, 0.83)	yes	3	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	0.20 (-2.05, 2.45)	yes	3	No
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	2.80 (0.47, 5.13)	unclear	4	No
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-0.10 (-3.42, 3.22)	unclear	3	No
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 20	248	5	169	1.88 (0.06, 3.70)	unclear	2	No
Bays (2007)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 10-80	559	4-26	178	0.80 (-0.72, 2.32)	yes	5	No
Berthold (2006)[51] Europe Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 40	24	Simvastatin 40	24	2-3	114	-2.20 (-7.79, 3.39)	unclear	2	Yes
Kosoglou (2004)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	11	Rosuvastatin 10	11	2	158	-2.80 (-11.57, 5.97)	unclear	2	Yes
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	simvastatin 20	101	24	119	3.00 (-2.84, 8.84)	yes	2	Yes

Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1940	Mixed	968	6	129	2.10 (1.20, 3.00)	yes	4	No
Participants requiring intensive lipid lowering therapy											
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	2.20 (-0.02, 4.42)	unclear	3	No
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	2.80 (0.47, 5.13)	unclear	4	No
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-0.40 (-2.91, 2.11)	unclear	5	No
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1940	Mixed	968	6	129	2.10 (1.20, 3.00)	yes	4	No
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 80	88	Simvastatin 80	94	12	136	-0.80 (0.43, 2.09)	unclear	3	No
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-0.10 (-3.42, 3.22)	unclear	3	No
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 20	248	5	169	1.88 (0.06, 3.70)	unclear	2	No

Blagden (2007)[35] COMPELL study North America Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	197	-0.30 (-4.22, 3.62)	unclear	4	No
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	2.32 (-0.83, 5.47)	unclear	1	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	0.20 (-2.05, 2.45)	yes	3	No
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363.00	96	318	2.40 (-0.23, 5.03)	yes	3	No
Lower (fixed) dose statin in combination versus higher dose simvastatin monotherapy in participants requiring intensive lipid-lowering therapy (diabetes mellitus)											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-0.10 (-3.42, 3.22)	unclear	3	No
Participants with LDL-c>190 mg/dL											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363.00	96	318	2.40 (-0.23, 5.03)	yes	3	No
Participants with diabetes mellitus											
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1940	Mixed	968	6	129	2.10 (1.20, 3.00)	yes	4	No
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 80	88	Simvastatin 80	94	12	136	-0.80 (0.43, 2.09)	unclear	3	No

Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-0.10 (-3.42, 3.22)	unclear	3	No
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	0.20 (-2.05, 2.45)	yes	3	No
Participants with vascular disease											
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	204	Simvastatin 10-20	207	6	123	-0.40 (-2.91, 2.11)	unclear	5	No
Blagden (2007)[35] COMPELL study North America Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	197	-0.30 (-4.22, 3.62)	unclear	4	No
All participants of African origin											
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, subgroup of African descent	Mixed	174	Mixed	93	6	129	2.10 (1.20, 3.00)	yes	4	No
All participants of Hispanic origin											
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy, subgroup of Hispanic origin	Mixed	94	Mixed	53	6	129	2.10 (1.20, 3.00)	yes	4	No

Table 5. Surrogate outcome – TC:HDL-c ratio using ezetimibe plus statin therapy compared with statin monotherapy

Total cholesterol: high-density lipoprotein cholesterol ratio											
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline											
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-0.61 (-0.76, -0.47)	unclear	1	no
Combination – monotherapy: difference in mean percentage change from baseline											
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	344	Simvastatin 80	78	12	136	-20.30 (-26.78, -13.82)	unclear	3	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	-10.90 (-13.01, -8.79)	yes	4	no
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 10-80	255	Atorvastatin 10-80	248	12	183	-10.10 (-12.53, -7.67)	unclear	2	no

Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	-13.10 (-15.59, -10.61)	yes	4	yes
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	181	Lovastatin 10-40	202	12	179	-13.00 (-15.78, -10.22)	unclear	3	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	-11.16 (-13.38, -8.94)	yes	4	no
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	Participants with CAD, statin naïve	Simvastatin 40	72	Rosuvastatin 40	73	12	197	-4.00 (-7.91, -0.09)	unclear	2	no
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	-9.20 (-11.97, -6.43)	unclear	3	no

Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	-19.90 (-22.31, -17.49)	unclear	4	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-13.50 (-18.22, -8.78)	unclear	3	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-10.36 (-12.62, -8.10)	unclear	4	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	-10.32 (-13.55, -7.10)	yes	3	no
Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	-3.00 (-3.83, -2.17)	yes	4	no
Bays (2007)[43] North America Pharm. Fund Multicenter	1o HC	Simvastatin 10-80	539	Simvastatin 10-80	559	4-26	178	-10.50 (-11.95, -9.05)	yes	3	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	4	186	-17.00 (-18.95, -15.05)	unclear	3	yes

Participants in need of intensive lipid lowering therapy											
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	215	Atorvastatin 20	207	6	124	-9.20 (-11.97, -6.43)	unclear	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	-19.90 (-22.31, -17.49)	unclear	4	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	344	Simvastatin 80	78	12	136	-20.30 (-26.78, -13.82)	unclear	3	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-13.50 (-18.22, -8.78)	unclear	3	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	160	-10.36 (-12.62, -8.10)	unclear	4	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	-10.32 (-13.55, -7.10)	yes	3	no
Lower dose simvastatin in combination versus higher dose simvastatin monotherapy – fixed dosing in participants with diabetes mellitus											

Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-13.50 (-18.22, -8.78)	unclear	3	no
All participants with diabetes mellitus , 13142}											
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Mixed	88	Mixed	94	8	136	-17.30 (-20.91, -13.69)	unclear	3	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	6-24	93	-13.50 (-18.22, -8.78)	unclear	3	no
Constance (2007)[3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	-10.32 (-13.55, -7.10)	yes	3	no
Participants with vascular disease [32]											
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	219	Atorvastatin 10-20	225	6	122	-19.90 (-22.31, -17.49)	unclear	4	no

Table 6. Carotid intima-media thickness (CIMT) using ezetimibe plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow -up (wk)	Mean Baseline LDL-c (mg/dL)	Combo-mono: mean difference (95% CI)	AAC	Jadad Score	ITTA
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	322	Simvastatin 80	320	96	318	0.01 (-0.01, 0.02)	yes	3	no

Table 7. Adverse events and adherence to treatment using ezetimibe plus statin compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Relative probability of participants adhering to treatment											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	300/283 1.49 (1.02, 2.17)	yes	3	no
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	87/92 0.57 (0.24, 1.36)	yes	2	yes
Ballantyne (2004_b)[53] North America Pharm. Fund	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	526	Atorvastatin 80	262	24	542	432/223 0.80 (0.54, 1.21)	unclear	3	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	278/290 0.92 (0.53, 1.62)	unclear	3	yes
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	353	Simvastatin 10-80	349	12	175	323/322 0.90 (0.52, 1.55)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	184/192 0.62 (0.30, 1.29)	yes	4	yes
Davidson (2002_1)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	67	Simvastatin 10	70	12	179	61/61 1.50 (0.50, 4.47)	yes	4	no
Davidson (2002_2)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	69	Simvastatin 20	61	12	179	58/53 0.80 (0.30, 2.13)	yes	4	no
Davidson (2002_3)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	73	Simvastatin 40	65	12	179	68/60 1.13 (0.31, 4.11)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_4)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	65	Simvastatin 80	67	12	179	52/63 0.25 (0.08, 0.83)	yes	4	no
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	71/61 13.97 (1.77, 110.52)	unclear	2	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	229	Atorvastatin 10-20	225	6	122	199/200 0.83 (0.47, 1.46)	unclear	4	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	239	Rosuvastatin 40	230	6	160	232/219 1.66 (0.63, 4.37)	unclear	1	no
Patel (2006)[37] Europe Pharm. Fund Multicenter	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	78	Simvastatin 20	75	6	160	76/68 3.91 (0.79, 19.48)	unclear	3	no
Relative probability of participants adhering to treatment - Fixed lower dose simvastatin in combination versus higher dose simvastatin alone											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_5)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	65	12	179	61/60 0.85 (0.25, 2.93)	yes	4	no
Davidson (2002_6)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	69	Simvastatin 80	67	12	179	58/63 0.33 (0.10, 1.11)	yes	4	no
Relative probability of participants experiencing an adverse event											
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	142/30 1.20 (0.60, 2.40)	unclear	2	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	355	Simvastatin 80	78	48	136	265/56 1.16 (0.67, 2.00)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	393/159 1.19 (0.84, 1.66)	yes	4	no
Ballantyne (2004_b)[53] North America Pharm. Fund	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	432	Atorvastatin 80	223	24	542	349/187 0.81 (0.53, 1.24)	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	457	Simvastatin 40	253	23	169	277/168 0.78 (0.56, 1.07)	unclear	2	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	190/193 1.02 (0.80, 1.31)	yes	5	no
Stein (2004)[41] International Pharm. fund	1° HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	193/184 1.24 (0.90, 1.71)	unclear	3	yes
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	71/69 1.05 (0.63, 1.73)	yes	5	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	134/129 1.13 (0.75, 1.69)	yes	4	yes
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	122/141 0.98 (0.65, 1.46)	unclear	3	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	268	Simvastatin 10-80	261	12	179	185/188 0.87 (0.60, 1.26)	yes	4	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	39/38 1.07 (0.62, 1.85)	unclear	2	yes
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	221	Atorvastatin 20	214	6	124	44/51 0.79 (0.50, 1.25)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	75/77 0.91 (0.62, 1.35)	unclear	1	no
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	106/176 0.86 (0.66, 1.13)	yes	3	no
Geiss (2005)[54]	Severe HC LDL-c>190 all on LDL-c-apheresis	Mixed 5-20	20	Mixed 5-20	20	2		0/0 0.00 (0.00, 0.00)	unclear	2	no
Kosoglou (2004)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	12	Rosuvastatin 10	12	23	158	11/9 3.67 (0.32, 41.59)	unclear	2	yes
Relative probability of participants experiencing an adverse event - Fixed lower dose simvastatin in combination versus higher dose simvastatin alone											
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvstatin 20	109	Simvastatin 40	253	23	169	74/168 1.07 (0.66, 1.73)	unclear	2	no
Relative probability of participants withdrawing from trial due to an adverse event											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC LDL-c>190	Simvastatin 80	357	Simvastatin 80	363	96	318	29/34 0.86 (0.51, 1.44)	yes	3	no
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	19/3 1.46 (0.41, 5.17)	unclear	2	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	355	Simvastatin 80	78	48	136	26/8 0.69 (0.30, 1.59)	unclear	3	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	2/5 0.41 (0.08, 2.17)	unclear	3	no
Ballantyne (2004_b)[53] North America Pharm. Fund	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	526	Atorvastatin 80	262	24	542	46/14 1.70 (0.92, 3.15)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	457	Simvastatin 40	253	23	169	23/14 0.90 (0.46, 1.79)	unclear	2	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	14/12 1.21 (0.55, 2.63)	yes	5	no
Stein (2004)[41] International Pharm. fund	1° HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	13/14 0.96 (0.44, 2.08)	unclear	3	yes
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	2/1 2.00 (0.18, 22.35)	yes	5	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	353	Simvastatin 10-80	349	12	175	16/7 2.32 (0.94, 5.71)	yes	4	no
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	9/3 3.11 (0.83, 11.65)	yes	4	yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	9/10 1.03 (0.41, 2.60)	unclear	3	yes
Davidson (2002_1)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	67	Simvastatin 10	70	12	179	2/4 0.51 (0.09, 2.87)	yes	4	no
Davidson (2002_2)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	69	Simvastatin 20	61	12	179	7/6 1.03 (0.33, 3.27)	yes	4	no
Davidson (2002_3)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	73	Simvastatin 40	65	12	179	3/2 1.35 (0.22, 8.34)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_4)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	65	Simvastatin 80	67	12	179	8/2 4.56 (0.93, 22.36)	yes	4	no
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	33	Mixed 80	17	12	309	2/0 2.78 (0.13, 61.17)	unclear	3	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	0/0	unclear	2	yes
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	64	Fluvastatin 80	69	12	174	5/6 0.89 (0.26, 3.07)	yes	5	yes
Constance (2007) [3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	10/2 2.51 (0.55, 11.56)	yes	3	no
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	217	Atorvastatin 20	210	6	124	1/0 2.92 (0.12, 72.00)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	2/1 2.10 (0.19, 23.34)	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	2/0 5.10 (0.24, 106.81)	unclear	5	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	6/1 6.82 (0.80, 58.11)	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	6/3 1.96 (0.48, 7.92)	unclear	1	no
Patel (2006)[37] Europe Pharm. Fund Multicenter	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	77	Simvastatin 20	75	6	160	5/1 5.14 (0.59, 45.07)	unclear	3	no
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	4/11 0.54 (0.17, 1.69)	yes	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	1/0 3.26 (0.12, 88.35)	unclear	2	no
Relative probability of participants withdrawing from trial due to an adverse event - Fixed lower dose simvastatin in combination versus higher dose simvastatin alone											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	104	Simvastatin 40	110	24	93	2/5 0.41 (0.08, 2.17)	unclear	3	no
Davidson (2002_1)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	65	12	179	2/2 0.41 (0.08, 2.17)	yes	4	no
Davidson (2002_2)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	360	Simvastatin 80	253	12	179	18/14 0.90 (0.44, 1.84)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-20	360	Simvastatin 40	253	23	169	18/14 0.90 (0.44, 1.84)	unclear	2	no
Relative probability of participants experiencing elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis											
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	1/0 0.68 (0.03, 16.98)	unclear	2	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	1/0 0.58 (0.02, 14.51)	unclear	3	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	530	Simvastatin 20-80	227	48	175	15/1 6.58 (0.86, 50.13)	yes	4	no
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	24	93	1/1 1.04 (0.06, 16.84)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2004)[53] North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	511	Atorvastatin 80	252	24	542	11/6 0.90 (0.33, 2.47)	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 40	248	23	169	2/0 2.76 (0.13, 57.80)	unclear	2	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	540	Simvastatin 10-80	559	14-26	178	8/7 1.19 (0.43, 3.29)	yes	5	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	3/1 3.13 (0.32, 30.25)	unclear	3	yes
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	yes	5	no
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	2/1 2.02 (0.18, 22.45)	yes	4	yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	1/0 3.45 (0.14, 85.29)	unclear	3	yes
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	29	Mixed 80	16	12	309	2/0 3.00 0.14, 66.40	unclear	3	no
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	64	Fluvastatin 80	69	12	174	1/1 1.08 (0.07, 17.62)	yes	5	yes
Davidson (2002_1)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 10	61	12	179	0/0	yes	4	no
Davidson (2002_2)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 20	53	12	179	1/1 0.91 (0.06, 14.96)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_3)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	68	Simvastatin 40	60	12	179	4/0 8.44 (0.45, 160.12)	yes	4	no
Davidson (2002_4)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	52	Simvastatin 80	63	12	179	1/1 1.22 (0.07, 19.92)	yes	4	no
Constance (2007) [3] International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	3/1 1.49 (0.15, 14.41)	yes	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	218	Atorvastatin 10-20	230	6	122	1/0 3.18 (0.13, 78.46)	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2005)[47] VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c	Simvastatin 10-80	933	Atorvastatin 10-80	939	6	178	1/11 0.09 (0.01, 0.70)	yes	2	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	3/0 6.85 (0.35, 133.38)	unclear	1	no
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Simvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/3 0.21 (0.01, 4.09)	yes	3	no
Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1437	Rosuvastatin 10-40	1447	6	173	9/3 3.03 (0.82, 11.23)	yes	3	no
Geiss (2005)[54]	Severe HC LDL-c>190 all on LDL-c-apheresis	Mixed 5-20	20	Mixed 5-20	20	5		0/0	unclear	2	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	0/0	unclear	2	no
Relative probability of participants experiencing elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis - Simvastatin Lower (fixed) dose simvastatin in combination versus higher simvastatin dose monotherapy											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	24	93	1/1 1.04 (0.06, 16.84)	unclear	3	no
Goldberg (2004_1)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	134	Simvastatin 40	77	48	175	1/0 1.74 (0.07, 43.28)	yes	4	no
Goldberg (2004_2)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	135	Simvastatin 80	73	48	175	1/1 0.54 (0.03, 8.72)	yes	4	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-20	354	Simvastatin 40	248	23	169	1/0 2.11 (0.09, 51.98)	unclear	2	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Davidson (2002_5)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 40	60	12	179	0/0	yes	4	no
Davidson (2002_6)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 80	63	12	179	1/1 1.09 (0.07, 17.80)	yes	4	no
Relative probability of participants experiencing elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis - Simvastatin Lower dose simvastatin in combination versus higher dose simvastatin monotherapy (fixed or conditionally titrated)											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	107	24	93	1/1 1.04 (0.06, 16.84)	unclear	3	no
Goldberg (2004_1)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	134	Simvastatin 40	77	48	175	1/0 1.74 (0.07, 43.28)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Goldberg (2004_2)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	135	Simvastatin 80	73	48	175	1/1 0.54 (0.03, 8.72)	yes	4	no
Davidson (2002_5)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 40	60	12	179	0/0	yes	4	no
Davidson (2002_6)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 80	63	12	179	1/1 1.09 (0.07, 17.80)	yes	4	no
Relative probability of participants experiencing myalgia											
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	1/0 0.68 (0.03, 16.98)	unclear	2	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	1/0 0.58 (0.02, 14.51)	unclear	3	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	15/7 0.91 (0.37, 2.26)	yes	4	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	2/5 0.41 (0.08, 2.12)	yes	5	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	24/28 0.88 (0.50, 1.55)	unclear	3	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	139	Simvastatin 10-80	237	12	179	0/1 0.57 (0.02, 13.97)	yes	4	no
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	221	Atorvastatin 20	214	6	124	6/5 1.17 (0.35, 3.88)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	3/4 0.79 (0.17, 3.57)	unclear	5	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	3/0 7.71 (0.39, 151.84)	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	7/7 0.97 (0.33, 2.80)	unclear	1	no
Kosoglou (2004_a)[49] Europe Pharm. Fund Single centre	Healthy participants with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	12	Rosuvastatin 10	12	2	158	2/2 1.00 (0.12, 8.56)	unclear	2	yes
Kosoglou (2004_b)[20] North America Pharm. Fund Single centre	Healthy participants of European descent with LDL-c >= 130 mg/dL and BMI < 31kg/m2. Low risk	Lovastatin 20-40	15	Lovastatin 20	8	2	177	1/0 1.76 (0.06, 48.19)	unclear	1	yes
Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	1/0 3.26 (0.12, 88.35)	unclear	2	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Berthold (2006)[51] Europe Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 40	24	Simvastatin 40	24	2	114	0/0	unclear	2	yes
Chenot (2007)[52] Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	0/0	unclear	1	yes
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal											
Kastelein (2008)[39] ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	356	Simvastatin 80	360	96	318	4/8 0.50 (0.15, 1.68)	yes	3	no
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	0/0	unclear	3	no
Landray (2006)[26] UK-HARP-II Europe Pharm. Fund Multicenter	Participants with renal disease and without definitive indication for cholesterol lowering	Simvastatin 20	102	Simvastatin 20	101	24	119	0/0	yes	2	yes
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	110	24	93	1/0 3.23 (0.13, 80.29)	unclear	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2004)[53] North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	510	Atorvastatin 80	252	24	180	3/0 3.48 (0.18, 67.68)	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	451	Simvastatin 40	248	23	169	1/2 0.27 (0.02, 3.03)	unclear	2	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	540	Mixed 10-80	559	14-26	178	1/1 1.04 (0.06, 16.59)	yes	5	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	0/1 0.34 (0.01, 8.48)	unclear	3	yes
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/1 0.33 (0.01, 8.13)	yes	5	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	2/1 2.00 (0.18, 22.17)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2003)[24] Ezetimibe Study Group International Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 10-80	248	Atorvastatin 10-80	235	12	183	1/0 2.85 (0.12, 70.42)	unclear	2	no
Melani (2003)[29] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	204	Pravastatin 10-40	205	12	178	0/2 0.20 (0.01, 4.17)	yes	4	yes
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	yes
Davidson (2002)[40] Ezetimibe study group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	239	Simvastatin 10-80	237	12	179	0/2 0.20 (0.01, 4.12)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
McKenney (2007_1)[7] COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	0/0	unclear	2	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	0/1 0.34 (0.01, 8.34)	unclear	2	yes
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	64	Fluvastatin 80	69	12	174	0/0	yes	5	yes
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	217	Atorvastatin 20	210	6	124	0/0	unclear	3	no
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	1/0 3.18 (0.13, 78.64)	unclear	5	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/0	unclear	4	no
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Pearson (2005)[34] EASE North America Pharm. Fund Multicenter	Participants not meeting ATP III target LDL-c despite statin therapy	Mixed	1965	Mixed	992	6	129	0/0	yes	4	no
Ballantyne (2005)[47] VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c	Simvastatin 10-80	933	Atorvastatin 10-80	939	6	178	0/1 0.34 (0.01, 8.24)	yes	2	no
Blagden (2007)[35] Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	yes
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	0/0	unclear	1	no
Goldberg (2006)[9] VYTAL North America Pharm. Fund Multicenter	T2DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dL	Atorvastatin 20-40	494	Atorvastatin 10-40	732	6	145	0/0	yes	3	no
Catapano (2006)[38] North America Pharm. Fund Multicenter	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1437	Rosuvastatin 10-40	1447	6	173	4/1 4.04 (0.45, 36.16)	yes	3	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Geiss (2005)[54]	Severe HC LDL-c>190 all on LDL-c-apheresis	Mixed 5-20	20	Mixed 5-20	20	5		0/0	unclear	2	no
Kosoglou (2002)[50] North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	0/0	unclear	2	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal - Lower dose simvastatin in combination versus higher dose simvastatin monotherapy (fixed or conditional titration)											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	110	24	93	1/0 3.23 (0.13, 80.29)	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-20	354	Simvastatin 40	248	23	169	0/2 0.14 (0.01, 2.91)	unclear	2	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal - Lower dose simvastatin in combination versus higher dose simvastatin monotherapy (fixed dosing only)											
Gaudiani (2005)[27] North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dL	Simvastatin 20	103	Simvastatin 40	110	24	93	1/0 3.23 (0.13, 80.29)	unclear	3	no
Relative probability of participants experiencing rhabdomyolysis (investigator defined)											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Masana (2005)[42] Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals	Simvastatin 80	296	Simvastatin 80	57	48	136	0/0	unclear	3	no
Goldberg (2004)[25] Ezetimibe Study Group International Pharm. fund	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	yes	4	no
Ballantyne (2004)[53] North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	432	Atorvastatin 80	223	24	180	0/0	unclear	3	no
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-40	457	Simvastatin 40	253	23	169	0/0	unclear	2	no
Bays (2004)[43] North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	0/0	yes	5	no
Stein (2004)[41] International Pharm. fund	1º HC , LDL >= 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	305	Atorvastatin 80	316	14	186	0/0	unclear	3	yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Rodney (2006)[28] Pharm. Fund Multicenter	African descent, 1º HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	yes	5	no
Kerzner (2003)[30] Ezetimibe Study Group North America Pharm. Fund Multicenter	1º HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	yes
Gagne (2002)[13] Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age	Mixed 40-80	29	Mixed 80	16	12	309	0/0	unclear	3	no
Shankar (2007)[44] Asia Pharm. Fund Multicenter	South Asians, heterogeneous 10-year CHD risk estimates	Simvastatin 10	114	Simvastatin 10	116	12	127	0/0	unclear	2	yes
Stein (2008)[46] International Pharm. fund	HC, Participants with documented statin associated myopathy	Fluvastatin 80	64	Fluvastatin 80	69	12	174	0/0	yes	5	yes
Barrios (2005)[45] International Pharm. fund	CHD or risk equivalent	Simvastatin 20	221	Atorvastatin 20	214	6	124	0/0	unclear	3	no
Cruz-Fernandez (2005)[32] International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/0	unclear	4	no

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Brohet (2005)[33] Europe Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	208	Simvastatin 10-20	210	6	123	0/0	unclear	5	no
Ballantyne (2007)[36] Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160	0/0	unclear	1	no
Chenot (2007)[52] Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	0/0	unclear	1	yes
Farnier (2005)[31] International Pharm. Fund Multicenter	Participants with CAD on low dose simvastatin	Simvastatin 10-20	181	Simvastatin 10-20	191	6	123	0/0	unclear	5	no
Relative probability of participants experiencing rhabdomyolysis (investigator defined) - Lower dose simvastatin in combination versus higher dose simvastatin monotherapy											
Feldman (2004)[10] North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 10-20	360	Simvastatin 40	253	23	169	0/0	unclear	2	no

Included Evidence for Fibrate plus Statin Therapy Compared With Statin Monotherapy

Table 8. Longer-term outcomes (clinical outcomes, serious adverse events and cancer) using fibrate plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Fibrate (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
All-cause Mortality, all trials												
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicentre	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	113	Rosuvastatin 40	53	18	149	1/1 0.46 (0.03, 7.57)	unclear	2	No
Napoli (1997)[55] Europe Single centre	FHC type IIb or FHCL, no vascular disease or DM	Pravastatin 20	Gemfibrozil 1200	14	Pravastatin 20	13	48-92	NR	0/0	unclear	1	No
Wiklund (1993)[56] Europe Pharm. Fund Multicentre	No specific risk reported	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/1 0.31 (0.01, 7.77)	unclear	2	No
Fatal myocardial infarction												

Trial	Population	Combination Statin Dose (mg/day)	Fibrate (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes
Wiklund (1993)[56] Europe Pharm. Fund Multicentre	No specific risk reported	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/1 0.31 (0.01, 7.77)	unclear	2	No
Non-fatal myocardial infarction												
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicentre	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	113	Rosuvastatin 40	53	18	149	1/1 0.46 (0.03, 7.57)	unclear	2	No
Any myocardial infarction												
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes
Acute coronary syndrome												
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes

Trial	Population	Combination Statin Dose (mg/day)	Fibrate (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Serious adverse event(s)												
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes
Grundy (2005)[58] SAFARI North America Multicentre	Combined HC 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	201	12	163	12/5 1.2 (0.42,3.46)	yes	2	No

Table 9. Surrogate outcome – Achieving ATP-III target LDL-c using fibrate plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Fibrate Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Athyros (2002)[59]	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	39/32 9.75 (1.16, 82.11)	unclear	1	yes
Durrington (2004)[1]	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	110	Rosuvastatin 40	50	18	149	83/43 0.50 (0.20, 1.24)	unclear	2	no

Table 10. Surrogate outcome, LDL-c using fibrate plus statin therapy compared with statin monotherapy

Low density lipoprotein cholesterol												
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Fibrate (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline												
Athyros (2005)[60] Europe	Participants with MetS (NCEP ATP III), without overt DM or CVD	Atorvastatin 20	Fenofibrate 200	100	Atorvastatin 20	100	54	151	-3.87 (-8.73, 0.99)	yes	2	Yes
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	-15.00 (-27.76, -2.24)	unclear	3	Yes
Athyros (2002)[59] Europe	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	-8.00 (-10.86, -5.14)	unclear	1	Yes
Muhlestein (2006)[61] DIACOR study North America Pharm. Fund Single center	Participants with mixed dylipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	0.00 (-8.55, 8.55)	unclear	2	Yes
Shah (2007_1)[62] Asia Single center	Participants with acute coronary syndrome who underwent PTCA procedure, regardless of DM	Atorvastatin 10	Fenofibrate 200	21	Atorvastatin 20	25	12	95	4.26 (-12.19, 20.71)	unclear	1	No
Shah (2007_2)[62] Asia Single center		Simvastatin 20	Fenofibrate 200	22	Simvastatin 40	23	12	95	0.00 (-15.38, 15.38)	unclear	1	No
Wiklund (1993)[56] Europe Pharm. Fund Multicenter	No particular risk described	Pravastatin 40	Gemfibrozil 1200	63	Pravastatin 40	63	12	228	-10.45 (-21.73, 0.83)	unclear	2	No
Smit (1995) [63]	Participants with combined HC	Fluvastatin 40	Gemfibrozil 1200	7	Fluvastatin 40	7	6	211	19.35 (-7.85, 46.55)	Unclear	2	Yes

Combination – monotherapy: difference in mean percentage change from baseline												
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 10	Fenofibrate 67	53	Rosuvastatin 40	51	18	149	4.50 (-4.10, 13.1)	unclear	2	No
Muhlestein (2006)[61] DIACOR study North America Pharm. Fund Single center	Participants with mixed dylipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	5.00 (-1.47, 11.5)	unclear	2	Yes
Grundy (2005)[58] SAFARI North America Multicenter	Combined HC 71% with MetS	Simvastatin 20	Fenofibrate 160	399	Simvastatin 20	201	12	163	-5.40 (-8.39, -2.4)	yes	2	No

Table 11. Surrogate outcome – HDL-c using fibrate plus statin therapy compared with statin monotherapy

High density lipoprotein cholesterol												
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Fibrate (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline												
Athyros (2005)[60] Europe	Participants with MetS (NCEP ATP III), without overt DM or CVD	Atorvastatin 20	Fenofibrate 200	100	Atorvastatin 20	100	54	151	7.74 (3.95, 11.53)	yes	2	Yes
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	7.00 (4.09, 9.91)	unclear	3	Yes
Athyros (2002)[59] Europe	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	5.30 (3.37, 7.23)	unclear	1	Yes
Muhlestein (2006)[61] DIACOR study North America Pharm. Fund Single center	Participants with mixed dylipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	0.70 (-1.93, 3.33)	unclear	2	Yes
Shah (2007_1)[62] Asia Single center	Participants with acute coronary syndrome who underwent PTCA procedure, regardless of DM	Atorvastatin 10	Fenofibrate 200	21	Atorvastatin 20	25	12	95	5.41 (0.22, 10.60)	unclear	1	No
Shah (2007_2)[62] Asia Single center		Simvastatin 20	Fenofibrate 200	22	Simvastatin 40	23	12	95	0.00 (-7.58, 7.58)	unclear	1	No
Wiklund (1993)[56] Europe Pharm. Fund Multicenter	No particular risk described	Pravastatin 40	Gemfibrozil 1200	63	Pravastatin 40	63	12	228	5.42 (0.56, 10.28)	unclear	2	No

Smit (1995) [63]	Participants with combined HC	Fluvastatin 40	Gemfibrozil 1200	7	Fluvastatin 40	7	6	211	7.74 (3.69, 11.79)	Unclear	2	Yes
Combination – monotherapy: difference in mean percentage change from baseline												
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	113	Rosuvastatin 40	51	18	149	4.81 (-0.56, 10.18)	unclear	2	No
Muhlestein (2006)[61] DIACOR study North America Pharm. Fund Single center	Participants with mixed dylipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	5.60 (-0.19, 11.39)	unclear	2	Yes
Grundy (2005)[58] SAFARI North America Multicenter	Combined HC 71% with MetS	Simvastatin 20	Fenofibrate 160	399	Simvastatin 20	201	12	163	8.80 (5.96, 11.64)	yes	2	No

Table 12. Surrogate outcome – TC:HDL-c ratio using fibrate plus statin therapy compared with statin monotherapy

Total cholesterol : High density lipoprotein cholesterol												
Trial	**Population**	**Combination Statin Dose (mg/day)**	**Fibrate (mg/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline												
Shah (2007_1)[62] Asia Single center	Participants with acute coronary syndrome who underwent PTCA procedure, regardless of DM	Atorvastatin 10	Fenofibrate 200	21	Atorvastatin 20	25	12	95	-0.29 (-0.87, 0.29)	unclear	1	No
Shah (2007_2)[62] Asia Single center		Simvastatin 20	Fenofibrate 200	22	Simvastatin 40	23	12	95	0.00 (-1.04, 1.04)	unclear	1	No
Wiklund (1993)[56] Europe Pharm. Fund Multicenter	No particular risk described	Pravastatin 40	Gemfibrozil 1200	63	Pravastatin 40	63	12	228	-8.90 (-13.4, -4.36)	unclear	2	No
Combination – monotherapy: difference in mean percentage change from baseline												
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 10	Fenofibrate 67	5 **Total cholesterol :** 3	Rosuvastatin 40	51	18	149	-2.70 (-10.46, 5.06)	unclear	2	No

Table 13. Adverse events and adherence to treatment using fibrate plus statin compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Fibrates Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Relative probability of participants experiencing an adverse event												
Derosa (2004)[57] Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	3/2 1.43 (0.22, 9.44)	unclear	3	yes
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	115	Rosuvastatin 40	53	18	149	24/14 0.73 (0.34, 1.57)	unclear	2	no
Wiklund (1993)[56] Europe Pharm. Fund Multicenter	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	31/16 2.42 (1.18, 4.99)	unclear	2	no
Relative probability of participants withdrawing from treatment due to an adverse event												
Athyros (2001)[21] Europe Single centre	Participants with familial combined HC	Simvastatin 20	Gemfibrozil 1200	136	Atorvastatin 20	134	52		7/1 7.22 (0.88, 59.48)	unclear	3	no
Athyros (2002)[59] Europe	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	0/0	unclear	1	yes

Trial	Population	Combination Statin Dose (mg/day)	Fibrates Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Durrington (2004)[1] 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	115	Rosuvastatin 40	53	18	149	2/3 0.29 (0.05, 1.82)	unclear	2	no
Grundy (2005)[58] SAFARI North America Multicenter	Combined HC, 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	13/5 1.31 (0.46, 3.74)	yes	2	no
Wiklund (1993)[56] Europe Pharm. Fund Multicenter	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	8/2 4.12 (0.84, 20.11)	unclear	2	no
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												
Athyros (2005)[60]	Participants with MetS (NCEP ATP III), without overt DM or CVD	Atorvastatin 20	Fenofibrate 200	100	Atorvastatin 20	100	54	151	0/1 0.33 (0.01, 8.20)	yes	2	yes
Athyros (2001)[21] Europe Single centre	Participants with familial combined HC	Mixed 20	Gemfibrozil 1200	262	Atorvastatin 20	131	52		4/0 4.58 (0.24, 85.68)	unclear	3	no
Athyros (2002)[59] Europe	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	0/0	unclear	1	yes

Trial	Population	Combination Statin Dose (mg/day)	Fibrates Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Durrington (2004)[1]	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	115	Rosuvastatin 40	53	18	149	6/0 6.35 (0.35, 114.85)	unclear	2	no
Relative probability of participants experiencing myalgia												
Athyros (2001)[21]	Participants with familial combined HC	Mixed 20	Gemfibrozil 1200	262	Atorvastatin 20	131	52		2/0 2.52 (0.12, 52.95)	unclear	3	no
Napoli (1997)[55]	Participants with familial combined HC (type IIb)	Pravastatin 20	Gemfibrozil 1200	14	Pravastatin 20	13	52-104		1/1 0.92 (0.05, 16.46)	unclear	1	no
Durrington (2004)[1]	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	115	Rosuvastatin 40	53	18	149	3/1 1.39 (0.14, 13.71)	unclear	2	no
Grundy (2005)[58]	Combined HC 71% with MetSyn	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	8/5 0.80 (0.26, 2.47)	yes	2	no
Wiklund (1993)[56]	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	7/1 7.21 (0.86, 60.14)	unclear	2	no
Shah (2007_1)[62]	Participants with acute coronary syndrome who underwent PTCA procedure, regardless of DM	Atorvastatin 10	Fenofibrate 200	25	Atorvastatin 20	25	12	95	0/0	unclear	1	no
Shah (2007_2)[62]		Simvastatin 20	Fenofibrate 200	25	Simvastatin 40	25	12	95	0/2 0.18 (0.01, 4.04)	unclear	1	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal												

Trial	Population	Combination Statin Dose (mg/day)	Fibrates Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Athyros (2002)[59]	Participants with combined HC, HbA1c <8.5%, T2DM and without CAD	Atorvastatin 20	Fenofibrate 200	40	Atorvastatin 20	40	24	162	0/0	unclear	1	yes
Durrington (2004)[1]	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 67	115	Rosuvastatin 40	53	18	149	0/0	unclear	2	no
Grundy (2005)[58]	Combined HC, 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	1/0 1.51 (0.06, 37.22)	yes	2	no
Muhlestein (2006)[61]	Participants with mixed dyslipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	0/0	unclear	2	yes
Wiklund (1993)[56]	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/0	unclear	2	no
Relative probability of participants experiencing rhabdomyolysis (investigator defined)												
Grundy (2005)[58]	Combined HC, 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	0/0	yes	2	no
Wiklund (1993)[56]	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/0	unclear	2	no
Muhlestein (2006)[61]	Participants with mixed dyslipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	0/0	unclear	2	yes

Included Evidence for Niacin plus Statin Therapy Compared With Statin Monotherapy

Table 14. Longer-term outcomes (clinical outcomes, serious adverse events and cancer) using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
All-cause mortality												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext Rls	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	yes	5	No
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10	Ext Rls	100	Lovastatin 40	33	20	198	0/0	yes	4	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Stein (1996)[65] North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprolein cholesteroL	Simvastatin 10	Imm Rls	60	Simvastatin 10	60	17	176	0/0	unclear	2	No
All-cause mortality – Adequate Allocation Concealment												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext Rls	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	yes	5	No
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10	Ext Rls	100	Lovastatin 40	33	20	198	0/0	yes	4	No
All-cause mortality – patients with vascular disease												

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Vascular death												
Hunninghake (2003)[6] North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 40	Ext Rls	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	unclear	4	Yes
Kuvin (2006)[66] North America Pharm. Fund Single center	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 100 mg/dL	Mixed	Ext Rls	27	Mixed	27	12	79	0/0	unclear	1	No
Vascular death – patients with vascular disease												
Kuvin (2006)[66] North America Pharm. Fund Single center	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 100 mg/dL	Mixed	Ext Rls	27	Mixed	27	12	79	0/0	unclear	1	No
Fatal myocardial infarction												

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext Rls	114	Lovastatin 40	61	28	189	1/0 1.63 (0.07, 40.51)	yes	5	No
Kuvin (2006)[66] North America Pharm. Fund Single center	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 100 mg/dL	Mixed	Ext Rls	27	Mixed	27	12	79	0/0	unclear	1	No
Any stroke												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	0/1 0.30 (0.01, 7.47)	yes	5	No
Acute coronary syndrome												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	2/2 0.91 (0.12, 6.62)	yes	5	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Percutaneous coronary intervention												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	4/1 3.78 (0.41, 34.68)	yes	5	No
Serious adverse events												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ext Rls	114	Lovastatin 40	61	28	189	5/2 1.35 (0.25, 7.19)	yes	5	No
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ext Rls	100	Lovastatin 40	33	20	198	5/1 1.68 (0.19, 14.96)	yes	4	No
Stein (1996)[65] North America Pharm. Fund Multicentre	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprolein cholesteroL	Simvastatin 10	Imm Rls	60	Simvastatin 10	60	17	176	1/0 3.05 (0.12, 76.39)	unclear	2	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Cancer												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ext Rls	114	Lovastatin 40	61	28	189	0/2 0.10 (0.00, 2.2)	yes	5	No

Table 15. Surrogate outcome – Achieving ATP-III target LDL-c using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Relative probability of attaining ATPIII LDL-c target												
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 40	Ext Rls 2000	53	Simvastatin 40	57	16	192	40/38 1.54 (0.67, 3.54)	unclear	1	no
Bays (2003_2)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 40	Ext Rls 2000	52	Atorvastatin 40	60	16	192	38/50 0.54 (0.22, 1.4)	unclear	1	no
Relative probability of attaining ATPIII LDL-c target - Participants with vascular disease												
Bays (2003)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels and vascular disease	Lovastatin 40	Ext Rls 2000	32	Mixed 40	34	16	192	21/19 1.51 (0.56, 4.08)	unclear	1	no

Table 16. Surrogate outcome – LDL-c using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Difference in mean LDL-c - change from baseline (mg/dL)												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	-1.00 (-8.32,6.32)	yes	5	No
McKenney (2007_2)[7] COMPELL study North America Pharm. Fund Multicenter		Atorvastatin 40	Ext Rls	60	Rosuvastatin 40	73	12	197	-9.00 (-13.84,-4.16)	unclear	2	No
O'Keefe (1995)[67] North America Single centre	Adults with total cholesterol levels >180 mg/dL, HDL levels <40 mg/dL, and triglyceride levels >150 mg/dL	Pravastatin 20	Imm Rls	21	Pravastatin 20	18	18	134	-22.00 (-38.94,-5.06)	unclear	1	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Gardner (1996)[68] North America Pharm. Fund Single centre	Participants with LDL-c >150 mg/dL	Lovastatin 20	Slow Rls	14	Lovastatin 40	14	6	203	-11.00 (-37.71,15.71)	unclear	3	No
Difference in mean LDL-c - change from baseline (mg/dL) - all with established vascular disease												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	22	Mixed >20	19	52	89	7.00 (4.02,9.98)	yes	5	No
Difference in mean percentage change from baseline - Lower dose statin in combination versus higher dose monotherapy												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext Rls	42	Lovastatin 40	53	28	189	-9.70 (-14.64, -4.76)	yes	5	No
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV	Rosuvastatin 10-40	Ext Rls	149	Rosuvastatin 40	46	24	145	9.00 (-2.45, 20.45)	unclear	2	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
	hyperlipidemia)											
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 40	Ext Rls	32	Lovastatin 40	33	20	198	-22.20 (-32.09, -12.31)	unclear	2	No
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 40	Ext Rls	23	Lovastatin 40	29	20	198	-22.20 (-31.64, -12.76)	yes	4	No
McKenney (2007_2)[7] COMPELL study North America Pharm. Fund Multicenter		Atorvastatin 40	Ext Rls	60	Rosuvastatin 40	73	12	197	-3.00 (-8.30, 2.30)	unclear	2	No
Vacek (1995)[69] North America Pharm. Fund Single centre	Cross-over trial; Participants with LDL >180	Lovastatin 20	Slow release	25	Lovastatin 20	25	12	204	-25.00 (-40.60, -9.40)	unclear	2	No
Difference in mean percentage change from baseline - Rosuvastatin Lower dose statin in combination versus higher dose monotherapy												

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ext Rls	36	Rosuvastatin 40	31	24	145	12.00 (2.36, 21.64)	unclear	2	No

Table 17. Surrogate outcome – HDL-c using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Comb o N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Difference in mean HDL-c - change from baseline (mg/dL)												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	-1.00 (-8.32, 6.32)	yes	5	no
O'Keefe (1995)[67] North America Single centre	Adults with total cholesterol levels >180 mg/dL, HDL levels <40 mg/dL, and triglyceride levels >150 mg/dL	Pravastatin 20	Imm Rls	21	Pravastatin 20	18	18	134	8.00 (2.05,13.95)	unclear	1	no

Gardner (1996)[68] North America Pharm. Fund Single centre	Participants with LDL-c >150 mg/dL	Lovastatin 20	Slow Rls	14	Lovastatin 40	14	6	203	5.00 (-6.05,16.05)	unclear	3	no
Difference in mean HDL-c - change from baseline (mg/dL) - Participants with vascular disease												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL, and diabetics	Mixed >20	Ext Rls	78	Mixed >20	71	52	89	7.00 (2.78,11.22)	yes	5	no
Difference in mean percentage change from baseline												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext Rls	42	Lovastatin 40	53	28	189	24.00 (17.50, 30.50)	yes	5	no
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 40	Ext Rls	71	Rosuvastatin 40	46	24	145	6.00 (-0.79, 12.79)	unclear	2	no

Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ext RIs	100	Lovastatin 40	33	20	198	24.00 (14.86, 33.14)	unclear	2	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ext RIs	77	Lovastatin 40	29	20	198	24.00 (15.36, 32.64)	yes	4	no
McKenney (2007_2)[7] COMPELL study North America Pharm. Fund Multicenter		Mixed 20-40	Ext RIs	125	Rosuvastatin 40	73	12	197	16.00 (11.43, 20.57)	unclear	2	no
Difference in mean percentage change from baseline - Rosuvastatin Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ext RIs	71	Rosuvastatin 40	46	24	145	12.00 (2.26, 21.74)	unclear	2	no

Table 18. Surrogate outcome – TC:HDL-c ratio using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Difference in changes in mean TC - HDL-c ratio												
O'Keefe (1995)[67] North America Single centre	Adults with total cholesterol levels >180 mg/dL, HDL levels <40 mg/dL, and triglyceride levels >150 mg/dL	Pravastatin 20	Imm Rls 3000	21	Pravastatin 20	18	18	134	-1.58 (-2.18, -0.98)	unclear	1	no
Difference in mean percentage change in TC-HDL-c ratio												
McKenney (2007_2)[7]		Mixed 20-40	Ext Rls 2000	125	Rosuvastatin 40	73	12	197	-6.00 (-9.60, -2.40)	unclear	2	no

Table 19. Carotid intima-media thickness (CIMT) using niacin plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ext Rls 1000	71	Mixed >20	78	52	89	-0.03 (-0.06, 0.003)	yes	5	no

Table 20. Adverse events and adherence to treatment using niacin plus statin compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Relative probability of participants adhering to treatment												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ex Rls 1000	87	Mixed >20	80	52	89	78/71 1.10 (0.41, 2.92)	yes	5	no
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex Rls 2000	152	Rosuvastatin 40	46	24	145	71/31 0.42 (0.21, 0.85)	unclear	2	no
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex Rel 2500	100	Lovastatin 40	33	20	198	96/32 0.75 (0.08, 6.96)	unclear	2	no
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	78	Simvastatin 10-40	76	16	192	73/73 0.60 (0.14, 2.60)	unclear	1	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Bays (2003_2)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	79	Atorvastatin 10-40	82	16	192	77/79 1.46 (0.24, 8.99)	unclear	1	no
McKenney (2007_2)[7] COMPELL study North America Pharm. Fund Multicenter		Mixed 20-40	Ex Rls 2000	125	Rosuvastatin 40	73	12	197	109/61 1.34 (0.60, 3.0)	unclear	2	no
Relative probability of participants adhering to treatment – Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex Rls 2000	80	Rosuvastatin 40	46	24	145	36/31 0.42 (0.19, 0.84)	unclear	2	no
Relative probability of participants experiencing an adverse event												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	110/49 6.73 (2.07, 21.93)	yes	5	no
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex Rls 2000	149	Rosuvastatin 40	46	24	145	126/34 1.93 (0.87, 4.28)	unclear	2	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	53/17 1.06 (0.48, 2.33)	unclear	2	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	88/24 2.75 (1.04, 7.29)	yes	4	no
Relative probability of participants experiencing an adverse event – Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex Rls 2000	78	Rosuvastatin 40	46	24	145	66/34 1.94 (0.79, 4.8)	unclear	2	no
Relative probability of participants withdrawing from treatment due to an adverse event												
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ex Rls 1000	87	Mixed >20	80	52	89	2/6 0.29 (0.06, 1.48)	yes	5	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Hunninghake (2003)[6] North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	22/6 2.19 (0.84, 5.74)	unclear	4	yes
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	22/6 2.19 (0.84, 5.74)	yes	5	no
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	18/3 2.20 (0.60, 7.99)	unclear	2	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	18/3 2.20 (0.60, 7.99)	yes	4	no
O'Keefe (1995)[67] North America Single centre	Adults with total cholesterol levels >180 mg/dL, HDL levels <40 mg/dL, and triglyceride levels >150 mg/dL	Pravastatin 20	Imm Rls 3000	27	Pravastatin 20	19	18	134	6/0 11.79 (0.62, 223.26)	unclear	1	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Stein (1996)[65] North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprolein cholesteroL	Simvastatin 10	Imm Rls 1500	60	Simvastatin 10	60	17	176	9/3 3.35 (0.86, 13.07)	unclear	2	no
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	78	Simvastatin 10-40	76	16	192	15/2 8.81 (1.94, 40.01)	unclear	1	no
Bays (2003_2)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	79	Atorvastatin 10-40	82	16	192	13/8 1.82 (0.71, 4.67)	unclear	1	no
Relative probability of participants experiencing Rhabdomyolysis												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	0/0	yes	5	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	HC type IIa or IIb statin naive	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	0/0	yes	4	no
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Taylor (2004)[64] ARBITER North America Single centre	Participants with coronary artery disease, and currently treated with a statin drug, with LDL-C < 130 mg/dL and HDL-C < 45 mg/dL	Mixed >20	Ex Rls 1000	78	Mixed >20	71	52	89	0/0	yes	5	no
Hunninghake (2003)[6] North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	unclear	4	yes
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex Rls 2000	152	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	4/0 3.12 (0.16, 59.58)	unclear	2	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	HC type IIa or IIb statin naive	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	4/0 3.12 (0.16, 59.58)	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Stein (1996)[65] North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprolein cholesteroL	Simvastatin 10	Imm Rls 1500	60	Simvastatin 10	60	17	176	0/1 0.33 (0.01, 8.21)	unclear	2	no
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no
Bays (2003_2)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	79	Atorvastatin 10-40	82	16	192	0/0	unclear	1	no
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis – Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex Rls 2000	80	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Relative probability of participants experiencing myalgia												

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Hunninghake (2003)[6] North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	5/4 0.65 (0.17, 2.53)	unclear	4	yes
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex Rls 2000	114	Lovastatin 40	61	28	189	5/7 0.35 (0.11, 1.17)	yes	5	no
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex Rls 2000	152	Rosuvastatin 40	46	24	145	1/3 0.09 (0.01, 0.94)	unclear	2	no
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no
Bays (2003_2)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	79	Atorvastatin 10-40	82	16	192	0/1 0.34 (0.01, 8.51)	unclear	1	no
Relative probability of participants experiencing myalgia – Rosuvastatin plus lower dose statin in combination versus higher dose monotherapy												

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex Rls 2000	80	Rosuvastatin 40	46	24	145	1/3 0.18 (0.02, 1.80)	unclear	2	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal												
Kos Pharm (MA-06)[5] MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ex Rls 2000	114	Lovastatin 40	61	28	189	0/0	yes	5	no
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex Rls 2000	152	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Insull (2004)[11] North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex Rls 2500	100	Lovastatin 40	33	20	198	0/0	unclear	2	no
Kos Pharm (MA-14)[4] MA-14 North America Multicenter	HC type IIa or IIb statin naive	Lovastatin 10-40	Ex Rls	100	Lovastatin 40	33	20	198	0/0	yes	4	no
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Bays (2003_1)[8] ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex Rls 2000	79	Atorvastatin 10-40	82	16	192	0/0	unclear	1	no
McKenney (2007_2)[7] COMPELL study North America Pharm. Fund Multicenter		Mixed 20-40	Ex Rls 2000	125	Rosuvastatin 40	73	12	197	0/0	unclear	2	no
Stein (1996)[65] North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprolein cholesteroL	Simvastatin 10	Imm Rls 1500	60	Simvastatin 10	60	17	176	0/0	unclear	2	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal – Rosuvastatin plus lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003)[12] 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex Rls 2000	80	Rosuvastatin 40	46	24	145	0/0	unclear	2	no

Included Evidence for Bile Acid Sequestrant plus Statin Therapy Compared With Statin Monotherapy

Table 21. Longer-term outcomes (clinical outcomes, serious adverse events and cancer) using BAS plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	BAS (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
All-cause Mortality, all trials												
Sprecher (1994_1)[16] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10	C-amine 8-16	36	Fluvastatin 10	39	24	209	0/1 0.35 (0.01, 8.9)	unclear	3	No
Sprecher (1994_2)[16] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 20	C-amine 8-16	37	Fluvastatin 20	38	24	209	0/0	unclear	3	No
Knapp (2001_1)[15] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10	C-lam 3.8	35	Simvastatin 10	36	6	187	0/0	yes	5	No

Trial	Population	Combination Statin Dose (mg/day)	BAS (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Knapp (2001_2)[15] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 20	C-lam 2.3	37	Simvastatin 20	39	6	187	1/0 3.25 (0.13, 82.2)	yes	5	No
Davidson (2001) [2] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8	50	Lovastatin 10	26	4	170	0/0	unclear	4	No
Fatal myocardial infarction												
Sprecher (1994_1)[16] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10	C-amine 8-16	36	Fluvastatin 10	39	24	209	0/1 0.35 (0.01, 8.91)	unclear	3	No
Sprecher (1994_2)[16] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 20	C-amine 8-16	37	Fluvastatin 20	38	24	209	0/0	unclear	3	No
Serious adverse event(s)												

Trial	Population	Combination Statin Dose (mg/day)	BAS (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	1/5 0.40 (0.05, 3.6)	unclear	1	No
Knapp (2001)[15] North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10-20	C-lam 2.3-3.8	68	Simvastatin 10-20	74	6	187	0/1 0.36 (0.01, 8.9)	yes	5	No

Table 22. Surrogate outcome – Achieving ATP-III target LDL-c using BAS plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ito (1996)[71] North America Pharm. fund	Participants with moderate HC, history of CAD, all with prior statin use	Pravastatin 20	C-amine 10	28	Pravastatin 40	31	12	181	13/5 4.51 (1.34, 15.1)	unclear	1	no

Table 23. Surrogate outcome, LDL-c using BAS plus statin therapy compared with statin monotherapy

Low density lipoprotein cholesterol												
Trial	**Population**	**Combination Statin Dose (mg/day)**	**BAS (g/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline												
Eriksson (1998)[22] PaCt trial Europe Pharm. Fund Multicenter	Participants with 1º HC, heterogeneous CHD risk estimates	Pravastatin 20	C-amine 8-16	270	Pravastatin 20	406	96	212	-16.64 (-21.89, -11.39)	yes	3	no
PMSG II (1993)[17] Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥160mg/dL), excluding those with hypersensitivity to C-amine	Pravastatin 40	C-amine 24	61	Pravastatin 40	57	16-24	235	-31.00 (-45.48, -16.52)	unclear	3	no
Ismail (1990)[72] North America Pharm. fund	Participants with primary HC	Pravastatin 40	C-amine 24	9	Pravastatin 40-80	17	8	269	-32.00 (-59.20, -4.80)	unclear	2	yes
Knapp (2001_1)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10	C-lam 3.8	34	Simvastatin 10	35	6	187	-32.00 (-45.52, -18.48)	yes	5	no
Knapp (2001_2)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 20	C-lam 2.3	37	Simvastatin 20	39	6	187	-19.00 (-29.60, -8.40)	yes	5	no
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	18	Atorvastatin 10	18	4	184	-21.00 (-36.31, -5.69)	unclear	4	yes

Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	-18.64 (-29.27, -8.01)	unclear	4	no
Isaacsohn (1997)[19] North America Single centre	Heterogeneous familial and polygenic HC (LDL-c ≥220 mg/dL	Mixed	C-pol 20	21	Atorvastatin 80	16	32	291	15.48 (-11.14, 42.10)	unclear	1	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	20	Atorvastatin 10	41	11	211	-19.35 (-49.63, 10.93)	unclear	1	no
Schrott (1995)[74] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 20	C-pol 5-10	23	Lovastatin 40	24	4-12	191	-23.00 (-33.17, -12.83)	unclear	2	no
Combination – monotherapy: difference in mean percentage change from baseline												
O'Brien (1990)[75] Pharm. Fund Multicenter	Participants with severe HC (LDL-c ≥215 mg/dL) or moderate HC + CAD	Simvastatin 40	C-amine 24	35	Simvastatin 40	15	40	298	-10.10 (-19.92, -0.3)	unclear	1	no
Isaacsohn (1997)[19] North America Single centre	Heterogeneous familial and polygenic HC (LDL-c ≥220 mg/dL)	Mixed	C-pol 20	21	Atorvastatin 80	16	32	291	5.43 (-1.84, 12.7)	unclear	1	no
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	11.00 (6.45, 15.6)	unclear	1	no
Sprecher (1994_1)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10	C-amine 8-16	35	Fluvastatin 10	38	24	209	-10.50 (-16.94, -4.1)	unclear	3	no
Sprecher (1994_2)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 20	C-amine 8-16	35	Fluvastatin 20	38	24	209	-11.90 (-18.06, -5.7)	unclear	3	no

PMSG II (1993)[17] Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥160mg/dL), excluding those with hypersensitivity to C-amine	Pravastatin 40	C-amine 24	61	Pravastatin 40	57	16-24	235	-13.70 (-18.76, -8.6)	unclear	3	no
Simons (1992)[18] Europe Pharm. Fund Single centre	Participants with primary HC, already in use of statins	Simvastatin 40	C-pol 5-10	39	Simvastatin 40	22	12	290	-11.34 (-17.82, -4.9)	yes	4	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	20	Atorvastatin 10	41	11	211	-10.00 (-16.95, -3.0)	unclear	1	no
Ballantyne (2004_a)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	75	Rosuvastatin 80	69	6	259	-4.10 (-9.10, 0.9)	yes	2	no
Knapp (2001_1)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10	C-lam 3.8	34	Simvastatin 10	35	6	187	-16.00 (-22.50, -9.5)	yes	5	no
Knapp (2001_2)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 20	C-lam 2.3	37	Simvastatin 20	39	6	187	-8.00 (-13.40, -2.6)	yes	5	no
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	18	Atorvastatin 10	18	4	184	-10.00 (-17.07, -2.9)	unclear	4	yes
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	-11.80 (-15.62, -8.0)	unclear	4	no

Table 24. Surrogate outcome – HDL-c using BAS plus statin therapy compared with statin monotherapy

Low density lipoprotein cholesterol												
Trial	**Population**	**Combination Statin Dose (mg/day)**	**BAS (g/day)**	**Combo N**	**Monotherapy Statin Dose (mg/day)**	**Mono N**	**Follow-up (wk)**	**Mean Baseline LDL-c (mg/dL)**	**Combo-mono: mean difference (95% CI)**	**AAC**	**Jadad Score**	**ITTA**
Combination – monotherapy: difference in post-treatment mean or mean change score from baseline												
Eriksson (1998)[22] PaCt trial Europe Pharm. Fund Multicenter	Participants with 1º HC, heterogeneous CHD risk estimates	Pravastatin 20	C-amine 8-16	272	Pravastatin 20-40	827	96	212	-0.97 (-3.03, 1.09)	yes	3	no
PMSG II (1993)[17] Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥160mg/dL), excluding those with hypersensitivity to C-amine	Pravastatin 40	C-amine 24	61	Pravastatin 40	57	16-24	235	-3.00 (-7.16, 1.16)	unclear	3	no
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	1.00 (-1.39, 3.39)	unclear	4	no
Isaacsohn (1997)[19] North America Single centre	Heterogeneous familial and polygenic HC (LDL-c ≥220 mg/dL	Mixed	C-pol 20	21	Atorvastatin 80	16	32	291	6.90 (-0.37, 14.17)	unclear	1	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	40	Atorvastatin 10	41	11	211	0.00 (-7.49, 7.49)	unclear	1	no
Schrott (1995)[74] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 20-40	C-pol 5-10	46	Lovastatin 40	24	4-12	191	0.37 (-6.12, 6.86)	unclear	2	no
Combination – monotherapy: difference in mean percentage change from baseline												

O'Brien (1990)[75] Pharm. Fund Multicenter	Participants with severe HC (LDL-c ≥215 mg/dL) or moderate HC + CAD	Simvastatin 40	C-amine 24	35	Simvastatin 40	15	40	298	-3.10 (-19.49, 13.29)	unclear	1	no
Isaacsohn (1997)[19] North America Single centre	Heterogeneous familial and polygenic HC (LDL-c ≥220 mg/dL)	Mixed	C-pol 20	21	Atorvastatin 80	16	32	291	7.66 (-2.04, 17.4)	unclear	1	no
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	3.00 (-0.39, 6.4)	unclear	1	no
Sprecher (1994_1)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10	C-amine 8-16	35	Fluvastatin 10	38	24	209	-2.60 (-8.47, 3.3)	unclear	3	no
Sprecher (1994_2)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 20	C-amine 8-16	35	Fluvastatin 20	38	24	209	-5.70 (-10.78, -0.6)	unclear	3	no
PMSG II (1993)[17] Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥160mg/dL), excluding those with hypersensitivity to C-amine	Pravastatin 40	C-amine 24	61	Pravastatin 40	119	16-24	235	0.77 (-4.02, 5.6)	unclear	3	no
Simons (1992)[18] Europe Pharm. Fund Single centre	Participants with primary HC, already in use of statins	Simvastatin 40	C-pol 5-10	39	Simvastatin 40	22	12	290	4.50 (-2.50, 11.5)	yes	4	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	40	Atorvastatin 10	41	11	211	1.00 (-6.03, 8.0)	unclear	1	no

Ballantyne (2004_a)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	75	Rosuvastatin 80	69	6	259	-1.00 (-6.68, 4.68)	yes	2	no
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	0.00 (-4.77, 4.8)	unclear	4	no

Table 25. Adverse events and adherence to treatment using BAS plus statin compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Relative probability of participants adhering to treatment												
Eriksson (1998)[22] PaCt trial Europe Pharm. Fund Multicenter	Participants with 1° HC, heterogeneous CHD risk estimates	Pravastatin 20	C-amine 8-16	261	Pravastatin 20-40	812	96	212	227/765 0.41 (0.26, 0.65)	yes	3	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	20	Atorvastatin 10	42	12	211	15/38 0.32 (0.07, 1.34)	unclear	1	no
Ballantyne (2004_a)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	75	Rosuvastatin 80	69	6	259	38/63 0.10 (0.04, 0.25)	yes	2	no
Johansson (1995)[23] Europe Pharm. Fund Multicenter	Participants with moderate to severe HC	Simvastatin 20	C-pol 5-10	57	Simvastatin 40	26	4-12	221	41/23 0.33 (0.09, 1.27)	unclear	2	no
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	19	Atorvastatin 10-80	39	4	184	17/35 0.97 (0.16, 5.84)	unclear	4	yes

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	19	Atorvastatin 80	20	4	184	17/18 0.94 (0.12, 7.5)	unclear	4	yes
Relative probability of participants experiencing an adverse event												
Sprecher (1994_1)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10	C-amine 8-16	36	Fluvastatin 10	39	24	209	31/18 7.23 (2.32, 22.5)	unclear	3	no
Sprecher (1994_2)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 20	C-amine 8-16	37	Fluvastatin 20	38	24	209	30/20 3.86 (1.36, 10.9)	unclear	3	no
Ballantyne (2004)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	76	Rosuvastatin 80	71	6	259	42/25 2.27 (1.17, 4.4)	yes	2	no
Knapp (2001_1)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10	C-lam 3.8	34	Simvastatin 10	35	6	187	21/22 0.95 (0.36, 2.5)	yes	5	no

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Knapp (2001_2)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 20	C-lam 2.3	34	Simvastatin 20	39	6	187	25/23 1.93 (0.72, 5.2)	yes	5	no
Johansson (1995)[23] Europe Pharm. Fund Multicenter	Participants with moderate to severe HC	Simvastatin 20	C-pol 5-10	57	Simvastatin 40	26	4-12	221	31/13 1.19 (0.47, 3.0)	unclear	2	no
Relative probability of participants withdrawing from treatment due to an adverse event												
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	6/1 14.37 (1.67, 123.4)	unclear	1	no
Sprecher (1994)[16] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), not on lipid-lowering medication	Fluvastatin 10-20	C-amine 8-16	73	Fluvastatin 10-20	77	24	209	4/1 4.41 (0.48, 40.4)	unclear	3	no
PMSG II (1993)[17] Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥160mg/dL), excluding those with hypersensitivity to C-amine	Pravastatin 40	C-amine 24	64	Pravastatin 40-80	126	16-24	235	1/2 0.98 (0.09, 11.1)	unclear	3	no
Heinonen (1996)[73] Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-pol 20	20	Atorvastatin 10	42	12	211	0/1 0.67 (0.03, 17.3)	unclear	1	no

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Ballantyne (2004_a)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	76	Rosuvastatin 80	71	6	259	2/0 4.80 (0.23, 101.7)	yes	2	no
Knapp (2001_1)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 10	C-lam 3.8	35	Simvastatin 10	36	6	187	1/1 1.03 (0.06, 17.1)	yes	5	no
Knapp (2001_2)[15] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL), statin naïve	Simvastatin 20	C-lam 2.3	37	Simvastatin 20	39	6	187	3/0 8.01 (0.40, 160.7)	yes	5	no
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8	50	Atorvastatin 10-80	26	4	170	4/0 5.13 (0.27, 99.0)	unclear	4	no
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8	19	Lovastatin 10	39	4	184	1/3 0.67 (0.06, 6.9)	unclear	4	yes
Hunninghake (2001)[14] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	19	Atorvastatin 80	20	4	184	1/1 1.06 (0.06, 18.2)	unclear	4	yes

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	0/0	unclear	1	no
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	0/0	unclear	4	no
Relative probability of participants experiencing myalgia												
Ito (1997)[71] North America Pharm. fund	Participants with moderate HC, history of CAD, all with prior statin use	Pravastatin 20	C-amine 10	28	Pravastatin 40	31	12	181	0/3 0.14 (0.01, 2.9)	unclear	1	no
Simons (1992)[18] Europe Pharm. Fund Single centre	Participants with primary HC, already in use of statins	Simvastatin 40	C-pol 5-10	39	Simvastatin 40	22	12	290	1/1 0.55 (0.03, 9.3)	unclear	4	no
Ballantyne (2004)[76]	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	76	Rosuvastatin 80	71	6	259	1/0 2.84 (0.11, 70.9)	yes	2	no
Davidson (2001)[2] North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	2/3 0.32 (0.05, 2.0)	unclear	4	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal												

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Simons (1998)[70] The Six Cities Study Pharm. fund	Participants with severe HC (LDL-c ≥190 mg/dL)	Simvastatin 40	C-amine 4	44	Atorvastatin 80	92	30	343	0/0	unclear	1	no
Ballantyne (2004)[76] North America Pharm. Fund Multicenter	Participants with severe HC (LDL-c 190-400 mg/dL), all with prior statin use	Rosuvastatin 80	C-amine 16	76	Rosuvastatin 80	71	6	259	0/0	yes	2	no

Included Evidence for Omega-3 Fatty Acid plus Statin Therapy Compared With Statin Monotherapy

Table 26. Longer-term outcomes (clinical outcomes, serious adverse events and cancer) using omega-3 fatty acid plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
All-cause mortality											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	286/265 1.08 (0.91, 1.28)	yes	2	yes
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	0/0	yes	4	no
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	21	Simvastatin 20	20	5	161	0/0	unclear	4	no
All-cause mortality – 24 weeks or more											

Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	286/265 1.08 (0.91, 1.28)	yes	2	yes
All-cause mortality – adequate allocation concealment											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	286/265 1.08 (0.91, 1.28)	yes	2	yes
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	0/0	yes	4	no
All-cause mortality – Asian											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	286/265 1.08 (0.91, 1.28)	yes	2	yes
Fatal Myocardial Infarction											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	11/14 0.78 (0.36, 1.73)	yes	2	yes

Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 20-40	26	24	149	0/1 0.29 (0.01, 7.39)	unclear	3	no
Non-fatal myocardial infarction											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	62/83 0.74 (0.54, 1.04)	yes	2	yes
Any myocardial infarction											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	71/93 0.76 (0.56, 1.04)	yes	2	yes
Hemorrhagic stroke											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	49/39 1.26 (0.82, 1.92)	yes	2	yes
Ischemic stroke											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	115/123 0.93 (0.72, 1.21)	yes	2	yes
Any stroke											

Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	166/162 1.02 (0.82, 1.27)	yes	2	yes
Serious adverse events											
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	4/1 4.44 (0.49, 40.29)	yes	4	no
Cancer											
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	242/218 1.11 (0.92, 1.34)	yes	2	yes

Table 27. Surrogate outcome, LDL-c using omega-3 fatty acid plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Difference in mean change from baseline (regardless of population characteristics)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-42.57 (-72.43, -12.71)	unclear	3	No
Meyer (2007)[81] Australia Single centre	Participants with persisting hypertriglyceridemia despite receiving statins	Mixed statins	26	Mixed statins	14	24	93	-4.45 (-24.07, 15.17)	yes	2	No
Liu (2003)[82] Europe Single centre	Participants with hyperlipidemia and statin naïve	Simvastatin 10	19	Simvastatin 10	18	12	173	4.65 (-18.32, 27.62)	unclear	1	no
Hong (2004)[83] Asia Single centre	Patients with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	-4.60 (-16.32, 7.12)	yes	4	No
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	0.30 (-5.17, 5.77)	yes	4	no
Chan (2002)[84] Australia Pharm. Fund Single centre	Participants were non-diabetic, dyslipidemic men with visceral obesity (BMI >29)	Atorvastatin 40	11	Atorvastatin 40	13	6	152	12.00 (-4.52, 28.52)	unclear	4	No
Nordoy (2001)[85] Europe Single centre	Participants with combined hyperlipidemia and total cholesterol >200 mg/dL.	Atorvastatin 10	22	Atorvastatin 10	20	5	197	5.81 (-4.71, 16.33)	unclear	4	yes

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	21	Simvastatin 20	20	5	161	-5.80 (-29.59, 17.99)	unclear	4	no
Difference in mean change from baseline (High-risk population)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-42.57 (-72.43, -12.71)	unclear	3	No
Hong (2004)[83] Asia Single centre	Patients with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	-4.60 (-16.32, 7.12)	yes	4	No
Difference in mean change from baseline (Participants with vascular disease)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-42.57 (-72.43, -12.71)	unclear	3	No
Difference in mean percentage change from baseline											
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	5.30 (1.45, 9.15)	yes	4	No
Chan (2002)[84] Australia Pharm. Fund Single centre	Participants were non-diabetic, dyslipidemic men with visceral obesity (BMI >29)	Atorvastatin 40	11	Atorvastatin 40	13	6	152	5.1 (-3.04, 13.24)	unclear	4	No

Table 28. Surrogate outcome – HDL-c using omega-3 fatty acid plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow -up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Difference in means - change from baseline HDL-c (mg/dL)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-11.61 (-18.80, -4.42)	unclear	3	No
Meyer (2007)[81] Australia Single centre	Participants with persisting hypertriglyceridemia despite receiving statins	Mixed statins	30	Mixed statins	15	24	93	3.41 (-3.68, 10.50)	yes	2	No
Liu (2003)[82] Europe Single centre	Participants with hyperlipidemia and statin naïve	Simvastatin 10	19	Simvastatin 10	18	12	173	-0.38 (-5.50, 4.74)	unclear	1	no
Hong (2004)[83] Asia Single centre	Patients with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months.	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	1.80 (-5.61, 9.21)	yes	4	No
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	5.10 (2.43, 7.77)	yes	4	no
Chan (2002)[84] Australia Pharm. Fund Single centre	Participants were non-diabetic, dyslipidemic men with visceral obesity (BMI >29)	Atorvastatin 40	11	Atorvastatin 40	13	6	152	8.13 (0.63, 15.63)	unclear	4	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow -up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Davidson (1997)[86] North America Single centre	Participants with combined hyperlipidemia	Simvastatin 10	9	Simvastatin 10	10	6-12		-0.30 (-9.14, 8.54)	unclear	2	No
Nordoy (2001)[85] Europe Single centre	Participants with combined hyperlipidemia and total cholesterol >200 mg/dL.	Atorvastatin 10	22	Atorvastatin 10	20	5	197	4.64 (-1.72, 11.00)	unclear	4	yes
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	21	Simvastatin 20	20	5	161	2.32 (0.33, 4.31)	unclear	4	no
Difference in means - change from baseline HDL-c (mg/dL) (High-risk population)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-11.61 (-18.80, -4.42)	unclear	3	No
Hong (2004)[83] Asia Single centre	Patients with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months.	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	1.80 (-5.61, 9.21)	yes	4	No
Difference in means - change from baseline HDL-c (mg/dL) (Population with vascular disease)											
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	29	Simvastatin 10-40	26	24	149	-11.61 (-18.80, -4.42)	unclear	3	No
Difference in percentage change from baseline HDL-c											

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow -up (wk)	Trial Baseline LDL-c (mg/dL)	Difference (95% CI) [combo-mono]	AAC	Jadad Score	ITTA
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	5.20 (2.95, 7.45)	yes	4	No
Chan (2002)[84] Australia Pharm. Fund Single centre	Participants were non-diabetic, dyslipidemic men with visceral obesity (BMI >29)	Atorvastatin 40	11	Atorvastatin 40	13	6	152	9.50 (-0.42, 19.42)	unclear	4	No
Davidson (1997)[86] North America Single centre	Participants with combined hyperlipidemia	Simvastatin 10	9	Simvastatin 10	10	6-12		3.20 (-6.76, 13.16)	unclear	2	No

Table 29. Surrogate outcome – TC:HDL-c ratio using omega-3 fatty acid plus statin therapy compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow-up (wk)	Trial Baseline LDL-c (mg/dL)	Combo/mono: number of participants with events Odds ratio (95% CI)	AAC	Jadad Score	ITTA
Difference in changes in mean TC - HDL-c ratio											
Hong (2004)[83] Asia Single centre	Participants with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months.	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	-0.41 (-1.43, 0.61)	yes	4	No
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	-0.60 (-0.83, -0.37)	yes	4	no
Davidson (1997)[86] North America Single centre	Participants with combined hyperlipidemia	Simvastatin 10	9	Simvastatin 10	10	6-12		0.29 (-0.70, 1.28)	unclear	2	no
Difference in changes in mean TC - HDL-c ratio (High-risk)											
Hong (2004)[83] Asia Single centre	Participants with CHD and CHD risk equivalents with mixed dyslipidemia and untreated for 6 months.	Simvastatin 10-20	20	Simvastatin 10-20	20	8	90	-0.41 (-1.43, 0.61)	yes	4	No
Difference in mean percentage change in TC-HDL-c ratio											
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	122	Simvastatin 40	132	8	91	-8.10 (-10.69, -5.51)	yes	4	No
Davidson (1997)[86] North America Single centre	Participants with combined hyperlipidemia	Simvastatin 10	9	Simvastatin 10	10	6-12		-3.10 (-12.84, 6.64)	unclear	2	No

Table 30. Adverse events and adherence to treatment using omega-3 fatty acid plus statin compared with statin monotherapy

Trial	Population	Combination Statin Dose (mg/day)	Omega-3 FA Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Relative probability of participants experiencing an adverse event												
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	1800	9326	Mixed 5-20	9319	240	182	2334/2004 1.22 (1.14, 1.30)	yes	2	yes
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	4000	29	Simvastatin 10-40	26	24	149	22/17 1.66 (0.51, 5.38)	unclear	3	no
Liu (2003)[82] Europe Single centre	Participants with hyperlipidemia and statin naïve	Simvastatin 10	9200	19	Simvastatin 10	18	12	173	0/0	unclear	1	no
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	4000	122	Simvastatin 40	132	8	91	51/63 0.79 (0.48, 1.29)	yes	4	no
Nordoy (2001)[85] Europe Single centre	Participants with combined hyperlipidemia and total cholesterol >200 mg/dL.	Atorvastatin 10	2000	22	Atorvastatin 10	20	5	197	0/0	unclear	4	yes

Trial	Population	Combination Statin Dose (mg/day)	Omega-3 FA Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	4000	21	Simvastatin 20	20	5	161	0/0	unclear	4	no
Relative probability of participants experiencing an adverse event - Trials 24 weeks or longer												
Yokoyama (2007)[77] JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	1800	9326	Mixed 5-20	9319	240	182	2334/2004 1.22 (1.14, 1.30)	yes	2	yes
Durrington (2001)[80] Europe Pharm. Fund Single centre	Participants with CHD and persisting hypertriglyceridemia, despite receiving simvastatin.	Simvastatin 20-40	4000	29	Simvastatin 10-40	26	24	149	22/17 1.66 (0.51, 5.38)	unclear	3	no
Relative probability of participants withdrawing from treatment due to an adverse event												
Davidson (2007) [78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	4000	122	Simvastatin 40	133	8	91	3/3 1.09 (0.22, 5.52)	yes	4	no
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	4000	122	Simvastatin 40	132	8	91	0/0	yes	4	no

Trial	Population	Combination Statin Dose (mg/day)	Omega-3 FA Max Dose (mg/day)	Combo N	Monotherapy Statin Dose (mg/day)	Mono N	Follow up (wk)	Trial Baseline LDL-c (mg/dL)	Number of Events Odds Ratio (95% CI) [combo/mono]	AAC	Jadad Score	ITTA
Nordoy (2001)[85] Europe Single centre	Participants with combined hyperlipidemia and total cholesterol >200 mg/dL.	Atorvastatin 10	2000	22	Atorvastatin 10	20	5	197	0/0	unclear	4	yes
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	4000	21	Simvastatin 20	20	5	161	0/0	unclear	4	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal												
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	4000	122	Simvastatin 40	132	8	91	0/0	yes	4	no
Nordoy (2001)[85] Europe Single centre	Participants with combined hyperlipidemia and total cholesterol >200 mg/dL.	Atorvastatin 10	2000	22	Atorvastatin 10	20	5	197	0/0	unclear	4	yes
Nordoy (1998)[79] Europe Pharm. Fund Single centre	Participants with combined hyperlipidemia and statin naïve	Simvastatin 20	4000	21	Simvastatin 20	20	5	161	0/0	unclear	4	no
Relative probability of participants experiencing rhabdomyolysis (investigator defined)												
Davidson (2007)[78] COMBOS trial North America Pharm. Fund Multicenter	Participants with persisting hypertriglyceridemia despite receiving simvastatin	Simvastatin 40	4000	122	Simvastatin 40	132	8	91	0/0	yes	4	no

Appendix E - GRADE

GRADE tables, assessing the evidence

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals (of the National Cholesterol Education Program), OR = odds ratio, BAS = Bile acid sequestrants, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

GRADE: Ezetimibe plus statin therapy compared with statin monotherapy

Table 31. GRADE: lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lower dose simvastatin combination therapy	higher dose simvastatin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 24 weeks)												
1	randomised trial	very serious[1]	serious[1]	serious[1,2]	very serious[1]	reporting bias[1]	0/104 (0%)	0/110 (0%)	OR 0 (0 to 0)	0 fewer per 1,000	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 23-24 weeks)												
2[3]	randomised trial[3]	serious[4]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	reporting bias[4]	118/146 (80.8%)	160/281 (57%)	OR 3.55 (2.18 to 5.79)	576 more per 1,000	LOW	IMPORTANT

[1] 1 trial reporting no deaths during a 24 weeks followup.[116] This trial had an unclear allocation concealment, double-blind procedure not described, no intention-to-treat analysis
[2] Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dl
[3] Both studies compared simvastatin (20mg/d) plus ezetimibe (10 mg/day) with simvastatin monotherapy (40 mg/day)
[4] 2 trials one with adequate allocation concealment and double-blind procedure,[38] no intention-to-treat analysis was described.[38,116]
[5] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus

Table 32. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statin plus ezetimibe	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 6-24 weeks)												
9[1]	randomised trial	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	2/1470 (0.1%)	4/1486 (0.4%)	OR 0.6 (0.15 to 2.39)	1 fewer per 1,000	VERY LOW	CRITICAL
Vascular death (follow-up 96 weeks)												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[4]	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.6)	3 more per 1,000	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)												
14	randomised trial	serious[5]	serious[6]	no serious indirectness	serious[6]	none	2826/3492 (80.9%)	1372/2708 (50%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] Four trials reported no deaths.[109,111,116,123]
[2] One long-term [116] and 8 short-term trials,[109-111,123,125-127,173] two with adequate allocation concealment,(6171, 13142} three with adequate double-blind procedure,[109-111] and one reported intention-to-treat analyses[123]
[3] Wide confidence intervals in each single trial and pooled data
[4] Single study with 96 weeks followup, adequate allocation concealment and reporting three vascular deaths.(16384} Double-blind, and intention-to-treat analysis procedures were not reported.[33]
[5] All short-term trials,[38,102,104,109-112,116,123,125,127,148,150,173] four with adequate allocation concealment,(317, 6171, 13142, 16386} four with adequate double-blind procedure,[104,109-111] and three reported intention-to-treat analyses[104,123,150]
[6] Results not pooled because of significant heterogeneity (I-squared 94%)

Table 33. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with baseline LDL-c > 190 mg/dL

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus ezetimibe	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Vascular death (follow-up 96 weeks)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[1]	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.6)	3 more per 1,000	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Single study with 96 weeks followup, adequate allocation concealment and reporting three vascular deaths.(16384} Double-blind, and intention-to-treat analysis procedures were not reported.[33]

Table 34. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with diabetes mellitus

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus ezetimibe	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 6-24 weeks)												
3[1]	randomised trial[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[1,2]	reporting bias[1]	1/936 (0.1%)	2/951 (0.2%)	OR 0.49 (0.06 to 4.02)	1 fewer per 1,000	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)												
6	randomised trial	serious[3]	serious[4]	no serious indirectness	very serious[4]	reporting bias[3]	1646/2019 (81.5%)	724/1433 (50%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] A single trial with followup of 24 weeks reported no deaths.[116] Data from two trials reporting 3 deaths were pooled.[127,173]
[2] Two short-term trials with adequate allocation concealment,[127,173] none with adequate double-blind procedure or intention-to-treat analysis
[3] All short-term trials,[110,112,116,127,148,173] three with adequate allocation concealment,[112,127,173] one with adequate double-blind procedure,[110] and none with intention-to-treat analysis
[4] Short-term trials with significant heterogeneity (I-squared = 92%)

Table 35. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with established vascular disease

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus ezetimibe	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up mean 6)												
5[1]	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	serious[1,2]	reporting bias[2]	0/757 (0%)	2/782 (0.2%)	OR 0.34 (0.04 to 3.25)	0 fewer per 1,000	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-12 weeks)												
5	randomised trial	serious[3]	serious[4]	no serious indirectness	serious[4]	reporting bias[3]	616/759 (81.2%)	211/779 (27%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] Three trials reported no deaths.[109,111,123]
[2] All short-term trials, with unclear allocation concealment,[109-111,123,126] three with adequate double-blind procedure,[109-111] and one reported intention-to-treat analysis.[123]
[3] All short-term trials, with unclear allocation concealment,[109-111,123,150] three with adequate double-blind procedure,[109-111] and two reported intention-to-treat analysis.[123,150]
[4] All studies favored combination therapy, however, due to significant heterogeneity (I-squared 72%) data was not pooled.

Abbreviations: OR = odds ratio, CI = 95% confidence interval

Table 36. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants of African descent

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	statins plus ezetimibe	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up mean 12 weeks)												
1	randomised trial[1]	serious[1,2]	very serious[1]	no serious indirectness	very serious[1]	reporting bias[1]	0/124 (0%)	0/123 (0%)	OR 0 (0 to 0)	0 fewer per 1,000	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up mean 6 weeks)												
1	randomised trial	very serious	serious	serious	no serious imprecision	reporting bias	85/135 (63%)	24/73 (33%)	OR 3.47 (1.9 to 6.33)	437 more per 1,000	VERY LOW	IMPORTANT
Serious adverse events - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		

[1] A single RCT with no deaths in combination or monotherapy was identified[128]
[2] adequate allocation concealment and double-blind procedure, no intention-to-treat analysis[128]
Abbreviations: OR = odds ratio, CI = 95% confidence interval

Table 37. GRADE GRADE: statins plus ezetimibe versus statins monotherapy in participants of Hispanic descent

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	statins plus ezetimibe	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up mean 6 weeks)												
1	randomised trial	very serious[1]	serious[1]	serious[1]	serious[1]	reporting bias[1]	46/71 (64.8%)	8/42 (19%)	OR 7.82 (3.14 to 19.45)	576 more per 1,000	VERY LOW	IMPORTANT
Serious adverse events - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Data from a sub-group population of a single trial.[112]. RCT with adequate allocation concealment and double blind, no intention-to-treat analysis performed.[112]

Table 38 GRADE: lower dose simvastatin plus ezetimibe therapy versus higher dose simvastatin monotherapy in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	lower dose simvastatin combination therapy	higher dose simvastatin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 24 weeks)												
1	randomised trial	very serious[1,2]	serious[1]	serious[2]	very serious[1]	reporting bias[1]	0/104 (0%)	0/110 (0%)	-	0 fewer per 1,000	VERY LOW	CRITICAL
Vascular death (follow-up 12 weeks)												
1	randomised trial	serious[3]	very serious[3,4]	no serious indirectness	very serious[3,4]	reporting bias[3,4]	1/58 (1.7%)	0/63 (0%)	OR 3.31 (0.13 to 82.96)	0 more per 1,000	VERY LOW	CRITICAL
Serious adverse events (follow-up 23-24 weeks)												
2	randomised trial[5]	serious[6]	serious[6]	no serious indirectness[7]	serious[8]	reporting bias[6]	28/464 (6%)	13/363 (3.6%)	OR 1.86 (0.6 to 5.74)	20 more per 1,000	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 23-24 weeks)												
2	randomised trial[5]	serious[6]	no serious inconsistency	no serious indirectness[9]	no serious imprecision	reporting bias[6]	118/146 (80.8%)	160/281 (49%)	OR 3.55 (2.18 to 5.79)	576 more per 1,000	LOW	IMPORTANT

[1] 1 trial reporting no deaths during a 24 weeks followup.[116] This trial had an unclear allocation concealment, double-blind procedure not described, no intention-to-treat analysis
[2] Participants with T2DM on stable thiazolidinediones, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dl
[3] 1 trial reporting one death during a 12 weeks followup.[135] This trial had an adequate allocation concealment and double-blind procedure, no intention-to-treat analysis was described
[4] 2 of the 8 arms presented contributed data for this outcome[135]
[5] Both studies compared simvastatin (20mg/d) plus ezetimibe (10 mg/day) with simvastatin monotherapy (40 mg/day)
[6] 2 trials one with adequate allocation concealment and double-blind procedure,[38] no intention-to-treat analysis was described.[38,116]
[7] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus[116] or CHD risk equivalent[38]
[8] Wide confidence intervals in each single trial and pooled data
[9] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus

Abbreviations: OR = odds ratio, CI = 95% confidence interval

Table 39. GRADE - statin plus ezetimibe therapy versus statin monotherapy in all participants followed for more than 24 weeks

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	statins plus ezetimibe therapy	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 24-52 weeks)												
4	randomised trial[1]	very serious[1,2]	very serious[3]	serious[4]	very serious[3]	reporting bias[3]	3/98 (3.1%)	0/102 (0%)	OR 7.51 (0.38 to 147.37)[3]	0 more per 1,000	VERY LOW	
Vascular death (follow-up mean 96 weeks)												
1	randomised trial	no serious limitations[5]	serious[6]	no serious indirectness	serious[6]	reporting bias[6]	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.59)	3 more per 1,000	VERY LOW	CRITICAL
Serious adverse events (follow-up 24-52 weeks)												
7	randomised trial	serious[7]	serious[8]	no serious indirectness	serious[8]	reporting bias[9]	137/1329 (10.3%)	54/564 (10%)	not pooled	not pooled	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		IMPORTANT

[1] 3 trials reported no deaths[39,116,130]
[2] 2 trials described adequate allocation concealment,[116,147] none described adequate double-blind, and 1 trial described intention-to-treat analysis[147]
[3] Results based on 3 deaths, and only one trial with analysable data[147]
[4] Participants with renal disease and without definitive indication for cholesterol lowering
[5] study with adequate allocation concealment, double-blind, no intention-to-treat analysis described[33]
[6] 1 trial reported 3 vascular deaths in a 96 weeks followup[33]
[7] 3 trials described adequate allocation concealment,[39,135,147] none described adequate double-blind, and 1 trial described intention-to-treat analysis[147]
[8] Results not pooled because of significant heterogenity (I-squared = 77%)
[9] SAE were reported by only half of the trials and from these 6 had a long-term followup

Abbreviations: OR = odds ratio, CI = 95% confidence interval

Table 40. GRADE - statin plus ezetimibe therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statin plus ezetimibe therapy	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 6-52 weeks)												
17	randomised trial[1]	serious[1]	serious[2]	no serious indirectness	serious[2]	reporting bias[3]	5/1568 (0.3%)	4/1588 (0.2%)	OR 0.94 (0.27 to 3.3)	0 fewer per 1,000	VERY LOW	CRITICAL
Vascular death (follow-up 12-96 weeks)												
2	randomised trial	very serious[4]	serious[5]	no serious indirectness	very serious[4]	reporting bias[4]	3/415 (0.7%)	1/416 (0.2%)	OR 2.28 (0.33 to 15.68)	0 more per 1,000	VERY LOW	CRITICAL
Serious adverse events (follow-up 6-52)												
20	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[7]	229/5907 (3.9%)	132/5221 (2.5%)	OR 1.07 (0.82 to 1.39)	1 more per 1,000	LOW	CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)												
21	randomised trial	serious[8]	serious[9]	no serious indirectness	serious[9]	reporting bias[10]	6669/8271 (80.6%)	4187/6922 (60%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] 11 trials reported no deaths,[39,109,111,112,116,123,128,130,132,134,172] 3 trials described adequate allocation concealment,[127,147,173] 1 trial described adequate double-blind,[110] , and 1 trial described intention-to-treat analysis[147]
[2] Results based on 9 deaths, and only one trial with analyzable data had a followup of > 24 weeks[147]
[3] Only 17 of the 37 included trials provided data on all cause mortality
[4] Only 2 out of 37 included trials reported 4 events of vascular death.[33,135] Both studies described adequate allocation concealment, did not describe the procedure for double-blind or intention-to-treat analysis.
[5] Results based on 4 deaths, and only one trial with analyzable data had a followup of > 24 weeks[33]
[6] 7 trials described adequate allocation concealment,[39,127,128,135,147,149,172] 4 trials described adequate double-blind,[109,111,128,149] , and 4 trials described intention-to-treat analysis[123,140,147,150]
[7] 20 out of 37 included trials reported this outcome
[8] 8 trials described adequate allocation concealment,[104,112,113,127,132,135,172,173] 2 trials described adequate double-blind,[104,111] , and 6 trials described intention-to-treat analysis[104,123,132,134,140,150]
[9] Results based only on short-term trials, with significant heterogeneity (I-squared = 94%)
[10] 21 out of 37 studies reported this outcome

GRADE: Fibrate plus statin therapy compared with statin monotherapy

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 41. GRADE: Rosuvastatin (5-10 mg/day) plus fenofibrate (67 mg/day) versus rosuvastatin (40 mg/day) in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rosuvastatin (5-10 mg/day) plus fenofibrate (67 mg/day)	rosuvastatin (40 mg/day)	Relative (95% CI)	Absolute		
All cause mortality (follow-up 18 weeks, all requiring intensive lipid-lowering therapy because of diabetes mellitus)												
1	randomised trial	very serious[1]	very serious[1]	no serious indirectness	very serious[1,2]	reporting bias[2]	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	10 fewer per 1000 (from 18 fewer to 109 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18 weeks, all requiring intensive lipid-lowering therapy because of diabetes mellitus)												
1	randomised trial	very serious[1]	very serious[1,2]	no serious indirectness	very serious[1,2]	reporting bias[2]	83/110 (75.5%)	43/50 (86%)	OR 0.5 (0.2 to 1.24)	349 fewer per 1000 (from 630 fewer to 131 more)	VERY LOW	IMPORTANT

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, short-term followup, and very sparse number of events
[2] Only one of the 11 included trials compared lower dose statin combination with higher dose monotherapy

Table 42. statin plus fibrate therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	all statins plus fibrate	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 18 weeks)												
1	randomised trial	very serious[1]	very serious[1]	serious[2]	very serious[1]	reporting bias[1,3]	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	10 fewer per 1000 (from 18 fewer to 109 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 52 weeks)												
1	randomised trial	very serious[1]	very serious[1]	serious[2]	very serious[1,3]	reporting bias[3]	0/25 (0%)	0/23 (0%)	OR 1.2 (0 to 0)	0 more per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)												
2	randomised trial	serious	very serious	no serious indirectness	very serious	reporting bias	122/150 (81.3%)	75/90 (83.3%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, short-term followup, and very sparse number of events
[2] All participants had diabetes mellitus
[3] Only one of the 5 trials performed in high risk population reported this outcome

Table 43. GRADE: statin plus fibrate therapy versus statin monotherapy in participants with diabetes mellitus

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	statins plus fibrate	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 18 weeks)												
1	randomised trial	very serious[1]	very serious[1,2]	no serious indirectness	serious[1,2]	reporting bias[3]	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	10 fewer per 1000 (from 18 fewer to 109 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	None	-	-	-	-	-	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)												
2	randomised trial	very serious[2,4]	very serious[2]	no serious indirectness	very serious[2]	reporting bias[3,5]	122/150 (81.3%)	75/90 (83.3%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, 18 weeks followup, and very sparse number of events
[2] Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)
[3] Only one of the 5 trials performed in high risk population reported this outcome
[4] All trials with unclear allocation concealment, none double-blind, one reported intention-to-treat analyses[143]
[5] Results based on a sub-group of 2 out of 11 included trials

Table 44. GRADE - statin plus fibrate therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus fibrate	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 12-18 weeks)												
3	randomised trial	serious[1]	serious[2]	no serious indirectness	very serious[2,3]	reporting bias[4]	1/188 (0.5%)	2/124 (1.6%)	OR 0.39 (0.05 to 3.22)	10 fewer per 1000 (from 15 fewer to 34 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0[5]	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 12-52 weeks)												
2	randomised trial	serious[6]	serious[7]	no serious indirectness	serious[7]	reporting bias[7]	12/428 (2.8%)	5/224 (2.2%)	OR 1.2 (0.42 to 3.46)	4 more per 1000 (from 13 fewer to 50 more)	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)												
2	randomised trial	serious[8]	very serious[9]	serious[10]	very serious[9]	reporting bias[11]	122/150 (81.3%)	75/90 (83.3%)	not pooled	not pooled	VERY LOW	IMPORTANT

[1] All trials with unclear allocation concealment, one double-blind,[105] none reported intention-to-treat analyses
[2] Results based on sparse number of events, three trials with short-term follow up
[3] Small sample size (individual trials and pooled data), wide confidence intervals
[4] Only 3 out of 11 included trials provided data on all cause mortality
[5] None of the 11 included RCTs, with followup duration of 6 to 92 weeks, provided information on vascular death
[6] One trial of unclear allocation concealment,[118] one trial did not reported intention-to-treat analysis[115]
[7] Results based on two small trials and sparse number of events
[8] All trials with unclear allocation concealment, none double-blind, one reported intention-to-treat analyses[143]
[9] Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)
[10] All participants had diabetes mellitus and might have increased risk
[11] Results provided in only two out of 11 included trials

Abbreviations: OR = odds ratio, CI = 95% confidence interval

GRADE: Niacin plus statin therapy compared with statin monotherapy

Table 45. GRADE - statin plus BAS therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	all statins plus niacin	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 52 weeks)												
1	randomised trial	very serious[1]	very serious[1]	no serious indirectness[2]	very serious[1]	reporting bias[1,3]	2/78 (2.6%)	1/71 (1.4%)	OR 1.84 (0.16 to 20.76)	11 more per 1,000	VERY LOW	CRITICAL
Vascular death (follow-up 12 weeks)												
1	randomised trial	very serious[4]	very serious[4]	no serious indirectness[2]	very serious[4]	reporting bias[4]	0/27 (0%)	0/27 (0%)	-	-	VERY LOW	CRITICAL
Serious Adverse Events - not measured												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)												
1	randomised trial	very serious[5]	very serious[5]	no serious indirectness[2]	very serious[5]	reporting bias[5]	21/32 (65.6%)	19/34 (56%)	OR 1.51 (0.56 to 4.08)	185 more per 1,000	VERY LOW	IMPORTANT

[1] Single study with adequate allocation concealment and double-blind procedure, no intention-to-treat analysis reported, long-term followup, and 3 deaths[175]
[2] All participants had established vascular diseases
[3] Only one of the 6 trials performed in high risk population reported this outcome
[4] Single study with unclear allocation concealment and double-blind procedure, no intention-to-treat analysis reported, short-term followup, and reporting 0 deaths[176]
[5] 1 short-term trial with unclear allocation concealment, double-blind procedure, and no description of intention-to-treat analysis.[40]

Table 46. GRADE: Statin plus niacin therapy compared with statin monotherapy, in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins + niacin	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 17-52 weeks[1])												
4	randomised trial[2]	no serious limitations[3]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2,3]	3/192 (1.6%)	2/132 (1.5%)	OR 1.08 (0.17 to 6.72)	1 more per 1,000	LOW	CRITICAL
Vascular death (follow-up 12-28 weeks[5])												
2	randomised trial[6]	serious[7]	serious[6,7]	no serious indirectness	very serious[6,7]	reporting bias[7]	1/114 (0.9%)	1/61 (1.6%)	OR 0.53 (0.03 to 8.64)	7 fewer per 1000 (from 16 fewer to 108 more)	VERY LOW	CRITICAL
Serious Adverse Events (follow-up 17-28 weeks)												
3	randomised trial	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	reporting bias[8]	11/274 (4%)	3/154 (3%)	OR 1.63 (0.48 to 5.56)	18 more per 1,000	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)												
1	randomised trial	very serious[10]	very serious[10]	no serious indirectness	very serious[10,11]	reporting bias[10]	78/105 (74.3%)	78/117 (83%)	-	-	VERY LOW	IMPORTANT

[1] Only the two long-term studies contributed data to the pooled analysis.[96,175]
[2] Two short-term trials reported no deaths.[95,151]
[3] 2 long-term trials with adequate allocation concealment, adequate double-blind procedure, and intention-to-treat analysis was described.[96,175]
[4] Results based on two studies and 5 deaths.
[5] Only the long-term trial contributed data to the analysis.[133]
[6] One short term trial reported no death.[176]
[7] 2 trials with unclear allocation concealment,[133], 13487} one long-term trial with adequate double-blind procedure and intention-to-treat analysis described[133]
[8] 1 long-term[96] and 2 short-term[95,151] trials, 2 with adequate allocation concealment, adequate double-blind procedure, and description of intention-to-treat analysis,[95,96]
[9] Wide confidence intervals in each single trial and pooled data
[10] 1 short-term trial with unclear allocation concealment, double-blind procedure, and no description of intention-to-treat analysis.[40]
[11] Data is provided in four arms of the same trial, but with significant heterogeneity (I-squared = 63%)

GRADE: BAS plus statin therapy compared with statin monotherapy

Table 47. GRADE: statin plus Omega-3 therapy compared with statin monotherapy, in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 4-24 weeks)				
3	1/73 (1.4%)	1/78 (1.3%)	OR 1.07 (0.11 to 10.51)	very low[1,2,3]
Vascular death - not measured				
0	0/0	0/0	-	-
Serious Adverse Events (follow-up 6-30 weeks)				
2	1/112 (0.9%)	6/166 (3.3%)	OR 0.39 (0.06 to 2.36)	very low[1,7,8]
Participants reaching ATPIII LDL-c goals (follow-up 12 weeks, all participants required lipid lowering therapy because of established vascular diseases)				
1	13/28 (46.4%)	5/31 (16%)	OR 4.51 (1.34 to 15.1)	very low[5,6]

[1] One trial had an adequate allocation concealment and adequate double-blind,[152] and no trial used an intention-to-treat analysis
[2] Results based on sparse number of events, two trials with short-term follow up
[3] Only 3 out of 17 included trials provided data on all cause mortality
[4] Analysis based on a single trial on which all participants required intensive lipid-lowering therapy because of established vascular diseases[99]
[5] One trial, unclear allocation concealment, no double-blind, no intention-to-treat analysis; short-term followup, and small sample size.[99] All participants required lipid lowering therapy because of established vascular diseases.
[6] Results provided in only one out of 17 included trials
[7] Results based on sparse number of events, two trials one with short-term follow up[152]
[8] In one trial all participants had LDL-c >190 mg/dL at baseline[177]

Abbreviations: OR = odds ratio, CI = 95% confidence interval

GRADE: Omega-3 fatty acid plus statin therapy compared with statin monotherapy

Table 48. GRADE: statin plus Omega-3 therapy versus statin monotherapy, in all participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus Omega-3	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 240 weeks[1,2])												
3	randomised trial[2]	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2,3]	286/9469 (3%)	265/9471 (2.8%) 2.8%	OR 1.08 (0.91 to 1.28)	2 more per 1,000 2 more per 1,000	MODERATE	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 8 weeks)												
1	randomised trial	very serious[4]	serious[4]	no serious indirectness	serious[4]	reporting bias[4]	4/122 (3.3%)	1/132 (0.8%)	OR 4.44 (0.49 to 40.29)	26 more per 1,000	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Three studies included, but only one long-term trial wit large sample size contributed data to the pooled analysis.[124]
[2] Two short-term trials reported no deaths.[157,160]
[3] One long-term trial with adequate allocation concealment and intention-to-treat analysis was described, no double-blind procedure reported.[124]
[4] One short-term trial with adequate allocation concealment and double-blind procedure, no intention-to-treat analysis was reported.[160]

Table 49. GRADE: statin plus Omega-3 therapy versus statin monotherapy, in participants of Asian origin

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	all statins plus Omega-3	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 240 weeks)												
1	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[1]	286/9326 (3.1%)	265/9319 (2.8%)	OR 1.08 (0.91 to 1.28)	2 more per 1,000	MODERATE	CRITICAL
								2.8%		2 more per 1,000		
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATPIII LDL-c goals - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] One long-term trial with adequate allocation concealment and intention-to-treat analysis was described, no double-blind procedure reported.[124]

Appendix F – References

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